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RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Ying-Yi Yuan; Production Department Director: Xu Gan; Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
October 26, 2022

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ONLINE SUBMISSION
https://www.f6publishing.com
New insights into the interplay between intestinal flora and bile acids in inflammatory bowel disease

Lie Zheng

Abstract

Intestinal flora plays a key role in nutrient absorption, metabolism and immune defense, and is considered to be the cornerstone of maintaining the health of human hosts. Bile acids synthesized in the liver can not only promote the absorption of fat-soluble substances in the intestine, but also directly or indirectly affect the structure and function of intestinal flora. Under the action of intestinal flora, bile acids can be converted into secondary bile acids, which can be reabsorbed back to the liver through the enterohepatic circulation. The complex dialogue mechanism between intestinal flora and bile acids is involved in the development of intestinal inflammation such as inflammatory bowel disease (IBD). In this review, the effects of intestinal flora, bile acids and their interactions on IBD and the progress of treatment were reviewed.

Key Words: Intestinal flora; Bile acids; Inflammatory bowel disease; Fecal microbiota transplantation; Prebiotics

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Zheng L. Interplay between intestinal flora and bile acids in IBD

Citation: Zheng L. New insights into the interplay between intestinal flora and bile acids in inflammatory bowel disease. World J Clin Cases 2022; 10(30): 10823-10839
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/10823.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.10823

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing disease, including Crohn's disease (CD) and ulcerative colitis (UC), which has become a public health problem worldwide. With changes in diet and lifestyle, the incidence of IBD is rising rapidly worldwide. The composition of intestinal flora is considered to be the main driver of intestinal immune dysfunction in IBD, but this concept has not been fully proven[1]. Bile acids (BAs) are steroid molecules produced by interaction between the host and gut flora. It is one of the largest bioactive substances found in mammals and acts on the G protein and nuclear receptor families[2]. In this review, we reviewed the effects of intestinal flora, BA receptors and their interactions on IBD and the progress of its treatment.

INTESTINAL FLORA AND IBD

IBD patients were found to have intestinal microbiota imbalance, which was mainly characterized by decreased intestinal microbiota diversity. The anti-inflammatory bacteria in feces of IBD patients, such as Faecalibacterium prausnitzii and Roseburia, have decreased. In the intestinal mucus layer, Roseburia can convert acetate to butyrate and produce secondary BAs, which may have anti-inflammatory effects[3]. The proportion of Bacteroides Fragilis in IBD patients also decreased significantly. The polysaccharide A produced by The bacterium induces the development of CD4+ T cells and the anti-inflammatory function of regulatory T cells (Treg)[4]. A recent study found that the use of short-term antibiotics at an early age increased the susceptibility of mice to colitis induced by Dextran sulfate sodium (DSS), suggesting that the imbalance of intestinal flora is closely related to the incidence of IBD[5].

The intestinal flora metabolizes to produce many bioactive molecules that interact with the host. The typical representatives are short chain fatty acids, which mainly include acetic acid, propionic acid and butyric acid. These bioactive molecules not only serve as energy for intestinal epithelial cells, but also increase the secretion of anti-inflammatory cytokines such as interleukin (IL-10) and the number of Treg cells by activating the G protein-coupled receptor 5 (TGR5) on intestinal cells and immune cells[6]. It can reduce tissue inflammation and maintain the stability of intestinal mucosal barrier function. Studies have shown that butyrate can promote the recovery of intestinal barrier function and accelerate the repair of intestinal epithelial cell injury through synaptopoptin, while the loss of bacterial flora blocks the expression of synaptopoptin and increases the sensitivity to colitis and intestinal permeability in mice[7].

Dietary tryptophan can be metabolized by intestinal flora into metabolites such as indoleacetic acid, indole-3-acetaldehyde, indole-3-aldehydes, indole-3-acrylics and indole-3-propionic acid, thus acting as ligands of aromatic hydrocarbon receptors, which are closely related to the pathogenesis of IBD[8].

Indoles, indoles propionic acid and indoles acrylic acid bind to progesterone X receptors, thereby reducing intestinal permeability and affecting mucosal homeostasis[9]. Indoleformaldehyde secretes IL-22 by activating aromatic hydrocarbon receptors on intestinal immune cells. Indole-3-propionic acid protects mice from DSS-induced colitis by binding to aromatic hydrocarbon receptors to produce IL-10[10]. Therefore, intestinal flora disorder can disrupt immune regulation and promote inflammation through its metabolites.

BA METABOLISM

BA is an important compound and structural component in human and animal Bile, and the liver is the main site of BA formation[11]. BA synthesis by the great influence of diet, the body from free cholic acid (CA), the primary BAs combined with secondary free CA and BA composition, type of free BA is by chenodeoxycholic acid (CDCA) and CA, primary BA combination type of cows sulfonated goose deoxycholic acid (DCA) and ammonia goose DCA, taurocholic acid as well as the composition of gca, Secondary free CA consists of CA and DCA[12]. BAs are a kind of important host-derived compounds, which have many important physiological functions and effects on the host and its intestinal flora. BAs are metabolites of cholesterol, and the transformation of BAs requires the help of intestinal microflora[13]. The classical pathway and the alternative pathway are two pathways of BA synthesis. It is regulated by cholesterol 7α-hydroxylase (CYP7A1), sterol 12α-hydroxylase (CYP8B1), cholesterol 27α-hydroxylase (CYP27A1) and other enzymes related to BA synthesis[14]. It has been confirmed that in
the classical pathway of BA synthesis, cholesterol in human liver is catalyzed by CYP7A1 to produce 7α-
hydroxy cholesterol, and then is catalyzed by 3β-hydroxysteroid dehydrogenase (3β-HSD), CYP8B1 and CYP27A1. 7α-hydroxy cholesterol is catalyzed to produce primary BAs, free CA and goose DCA (CDCA)[15].

In the alternative pathway, cholesterol is catalyzed by CYP27A1 to produce 27α-hydroxy cholesterol, followed by DCA in response to CYP7B1[16]. The free CA then binds to glycine and taurine by its own amide bond to form conjugated BAs which enter the intestinal tract of the body[17]. Taurocholic acid forms DCA after hydroxy release by intestinal bacteria. In the metabolism of goose DCA, goose DCA is a combination of glycine and goose DCA[18]. The intestinal bacteria of the body hydrolyze goose DCA and dehydroxy to form stone CA[19]. Goose DCA can also react with taurine to form taurocholic acid. CYP7A1 is a rate-limiting enzyme of BA synthesis in the body, and its activity can regulate the rate of BA synthesis in the process of BA synthesis, which has been proved in an experimental study[20]. Rats in the experimental group were fed BA, and the activity of 7α-hydroxylase was decreased and the rate of BA synthesis was also significantly decreased in the experimental group compared with normal rats[21]. After BA synthesis by bile salt export pump into the gall bladder stores, when the body after eating, in the gallbladder bile into the intestine to help the body absorb the lipid in food, the BA level in the body is not fixed, it is in the steady state environment, in the terminal ileum 95% BA enterohepatic circulation will be absorbed by weight, over 5% of conjugated BA eduction of excrement and urine, Limited BAs are reused through the enterohepatic circulatory system[22]. This process, called BA enterohepatic circulation, occurs about six times a day in the body. Most BAs are reabsorbed at the terminal ileum via the apical membrane sodium-dependent bile salt transporter (ASBT) of intestinal cells, where bile salts are transported from the intestinal epithelial cells to the basal outer membrane side into the blood with the help of intestinal BA proteins[23].

**BA AND IBD**

Repeated stimulation of intestinal epithelial cells with high concentration of BAs is important risk factor for the pathogenesis of IBD, which will destroy host material metabolism and signal transduction[24]. In rats with colitis induced by Trinitrobenzenesulfonic acid, apical sodium-dependent BA transporter, ASBT expression decreased. When intestinal inflammation occurs, the intestinal barrier is damaged, which leads to the reduction of ASBT expression, and finally the destruction of enterohepatic circulation leads to the accumulation of BAs in the intestinal mucosa, and the intestinal inflammation is aggravated. In IBD patients, ileal inflammation blocks hepatoenteric circulation of BAs, leading to reduced ileal reabsorption, which may be due to inhibition of ASBT promoter expression by inflammatory cytokines, thus increasing fecal BAs[25].

Hepatic BA synthesis is regulated by the Farnesoid X receptor (FXR)-FGF15/19 signaling pathway. Activation of this signaling pathway reduces the expression of enzymes related to hepatic BA synthesis and reduces BA synthesis[26]. Activation of FXR can improve colon inflammation, protect intestinal inflammation, reduce intestinal permeability, and reduce goblet cell extinction. The activation of FXR can also inhibit the secretion of tumor necrosis factor-α (TNF-α), interferon (IFN)-γ, IL-17 and other inflammatory cytokines in the mucosal cells of IBD patients, and up-regulate the expression of anti-inflammatory factor IL-10 in the intestinal tract[27]. Therefore, compared with the healthy control group, the enterohepatic circulation of IBD patients is blocked, the negative regulatory pathway of intrahepatic BA synthesis is reduced, and the total amount of BAs in the intestinal lumen is increased, leading to intestinal inflammation[28].

**BA-ACTIVATED RECEPTORS IN IBD**

BA receptors mainly consist of TGR5, FXR, and pregnane X receptor (PXR). Constitutive Androstane receptor (CAR), Vitamin D receptor (VDR), PXR. It has the functions of regulating BA metabolism, glucose utilization, fatty acid synthesis and oxidation, energy homeostasis balance, immune cell function, nerve activity and so on.

**TGR5 and IBD**

TGR5 is a membrane receptor containing seven transmembrane regions. TGR5 mRNA expression was found in almost all human and rodent tissues, especially in gallbladder, ileum and colon[29]. Lithocholic acid (LCA) was the most effective in TGR5 stimulation. The rest were DCA, CDCA and CA. Activation of TGR5 can trigger the elevation of cyclic adenosine monophosphate (C-AMP) or epidermal factor growth. The activation of receptor (EGFR)-sarcoma (SRC) kinase affects the physiological state of cells [30].

IBD is caused by an overactive immune response to intestinal antigens. TGR5 deletion has been found to exacerbate intestinal inflammation in DSS-induced colitis mice[31]. There was no significant difference in TGR5 expression in colonic mucosa between patients with UC and the control group[32].
However, a recent study showed that TGR5 expression was significantly elevated in the colonic mucosa of children with UC, and was concentrated in lamina propria phagocytes[33]. TGR5-specific activation of macrophages isolated from the intestines of patients with CD significantly inhibited the production of TNF-α in macrophages, suggesting that the TGR5 signaling pathway may play an immunomodulatory role in IBD[34].

TGR5 is highly expressed in mononuclear macrophages, and intestinal macrophages, as the main source of cytokines, play an important role in immune homeostasis[35]. Polarization of macrophages is generally divided into two types, M1, which promotes inflammation, and M2, which suppresses inflammation. Rather than inducing macrophage activation to either phenotype alone, BA-activated TGR5 induces "mixed phenotype" macrophages, where an elevated IL-10/IL-12 ratio indicates the dominance of the immunosuppressive M2 phenotype[36]. TGR5 specific activation can reduce the production of pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α in THP1 cells, and TGR5 activation can inhibit the secretion of inflammatory cytokines in intestinal macrophages in a dose-dependent manner[37]. In terms of mechanism, TGR5 activates C-AMP and EGFR-SRC kinase pathways in response to BAs. On the one hand, BA-activated TGR5 mediated the activation of C-AMP, which further activated PKA, up-regulated the expression and activity of C-AMP binding element, and finally inhibited the translocation of NF-κB into the nucleus through a series of steps[38]. Meanwhile, the expression of anti-inflammatory factor IL-10 was significantly increased after the activation of C-AMP binding element[39]. On the other hand, in M1-type macrophages, TGR5-dependent EGFR trans-activated SRC kinase activation leads to NF-κB activation through downstream protein kinase C, and increased expression of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α[40]. In summary, BA-TGR5 signal transduction regulates a complex balance between pro-inflammatory and anti-inflammatory cytokines in the gut.

**FXR and IBD**

A nuclear receptor superfamily member, FXR, with BA ligand activity was first identified in a 1995 study of rat liver C DNA[41]. FXR mainly exists in the intestine, liver and kidney, especially in the ileum, colon and liver, and is involved in the regulation of a large number of physiological activities of the human body. In addition to regulating BA metabolism and transport, FXR also plays a key role in regulating lipid and glucose homeostasis, inflammatory response, and barrier function[42].

BAs can be classified according to their affinity for binding FXR in vitro. CDCA has the highest excitatory effect on FXR, followed by CA, DCA and LCA[43]. Compared with their natural forms, the sugar-taurosulfo-conjugated forms of CDCA, DCA and LCA are more effective agonists. Among the synthesized FXR agonists, GW4064 selectively excites FXR with high affinity, which is widely used in experimental studies[44].

FXR plays an important role in the development and progression of IBD. Early colon cell tests showed that FXR gene knockout mice were more likely to develop severe intestinal inflammation than wild-type mice, suggesting that intestinal FXR could reduce intestinal inflammation[45]. It has been found that activation of intestinal FXR can inhibit NF-κB activation and reduce intestinal inflammation through multiple pathways[46]. FXR attenuates the translocation of NF-κB subunit P65, thereby inhibiting NF-κB transcription, reducing the gene expression of pro-inflammatory factor IL-8, and alleviating intestinal inflammation[47]. Activation of intestinal FXR expression can inhibit intestinal toll-like receptor 4-myeloid differentiation factor 88 signaling pathway, thereby down-regulating NF-κB expression and alleviating intestinal inflammation[48]. In addition, activation of FXR can up-regulate the expression of IL-10, an anti-inflammatory factor in the intestinal tract, thus exerting an anti-inflammatory effect. It is concluded that activation of intestinal FXR can reduce intestinal inflammation and play a protective role in IBD intestine, and FXR is expected to become a drug target for IBD treatment[49]. It is important to note that FXR has different functions in different tissues, and currently there are no intestinal FXR specific agonists. Therefore, when FXR is used as a treatment for IBD, it may activate hepatic FXR and cause adverse reactions[50].

Intestinal BA accumulation can cause the proliferation and apoptosis of intestinal epithelial cells, leading to IBD. FXR can regulate BA synthesis and reabsorption to maintain intestinal BA homeostasis[51]. On the one hand, FXR can regulate the expression of fibroblast growth factor (FGF), thereby inhibiting the expression of CYP7A1 and reducing BA synthesis[52]. On the other hand, intestinal FXR also promotes the expression of organic solute transporter alpha-beta (OSTα/β), Inhibit the expression of ASBT in ileum, thus promoting the excretion of intestinal BA[53]. Therefore, intestinal FXR has a protective effect on the intestinal tract of IBD and can be used as a therapeutic target for IBD. As a synthetic FXR agonist, GS-9674 alleviates cholestatic intestinal injury by activating FXR in intestinal epithelial cells to up-regulate FGF19 expression[54]. Based on 6-alpha-ethyl-chenodeoxycholic acid (6-ECDCA), which is mainly used for the treatment of cholestatic diseases, the 6-ECDCA can activate FXR, regulate the expression of OSTα/β and ASBT, and improve the intestinal cholestasis[55]. However, there is no clinical trial of 6-ECDCA as a treatment for IBD, but with the deepening of basic research, it is expected to become a treatment for IBD targeting FXR.

**PXR and IBD**

PXR is an important member of the nuclear receptor superfamily and is mainly expressed in colon and liver. Studies have shown that PXR plays an important role in maintaining intestinal homeostasis, and
its gene deletion leads to an increased risk of IBD\cite{56}. Moreover, PXR not only participates in intestinal immune response by regulating inflammatory signaling pathways, but also can receive endogenous signals to regulate intestinal homeostasis, so it is expected to become a new therapeutic target.

Excessive inflammatory response is the most prominent feature of IBD. NF-κB is the most classic inflammatory signaling pathway, and when activated, it releases a large number of inflammatory factors, exacerbating IBD\cite{57}. The nuclear receptor PXR is an upstream regulatory factor of NF-κB, and can regulate NF-κB through PXR to reduce intestinal inflammation. We found that compared with wild-type mice, NF-κB was activated in the colon of PXR knockout mice, resulting in the release of a large number of inflammatory factors (such as TNF-α, IL-6, etc.), and increased intestinal inflammation\cite{58}. It is speculated that PXR gene deletion may activate NF-κB pathway and increase intestinal inflammation.

Activation of PXR receptor can inhibit NF-κB expression in the intestinal tract, thereby reducing the level of downstream inflammatory factors and reducing intestinal inflammation\cite{59}. PXR protects the intestine by regulating NF-κB signaling. In addition, PXR also regulates non-classical inflammatory pathways, such as transforming growth factor (TGF-β1) expression, which plays a role in reducing intestinal inflammation. Therefore, PXR is considered as one of the most promising targets for IBD treatment\cite{60}.

Intestinal mucosal barrier is an important physical barrier to prevent toxic substances from invading the intestine, maintaining intestinal mucosal homeostasis and avoiding intestinal injury. When the intestinal permeability is increased, the intestinal mucosal barrier function is reduced, which can directly lead to the occurrence or exacerbation of IBD symptoms. Increased intestinal permeability in IBD patients is closely related to the abnormal expression of Myosin light-chain kinase (MLCK) and C-Jun n-terminal kinase 1/2 (JNK1/2)\cite{61}. However, nuclear receptor PXR can reduce intestinal permeability by down-regulating the expression of MLCK and JNK1/2, and play a role in maintaining intestinal mucosal barrier function. It was found that MLCK expression and myosin light chain phosphorylation level in colon tissue of IBD patients were significantly increased, and intestinal permeability was increased\cite{62}. Pregnenolone 16-alpha carbonitrile (PCN), a PXR agonist, can inhibit MLCK and myosin II light chain phosphorylation, reduce the permeability of the intestinal barrier, and avoid intestinal injury. The up-regulation of JNK1/2 expression in intestinal cells of IBD patients increases intestinal permeability, while PCN can down-regulate intestinal JNK1/2 expression by inducing GADD45β protein transcription, reducing intestinal permeability and avoiding toxin invasion \cite{63}. Therefore, PXR can maintain intestinal mucosal barrier function, and its ligand can be used to treat IBD. However, PXR receptor agonist PCN is only used in animal experimental studies, and has not been used for clinical treatment. The study of intestinal protective mechanism of PXR will promote the application of PXR agonists in clinical treatment\cite{64}.

In human body, metabolic enzymes and transporters are highly expressed in the intestine, among which metabolic enzymes are mainly involved in the detoxification process of intestinal toxic substances, such as CYP3A4 and CYP3A11\cite{65}. Transporters are mainly involved in the excretion of intestinal cytotoxic substances, such as P-glycoprotein (P-GP)\cite{66}. Studies have shown that the reduced expression of metabolic enzymes and transporters involved in the metabolism of heterogenic substances in the intestine of IBD patients leads to the accumulation of intestinal toxins, and PXR is an upstream regulatory factor of multiple metabolic enzymes and transporters, which can regulate their expression to play a detoxification role\cite{67}. Activation of PXR can significantly up-regulate the expression of CYP3A4 gene in wild-type mice, thus improving the symptoms of abdominal pain and diarrhea. The expression level of P-GP in colon tissues of IBD mice prepared by DSS was down-regulated, and the poison was accumulated in intestine. PXR could reduce the accumulation of poison by regulating the expression of P-GP\cite{68}. PXR can up-regulate the expression of drug metabolism enzymes and transporters to eliminate intestinal toxicity, and has a protective effect on IBD intestinal tract. Tanshinone II A, the active ingredient of Salvia miltiorrhiza in labiaceae, is A highly active PXR agonist, which mainly upregulates the expression of PXR to increase the expression of downstream metabolic enzymes and transporters, thereby promoting intestinal toxin metabolism and efflux, and improving the symptoms of IBD\cite{69}. PXR agonists speed up the metabolism of other drugs in the body, reducing the potential for adverse reactions to these drugs. However, large-scale activation of PXR can up-regulate the expression of metabolic enzymes and transporters, and then affect the metabolism of other drugs, leading to decreased efficacy and even induced drug interactions, which may limit the clinical application of PXR agonists in the treatment of IBD\cite{70}. It can be seen from the above that the protective effect of PXR on the intestinal tract of IBD has been preliminarily confirmed. Based on its protective mechanism, PXR can be used as a target for drug therapy of IBD, providing a new perspective for innovative drug research and IBD treatment.

**CAR and IBD**

CAR is a nuclear receptor for steroidal hormones, which is mostly expressed in intestinal epithelial cells. Although the protective mechanism of CAR against IBD is not fully understood, there is increasing evidence that it also plays a key role in regulating intestinal inflammation and protecting the intestinal mucosal barrier\cite{71}. Biopsies of the intestinal mucosa of IBD patients showed that CAR gene expression was strongly associated with intestinal inflammation levels. In IBD mice, intestinal mucosal barrier was disrupted, and the activation of p38MAP kinase by CAR agonist CITCO enhanced IEC cell migration.
and accelerated intestinal mucosal healing[72]. In addition, CAR significantly regulates metabolic enzymes and transporters located in the intestine, and protects the intestine from toxic interference by inducing the expression of metabolic enzymes and transporters[73]. These results suggest that CAR, like PXR and FXR, can play a protective role in IBD by reducing intestinal inflammation and maintaining intestinal mucosal homeostasis, but the specific mechanism remains to be studied[74]. In conclusion, CAR is also a promising drug target for IBD treatment, and further study of its protective mechanism against IBD can provide reference for drug development targeting CAR.

**VDR and IBD**

VDR is a member of the nuclear hormone receptor superfamily, which exists in all the target tissues of vitamin D3, such as intestinal tract and liver[75]. VDR, as an important nuclear transcription factor, intervenes in many downstream genes through specific binding with ligands. Studies have confirmed that VDR gene polymorphism is associated with the risk of IBD, and there are differences in VDR genotypes among different genders and populations[76]. Human proteomics shows that VDR is highly expressed in the normal small intestine and colon, but reduced intestinal VDR expression and impaired VD/VDR signaling pathway were observed in patients with CD and UC[77]. Therefore, intestinal VDR plays an important role in the occurrence and development of IBD.

Loss of VDR in intestinal epithelial cells leads to activation of NF-κB signaling, which promotes production of pro-inflammatory cytokines[78]. A genome-wide association analysis showed that VDR binds to 42 disease-associated single nucleotide polymorphisms, of which one-third significantly affect transcription factor NF-κB binding and gene regulation. Immunoprecipitation results suggested that VDR had a protein-protein interaction with IKKβ upstream of NF-κB[79]. VDR inhibited ser-177 phosphorylation of IKKβ by binding to IKKβ, thereby inhibiting NF-κB activation and IL-6 elevation induced by TNF-α, and improving intestinal inflammation[80].

A meta-analysis shows that variations in the VDR gene significantly affect the human gut microbiome[81]. It was found that the protective effect of probiotics on IBD depends on the epithelial VDR signaling pathway. In the normal intestinal flora of mice, the distribution and abundance of bacteria in the intestinal epithelium after VDR knockout were significantly changed, mainly manifested as increased abundance of Bacteroides fragilis in mice with VDR deletion[82]. In addition, intestinal epithelial VDR deletion exacerbated the intestinal inflammatory damage caused by sodium glucan sulfate modeling in mice, while the intestinal epithelial VDR deletion mice and wild-type control mice were reared in the same cage for modeling, this difference in intestinal inflammation caused by different genotypes among different genders and populations[76]. Studies have confirmed that VDR gene polymorphism is associated with the risk of IBD, and there are differences in VDR genotypes among different genders and populations[76]. Human proteomics shows that VDR is highly expressed in the normal small intestine and colon, but reduced intestinal VDR expression and impaired VD/VDR signaling pathway were observed in patients with CD and UC[77]. Therefore, intestinal VDR plays an important role in the occurrence and development of IBD.

Some studies have speculated that metabolites of intestinal flora regulate intestinal immune responses in a VDR dependent manner[86]. Butyrate is a short-chain fatty acid produced by intestinal microorganisms. 2% sodium butyrate in drinking water increased intestinal VDR expression and inhibited inflammation in mice with colitis[87]. In addition, secondary BAs and shicholic acids produced by intestinal flora metabolism inhibit Th cell immune response by activating VDR of CD4+Th cells, thereby reducing IFN-γ and IL-2 production in intestinal inflammation[88]. In conclusion, VDR genes may play an important role in homeostasis and signal transduction between the microbiome and host in intestinal inflammation.

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**Sphingosin1-phosphate receptor 2 and IBD**

Sphingosine-1 (S1P) is an active sphingosine-1 that participates in the regulation of various cell functions under physiological and pathological conditions[89]. S1P can function directly as intracellular signaling molecules or extracellular by activating 5 G protein-coupled receptors (GPCRs). S1P has been shown to be a key regulator of proliferation, migration, and survival of many cell types. The expression of S1PRs was different in different tissues or organs. All five S1PRs were detected in the human intestine, but the expression levels of S1PRs were different[90]. It has been reported that S1P regulates the expression of e-cadherin by activating S1PR2 to enhance intestinal epithelial cell barrier function. It has also been reported that S1P reduces intestinal epithelial cell apoptosis through the Akt dependent pathway[91,92]. These studies suggest that S1P and its receptor can promote intestinal epithelial cell proliferation and enhance epithelial cell barrier function, and play a protective role in intestinal mucosal barrier.

**Retinoid-related orphan receptor gamma and IBD**

Retinoid-related orphan receptor gamma (ROrγ T) is a specific transcription factor controlling Th17 cell differentiation. Treg cells are from the same source as Th17 cells, and they are closely related[93].
Treg cells play an important role in maintaining the body's immune tolerance state and the stability of internal environment, and preventing the occurrence of autoimmune diseases. Th17 cells, a new type of CD4+ cell subpopulation discovered in 2003, play a pro-inflammatory role mainly by secreting cytokines such as IL-17, IL-22 and IL-21\[94]. RORγ T is a transcriptional activator that plays a key role in the differentiation of Th17 cells. Inhibition of RORγ T expression can inhibit the differentiation of proinflammatory T cells into Th17 cells\[95]. It has been found that RORγ T directs the differentiation of proinflammatory Th17 cells and regulates the production of IL-17 in peripheral blood\[96]. Therefore, it is reasonable to believe that RORγ T can be used as an important target for the treatment of autoimmune and inflammatory diseases. Treg cells are newly discovered T cell subsets that negatively regulate the body's immune responses, and their immune regulatory function is closely related to the continuous expression of Foxp3\[97]. Foxp3 is considered to be a key transcription factor and specific marker of Treg cells, which can regulate the expression and function of multiple genes after binding to chromosomes, thus controlling the development and function of Treg cells\[98]. In vitro studies have shown that TGF-β can inhibit RORγt function and promote Treg differentiation by inducing Foxp3 expression, and the full-length Foxp3 subtype can bind to RORγ T to inhibit RORγ T function\[99]. In the presence of proinflammatory cytokines, Foxp3 levels decreased and RORγ T levels increased, ultimately promoting Th17 cell differentiation. In a mouse model of colitis, RORγ T binding reduced IL-17 production and Th17 cell count and reduced intestinal inflammation\[100]. Studies have shown that Th17 lymphocytes are involved in the pathogenesis of CD and UC. Increased IL-17 expression in mucosa and serum of IBD patients was associated with increased RORγ T expression and Th17 cell number\[101]. Therefore, Th17 and Treg cells antagonize each other functionally and are closely related in differentiation. Under normal circumstances, they maintain a relative balance, which is beneficial to maintain the immune stability of the body\[102]. At present, the relationship between Th17/Treg cell imbalance and disease occurrence and development has become the focus of people's attention.

INTERACTION BETWEEN INTESTINAL FLORA AND BAS

Intestinal flora and BA synthesis

Intestinal flora can further modify the synthetic BAs to form a series of intestinal BA metabolites. These metabolites can act as important signaling molecules to regulate cholesterol metabolism and energy balance of the host through BA receptors\[103]. The involvement of intestinal flora in the synthesis of BAs increases the diversity of BAs and the hydrophobicity of BA pools, which is conducive to BA excretion\[104]. The modification of BAs by intestinal flora mainly includes early uncoupling, dehydroxylation, dehydroxylation and differential isomerization of BAs. Bile salt-hydroxylases (BSHs) produced by intestinal bacteria catalyze BSHs, and then uncouple bile c-24 with n-acetyl amino bonds bound to amino acids to form free BAs\[105]. Studies have found that there are many bacteria in the intestinal tract of the organism that can produce BA salinases, such as bifidobacterium, Lactobacillus, Bacteroides, Listeria and Clostridium have BA salinase activity\[106]. 7α-hydroxyl dehydrogenation occurs in free BAs under the catalytic action of Clostridium and Clostridium, and hydroxyl steroid dehydrogenase (HSDH) produced by intestinal microflora such as Clostridium, Eubacter, Ruminococcus, Bacteroidetes and Digestive streptococcus dehydrogenases at the positions of C-3, C-7 and C-12. Secondary BAs DCA and shicholic acid (LCA) were then produced, as shown in Figure 1. Increased LEVELS of DCA have been associated with obesity and cancer in mice, further supporting the important role of BA conversion in the intestinal flora in host metabolism\[107].

Metabolome study found that in C57BL/6 mice, under the action of intestinal microflora on BA dehydroxylation and decoupling, the primary BA gradually decreased and the secondary BA gradually increased during the continuance process from small intestine to large intestine\[108]. Compared with specific pathogen-free (SPF) mice fed a normal rich-diet diet, the changes of BA components in feces of SPF mice fed with minimal chemical diet and germ free (GF) mice fed with normal diet were detected by mass spectrometry. Levels of liver-derived taurine conjugated primary BAs in the intestinal tract of the minimal pathogen-free mice were significantly decreased compared with those in the RICH-diet SPF mice, while they were increased in the RICH-diet GF mice\[109]. The results indicate that diet can directly control the hepatic synthesis of BAs, and the intestinal flora mainly controls the modification process of BAs in the intestine.

As a potential regulator of gut microbiota composition and host metabolism, microbial HSDH may open up new pathways for how the microbiota regulates signaling pathways in the host.

THE EFFECT INTESTINAL FLORA ON BAS VIA FXR

Study method of alcohol receptor in closely related to the metabolism of BA synthesis of highly expressed in the organs, such as the liver, small intestine, BA synthesis of organisms play a regulatory role of BA in the BA, goose DCA and LCA and DCA is liver alcohol receptor agonist, CYP7A1 is the
Figure 1 Synthesis and metabolism of bile acids. DCA: Deoxycholic acid; LCA: Lithocholic acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid.

promoter of BA synthesis[110]. In the liver, BA-activated FXR induces the expression of a small heterodimer partner (SHP) that binds to liver receptor homologous protein-1, thereby inhibiting Cyp7a1 gene expression. In addition to local effects in the liver, FXR is also activated by BAs in the distal ileum. FXR induces expression of FGF15 (FGF19 in humans) in the ileum. So farnesol receptor-FGF15/19 signaling pathway plays an important role in BA synthesis. In the study of lactobacillus rhamnosus GG (LGG) on BDL mice, it was found that compared with the sham operation group, in BDL mice, the content of DCA (deoxycholic acid is a strong agonist of FXR) and the concentration of T-αMCA and T-βMCA (MCA is an antagonist of FXR) were decreased, and the mRNA expression of CYP7A1 and FGF15 in BDL mice were increased[111]. The BA content and the size of total BA pool in liver were significantly increased, and the BA content and total BA pool size were significantly decreased after LGG treatment. At the same time, it was found that the mRNA expression level of FXR target gene SHP and FGF15 were significantly decreased in the ileum of BDL mice, while LGG could inhibit the decrease of FGF15 protein level[112].

This confirms that in BDL mice, LGG treatment-mediated reduction in BA synthesis is achieved through upregulation of the intestinal FXR-FGF15 signaling pathway[113]. Other studies confirm the BA levels of traditional breeding mice, and the germ-free mice raised in BA levels, may be due to the traditional breeding mice intestinal microbial flora make mice reduced levels of MCA, activation of FXR, make FGF15 higher expression, thus inhibiting the activity of CYP7A1 to inhibit the synthesis of BA[114].

It was found that after fecal microbiota transplantation (FMT) of sterile mice received FMT, the expression of FXR in intestinal epithelium was up-regulated, and FXR further induced the expression of FGF15, thereby inhibiting the activities of CYP7A1, CYP8B1 and other enzymes. Thus inhibiting the synthesis of BAs[115]. The expression of FGF15 in ileum was inhibited by antibiotics, and the expression level and activity of CYP7A1 in liver increased significantly, resulting in BA synthesis. Parabacteroides distasonis was used to treat obese mice. It was found that Parabacteroides distasonis can hydrolyse a variety of conjugated BAs, convert primary BAs into secondary BAs (LCA, UDCA, etc.), and produce a large amount of succinic acid[116]. LCA and other secondary CAs increased the level of FGF15 in serum and colon, and decreased the level of CYP7A1 in liver by activating the intestinal FXR signaling pathway. UDCA can repair intestinal wall integrity and succinic acid can improve host sugar metabolism disorder[117].

TGR5 can also be activated by intestinal flora to inhibit BA synthesis. TGR5 is a GPCR, and it has been found that compared with WT mice, the BA pool size of mice lacking the TGR5 gene in a high-fat diet decreased by 21% to 25%, and body fat accumulation increased, and body mass increased[118]. Intestinal bacteria can also induce the expression of cardiac transcription factor 4 in intestinal epithelial cells by stimulating them continuously, and inhibit the expression of ABST, resulting in reduced BA reabsorption in the terminal ileum[119].

In conclusion, intestinal flora not only participates in the processes of BA decoupling, dehydrogenation and dehydroxylation, but also negatively regulates BA synthesis through the FXR-FGF15/19 pathway.
INTESTINAL FLORA PARTICIPATES IN THE REGULATION OF NORMAL METABOLISM OF BAS

The metabolism of BAs in the body is mediated by intestinal flora. The whole metabolic process of BAs synthesized in liver cells is regulated by intestinal flora. The intestinal flora in patients with gallstones is unbalanced and the metabolism of BAs is also in disorder, which may be because the imbalance of intestinal flora in the body affects the hepatointestinal circulation of BAs in the body and causes the metabolic disorder of BAs and cholesterol. BSHs produced by bifidobacterium, Clostridium, Lactobacillus, Listeria, enterococcus, bacteroidetes and other bacteria in the intestinal tract of the body can reduce the production of cholesterol in serum[120]. BSHs is mainly involved in the uncoupling of conjugated BAs to form free BAs in the body. When intestinal flora in the body is unbalanced, BSH activity increases and free BA content increases, which then activates the NEGATIVE feedback regulation system of FXR-FGF15/19 BA, resulting in reduced BA synthesis content and over-saturated cholesterol[121]. If it is not dissolved effectively by BAs, it will remain as a deposit, slowly turning into a stone state. In addition, lactobacillus and bifidobacterium in intestinal flora also has the ability of removing cholesterol, mainly through the intake to the cholesterol assimilation or binding to the cell or and BA form coprecipitation[122], some intestinal bacteria also can produce cholesterol reductase, catalytic cholesterol into insoluble prostaglandins, and turn it into the feces. Other studies have confirmed that intestinal flora mediates normal metabolism of BAs. In the study of liver cancer, antibiotics can increase the Natural kilkR T cell (NKT) in mouse liver, and CXCL16, a chemokine expressed by hepatic sinusoid endothelial cells, can inhibit the growth of liver tumors by regulating hepatic NKT cells[123]. The primary BAs in liver can promote the expression of CXCL16, while the secondary BAs can inhibit the expression of CXCL16. When mice were treated with vancomycin (an antibiotic), vancomycin eliminated gram-positive bacteria (including those involved in primary BA conversion) from their intestines and induced the accumulation of hepatic NKT cells, thereby inhibiting the development of liver cancer[124]. At the same time, vancomycin-treated mice were fed with secondary BAs or clostridium bacteria that colonized and transformed primary BAs, and the accumulation of NKT cells in the liver was reduced and the anti-tumor effect was reduced[125].

Studies have shown that in patients with UC, the levels of secondary BAs (deoxycholic acid and stone CA) in the intestinal tract are reduced, and rumen bacteria and other bacteria that convert primary BAs into secondary BAs are also reduced[126]. Supplementation of secondary BAs with G-protein-coupled receptor for BAs (TGR5) improved intestinal inflammation in mice with colitis. In the enterohepatic circulation with normal enteral nutrition, BAs activate the enterofarnicol receptor (FXR), triggering the release of FGF19 into the portal vein circulation[127]. FGF19 regulates the synthesis of intrahepatic BAs through enteral nutrition. This signaling pathway is impaired in patients with total venous nutrition (TPN), and studies have shown a decrease in serum FGF19 levels in subjects receiving TPN. Due to intestinal dysfunction, the intestinal microbiota in TPN patients is severely altered. Changes in intestinal flora can affect patients' immune response and promote endotoxin secretion, thus negatively affecting liver function, suggesting that intestinal flora affects the related BA signaling pathway in the treatment of TPN[128].

BAS AFFECT THE COMPOSITION OF INTESTINAL FLORA

The regulation between intestinal flora and BA metabolism is bidirectional, intestinal flora can participate in the synthesis and normal metabolism of BA, and BA can in turn regulate the composition of intestinal flora. The effects of BAs on intestinal flora include damage to bacterial cell membrane, destruction of bacterial amino acids, nucleotides and carbohydrate metabolism, activation of innate immune genes in the small intestine to change the composition of intestinal flora and affect body metabolism[129]. The size and diversity of BA pools can affect the intestinal flora of the body. Studies on colorectal cancer (CRC) patients found higher concentrations of Clostridium 7α-dehydroxy in feces, which can promote the production of secondary BAs. High levels of clostridium 7α-dehydroxy increase the content of secondary BAs in the intestinal tract, leading to an imbalance of intestinal microflora that promotes the development of CRC[130]. High-fat diet can cause the imbalance of intestinal flora in mice. When adding ursodeoxycholic acid into the diet of high-fat diet mice, it was found that the intestinal flora in mice restored to the similar level as normal mice (for example, the contents of Faecalis and Achnmanniella increased, while the contents of Spironella and ruminococcus decreased)[131]. The effects of BAs on the composition of intestinal flora can also be mediated by FXR. When mice were fed a high-fat diet, the levels of T-βMCA in FXR deficient mice increased and the abundance of Firmicutes increased while the abundance of Bacteroidetes decreased compared with the control mice. It is possible that the FXR-mediated high-fat diet altered the BA pool in mice, leading to changes in gut microbiota[132].

BAs can also change the composition of intestinal flora by inhibiting the growth of intestinal bacteria, and the antimicrobial activity of non-conjugated BAs is stronger than conjugated BAs, and the sensitivity of gram-positive bacteria to BAs is stronger than gram-negative bacteria[133]. It was found that the synthesis of BA in rats with liver cirrhosis was lower than that in healthy rats, and the total
bacterial content in ileum and bacterial translocation rate were increased. After BA injection, the bacterial quantity in ileum of cirrhotic rats returned to healthy level and the bacterial translocation rate decreased. Obeccholic acid (OCA) is a BA derivative that activates FXR to inhibit endogenous BA synthesis. When healthy subjects were given doses of OCA, they found increased levels of gram-positive bacteria in their small intestines, such as Lactococcus lactis, Lactobacillus casei and Streptococcus thermophilus, while normal levels of BA inhibited the growth of these bacteria. When healthy mice were fed OCA, the BA content in their small intestine decreased, while the content of firmicite bacteria, mainly gram-positive bacteria, increased, suggesting that OCA can inhibit BA synthesis through activation of FXR and thus alter the intestinal microflora.

**INTESTINAL FLORA, BA METABOLISM AND IBD**

**Probiotics and prebiotics**
Exogenous supplementation of probiotics to regulate BAs to prevent or treat diseases has been demonstrated in metabolic diseases, such as hypercholesterolemia or obesity. Probiotics can relieve the clinical symptoms of IBD patients to different degrees. Probiotic mixture VSL#3 can significantly reduce cryptitis, and Clostridium butyricum MIYAIRI is also better than placebo in clinical efficacy, but its exact efficacy needs to be further studied. BA levels are reduced in IBD patients and experimental enteritis animals. However, the improvement of enteritis symptoms by exogenous Clostridium scindens supplementation has only been demonstrated in animals, and clinical studies on strains that regulate BSH or 7α dehydroxylase in a targeted way are lacking.

**Fecal microbiota transplantation**
FMT is a process in which feces from healthy people are transferred to patients, and it was first used to treat patients with recurrent Clostridium difficile infection. Recent studies have shown that FMT can significantly improve the composition of BAs in the gut of patients with C. difficile, increase the content of secondary BAs and prevent C. difficile colonization. Because of its apparent efficacy in treating recurrent C. difficile infection, it has been applied to other intestinal diseases, such as IBD, IBS, and pancreatitis. In IBD studies, FMT has shown significant efficacy in inducing remission of UC. A study of UC in children showed that the gut microbiota and metabolome of FMT responders were significantly more similar to those of healthy people.

**Antibiotics**
Studies have found that antibiotics on DCA induced inflammation of the intestinal protective, may significantly reduced intestinal flora diversity and broad-spectrum antibiotics, reduced intestinal tract has 7 alpha to hydroxylase enzyme bacteria, lead to waste source of primary BA dominate in the host, and the source of intestinal flora secondary BA decreased. However, the choice of antibiotics is also important. In a 12-wk clinical study, the nonabsorbable antibiotic rifaximin showed higher remission rates in patients with active CD. Given that different antibiotics have different effects on BA concentration and composition as well as IBD, antibiotic and patient selection will be important in evaluating antibiotic efficacy against IBD in the future.

**CONCLUSION**
Changes in lifestyle and diet have contributed to the increasing incidence of IBD. High fat diet not only changes the characteristics of intestinal flora, but also affects the metabolism of BAs in intestinal lumen. Therefore, studies focusing on BAs and gut microbiota have attracted much attention in digestive diseases. Characteristic changes in the gut microbiota in IBD patients affect the composition of the BA pool. Secondary BAs, as anti-inflammatory factors, may be non-invasive biomarkers in mucosal healing. The emergence of novel metabolomics has revealed the bacterial species that transform BAs and the mechanism of signaling pathways that regulate the development of IBD disease. The interaction between gut microbiota and BAs represents a promising new therapeutic approach for IBD. Some animal studies have shown the important value of the gut microbial-BA axis. However, there is no clear evidence of a similar effect in clinical practice, and further clinical studies are needed to verify it.

**FOOTNOTES**

Author contributions: Zheng L reviewed the literature, prepared the manuscript, performed to the writing, revising of the manuscript, contributed to design this work, and performed overall supervision, wrote and revised the paper, approved the final manuscript.
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Zheng L. Interplay between intestinal flora and bile acids in IBD


Role of visfatin in obesity-induced insulin resistance

Mona Mohamed Ibrahim Abdalla

Abstract
The growing worldwide burden of insulin resistance (IR) emphasizes the importance of early identification for improved management. Obesity, particularly visceral obesity, has been a key contributing factor in the development of IR. The obesity-associated chronic inflammatory state contributes to the development of obesity-related comorbidities, including IR. Adipocytokines, which are released by adipose tissue, have been investigated as possible indicators of IR. Visfatin was one of the adipocytokines that attracted attention due to its insulin-mimetic activity. It is released from a variety of sources, including visceral fat and macrophages, and it influences glucose metabolism and increases inflammation. The relationship between visfatin and IR in obesity is debatable. As a result, the purpose of this review was to better understand the role of visfatin in glucose homeostasis and to review the literature on the association between visfatin levels and IR, cardiovascular diseases, and renal diseases in obesity.

Key Words: Homeostatic model assessment for insulin resistance; Insulin resistance; Obesity; Visfatin; pre-B cell colony enhancing factor; Nicotinamide phosphoribosyltransferase enzyme; Diabetes; Adipocytokines

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Core Tip: Visfatin is an adipocytokine that is produced by visceral fat and other sources. It has been shown to influence glucose and lipid metabolism, as well as enhance the chronic inflammatory state linked to obesity. The findings on the relationship between visfatin and IR in obese patients are controversial. This review aims to better understand how visfatin contributes to the emergence of IR and to assess the possibility of utilizing visfatin levels as a biomarker for the early detection of IR and IR-related diseases, including cardiovascular and renal diseases.
INTRODUCTION

Accumulation of adipose tissue, particularly visceral adiposity, is the most common contributory factor in the development of insulin resistance (IR). Adipose tissue is an endocrine tissue that secretes many peptides that are adipokines including leptin, adiponectin, resistin and visfatin. Adipokines are reported to affect glucose and lipid metabolism as well as food intake[1]. Alterations in the levels of adipokines and genetic polymorphism such as adiponectin SNP +45 are related to the emergence of IR and its related comorbidities[2]. The serum and salivary levels of these adipokines were extensively assessed as biomarkers for early diagnosis of IR and its consequences for cardiovascular and renal diseases. Visfatin is an adipokine that has attracted the attention of researchers for its role in the pathogenesis of IR and the possibility of using its levels as a biomarker for IR detection[3-7].

VISFATIN’S JOURNEY FROM AN INSULIN-MIMETIC TO AN ENZYME KNOWN AS NICOTINAMIDE PHOSPHORIBOSYLTRANSFERASE ENZYME

Visfatin is a 52-kDa molecule, first described in 2004 by Fukuhara et al[7] as an insulin-mimetic adipokine. It was named visfatin because it was thought to be produced exclusively from visceral adipose tissue[6,7], in addition to other sources including subcutaneous adipose tissue[8], skeletal muscle[9], liver[10], immune cells[11], cardiomyocytes[12], brain cells[13] and renal glomeruli[14].

Visfatin’s insulin-like actions were demonstrated by a reduction in plasma glucose concentration 30 min after intravenous infusion of recombinant visfatin into c57BL/6j mice and insulin-resistant obese mice[7]; an outcome that the authors hypothesized was independent of insulin. The insulin-mimetic action of visfatin might be mediated by an increase in peripheral tissue glucose uptake, a decrease in both gluconeogenesis and glucose release, and stimulation of the insulin signaling cascade[7]. The glucose-lowering effect of visfatin attracted researchers’ curiosity about the prospect of visfatin becoming a novel diabetic medication. Extensive research has been conducted to investigate the relationship between visfatin levels, type 2 diabetes mellitus (T2DM), and IR. However, the findings are inconsistent, ranging from a positive correlation between plasma visfatin level and T2DM[15,16] to the existence of an inverse relationship between plasma visfatin level and type 1 diabetes[17].

Visfatin is structurally identical to the pre-B cell colony enhancing factor (PBEF)[18], a cytokine that was isolated in 1994 from a human lymphocyte and was known to accelerate the maturation of B cell precursors[19]. PBEF (visfatin) is regarded as a proinflammatory cytokine that has been shown to have multiple physiological functions related to cell metabolism[20,21], immunomodulation[20,22] and inflammation[23,24]. It has been found in various immune cells other than B cells and has been shown to inhibit apoptosis of macrophages[20]. Extracellular PBEF promotes proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-16, transforming growth factor (TGF)-β1, as well as the chemokine receptor CCR3. PBEF also boosts IL-6, TNF-α and IL-1 production in CD14+ monocytes, macrophages, and dendritic cells, improves T cell function, and is required for the development of B and T lymphocytes[20].

In 2001, Martin et al[24] discovered a significant homology between the mammalian PBEF gene and nicotinamide phosphoribosyltransferase (NAMPT); the enzyme that is required for production of NAD, and subsequently, is capable of modulating its intracellular levels[25-27]. NAD is a crucial coenzyme involved in a variety of cellular activities, including the generation of ATP[28] and the synthesis of regulatory proteins such as silent information regulator 2 (Sir2), which has seven types of deacetylase proteins known as sirtuins: SIRT1–SIRT7[29]. Sirtuins are involved in various metabolic functions[30-32]. SIRT1 deacetylases have been demonstrated to regulate many transcription factors required for cell survival, apoptosis and proliferation, including tumor suppressor p53[33-35], a protein forkhead box class O protein[36-38], and peroxisome proliferator-activated receptor-γ coactivator-1α[39,40]. SIRT1 also inhibits the signaling of nuclear factor-κB and suppresses inflammation[41-43]. Visfatin may thus alter metabolic processes involved in glucose and lipid metabolism via its NAMPT enzyme-like activity[3,44,45]. Figure 1 depicts the discovery of visfatin as a structurally similar hormone to the cytokine PBEF, whose gene is homologous to the NAMPT enzyme. As a result, PBEF and NAMPT are synonyms for visfatin.
REGULATION OF VISFATIN

Despite several research published since the discovery of visfatin, the regulation of visfatin (PBEF/NAMPT) appears to be complex. The majority of published research is inconsistent and provides conflicting results. Dexamethasone raised visfatin mRNA expression in 3T3-L1 adipocytes while growth hormone and TNF-α decreased it\[18,46,47\]. Glucose infusion elevated plasma visfatin levels in healthy participants during clamp testing\[48\]. However, another study published in 2011 by Bala et al\[49\] found that 75 g carbohydrate intake following a 2-h oral glucose tolerance test (OGTT) significantly reduced plasma visfatin levels primarily in overweight and female participants, who were more affected than normal healthy glucose-tolerant individuals. The significant inhibitory effect of insulin and glucagon-like peptide (GLP)-1 on visfatin production following oral glucose ingestion might explain the effects of intravenous versus oral glucose consumption\[49\]. Insulin and GLP-1 dramatically decreased visfatin secretion in vitro and in animal experiments. According to Bala et al\[49\], insulin infusion dramatically reduced visfatin release from 3T3-L1 adipocytes by nearly 50%, and GLP-1 lowered visfatin production from 3T3-L1 adipocytes by roughly 50%. According to the same study, insulin and GLP-1 under an oral glucose load, reduce visfatin levels among those who are healthy, insulin-sensitive and have normal glucose tolerance\[49\]. The authors concluded that the inhibitory effect of GLP-1 on visfatin production during OGTT may indicate the emergence of a novel incretin-like action described by a GLP-1/visfatin/axis; the significance of which remains unknown. In another investigation, researchers discovered that intravenous glucose, mannitol, and sex hormones (estradiol and testosterone) had no effect on visfatin release\[50\]. Figure 2 summarizes the control of visfatin secretion in normal, healthy and glucose-tolerant individuals.

PHYSIOLOGICAL VERSUS PATHOLOGICAL EFFECTS OF VISFATIN

Visfatin (NAMPT), with its two isoforms, the extracellular (eNAMPT) and intracellular (iNAMPT) forms, is crucial for NAD biosynthesis, with the higher activity of the extracellular form. NAD is required for various processes, including metabolic processes, glucose-stimulated insulin secretion, cell survival, cell cycle control, and apoptosis\[51\]. However, elevated levels of visfatin have been linked to increased levels of inflammatory markers such as IL-6, IL-8, C-reactive protein, and monocyte chemotactic protein-1\[52,53\], endothelial dysfunction\[54\], and increase in oxidative stress\[55-58\]. These findings point to the existence of an average physiological level of visfatin at which it is properly controlled and fulfils its physiological functions, as well as a threshold level at which its pathological consequences occur. Studies have shown that an increased level of visfatin is associated with IR and T2DM\[15,59\], metabolic syndrome (MetS)\[60\], polycystic ovary syndrome\[61\], and T2DM-associated complications such as cardiovascular\[62,63\], cerebrovascular\[64,65\], and renal\[66-68\] diseases. The significance of visfatin in the pathogenesis of IR and its associated consequences reflects the potential utility of visfatin as an early biomarker for IR in high-risk patients, especially obese adults, and as a biomarker for T2DM sequelae.

VISFATIN LEVEL AND IR

The impairment of glucose metabolism and the development of multiorgan IR following the adipose-tissue-specific deletion of visfatin\[69\] has demonstrated that visfatin is a major target in obesity, diabetes, and dyslipidemia\[70\]. Visfatin interacts with insulin receptors at locations other than insulin-
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Figure 2 Regulation of visfatin in normal healthy-glucose tolerant individuals. GLP-1: Glucagon-like peptide 1.

VISFATIN LEVEL AND CARDIOVASCULAR DISEASES, INCLUDING STROKE

Increased visfatin levels are associated with endothelial dysfunction, smooth muscle cell proliferation in the arterial wall, the formation of atherosclerotic plaques, and acute coronary syndrome[21, 54, 73]. The proliferative, proinflammatory and proangiogenic effects of visfatin are mediated via stimulation of PI3K, nuclear factor (NF)-B, signal transducer and activator of transcription (STAT), extracellular signal-regulated kinases (ERKs) and Toll-like receptor 4[54, 76, 77]. The visfatin-induced cell proliferation is dose-dependent, and it is mediated by increasing the release of vascular endothelial growth factor, fibroblast growth factor-2 (FGF-2), MCP-1, IL-6, and thromboxane A2[77-80]. The increased levels of visfatin in patients with atherosclerosis and acute coronary syndrome are caused by the expression of visfatin by the foam cells and smooth muscle cells of the atherosclerotic plaques, in addition to the increased expression of visfatin by the epicardial and perivascular adipose tissue, in which it is suggested to function in a paracrine fashion on the blood vessels[11, 81]. Studies have shown that visfatin stimulates the release of inducible nitric oxide synthase (iNOS), a proinflammatory enzyme associated with vascular complications in diabetic patients[82-84]. The changes in visfatin levels in ST-elevation myocardial infarction (STEMI) followed the same pattern as the troponin levels, suggesting the usefulness of visfatin as a biomarker for STEMI[85]. Visfatin levels are also associated with cardiac fibrosis, as visfatin induces the proliferation of fibroblasts and increases the release of type I and III collagen[86].

Stroke is one of the cardiovascular diseases escalating in both developed and developing countries[87]. Diabetes is an established risk factor for stroke because of the cerebrovascular changes induced by
Recent research has found an increase in visfatin levels in stroke patients, indicating that a high visfatin level may be a risk factor for strokes[89,90]. The association observed between high visfatin levels and cerebrovascular strokes can be explained by the endothelial dysfunction induced by high visfatin levels[54,90].

**VISFATIN LEVEL AND KIDNEY DISEASES**

The global prevalence of chronic kidney disease (CKD) among diabetic patients is steadily increasing [91]. An increased visfatin level is associated with the progression of CKD in diabetic and nondiabetic patients[92,93]; an observation that can be explained by endothelial dysfunction associated with high visfatin levels[93], IR[3], inflammation[53,74,94], oxidative stress[57,58], synthesis of profibrotic molecules in the mesangial cells, and increased expression of renin, angiotensinogen, and angiotensin receptors, as well as angiotensin II[95,96], thus increasing the activity of NADPH oxidase. This proinflammatory enzyme causes an increase in glomerular permeability[97]. A decrease in serum visfatin level was noted upon improving endothelial dysfunction following renal transplantation[98]. Overall, these data imply that visfatin has a role in mediating the CKD associated with T2DM. However, more studies are required to elucidate the relative contribution of visfatin compared with other inflammatory biomarkers, and to indicate the threshold level of visfatin at which those complications appear.

**ASSOCIATION BETWEEN VISFATIN LEVEL AND IR IN OBESITY**

To assess the evidence on the relationship between visfatin levels and IR in obesity, PubMed and Google Scholar were searched for articles published between 2015 and March 2022. The search was limited to English-language articles. The references in the discovered texts were further analyzed for other relevant articles. After the search, 15 papers were chosen for evaluation and they are discussed in ascending sequence.

The first research chosen was by Nourbakhsh et al[99] in 2015. The study was conducted among 73 children in Iran; 42 obese patients versus 31 controls. The study involved the measurement of serum visfatin and insulin using ELISA, and IR was assessed using the homeostatic model assessment for IR (HOMA-IR). Fasting plasma glucose (FPG) and lipid profile were also tested, and MetS was defined using the International Diabetes Federation (IDF) criteria. The study revealed that obese children had significantly greater serum visfatin than nonobese children without MetS or IR. In obese individuals, visfatin levels correlated with FPG, insulin, and HOMA-IR[99].

A positive correlation between serum visfatin levels and IR among obese children was further investigated by Salama et al[100] in 2015. The study was conducted among 33 Egyptian children (22 obese and 11 control). Anthropometric measurements such as body mass index (BMI), waist circumference (WC),
hip circumference (HC), and waist-to-hip ratio (WHR) were measured using standardized methods. The serum levels of insulin and visfatin were measured using ELISA. IR was calculated using HOMA-IR. The lipid profile and FPG were also measured. The study revealed significantly higher levels of serum visfatin in obese children (9.18 ± 3.04) compared with controls (4.33 ± 3.01). In obese children, Spearman’s correlation analysis revealed a positive correlation between serum visfatin with height, body weight, BMI, WC, HC and HOMA-IR[100].

The association between serum visfatin and IR was further evaluated in a study conducted in Turkey, Bursa, in 2015 by Gul et al[101]. The study evaluated the plasma levels of visfatin, insulin, and HOMA-IR in 18 obese versus 19 nonobese premenopausal women with polycystic ovary syndrome (PCOS). The study revealed a significantly higher HOMA-IR among obese patients with PCOS than nonobese PCOS patients and controls with no significant difference between the groups in serum visfatin levels. The study also revealed an absence of correlation between serum visfatin levels and HOMA-IR in the studied groups[101]. The difference between this result and the previous studies’ results can be explained by the difference in the demographics of the studied groups: Age, gender, and associated conditions.

In Poland, Liang and co-researchers evaluated the correlation between serum visfatin with glucose and lipid metabolism among pregnant women with gestational diabetes mellitus (GDM) in a prospective study conducted between 2012 and 2013. The BMI, FPG, serum visfatin, HOMA-IR and lipid profile were assessed. The study revealed significantly higher levels of serum visfatin, FPG, hemoglobin A1c, and HOMA-IR in women with GDM than the control group. Correlation analysis showed a negative correlation between serum visfatin with FBG and HOMA-IR among the control group. In contrast, a positive correlation is reported between serum visfatin levels with HOMA-IR, weight gain during pregnancy, and BMI at childbirth in women with GDM. The data of this study were first published in 2015[102]. The increase in serum visfatin levels associated with increased FPG in pregnant women may represent a regulatory response to control blood glucose levels; however, any further increase in visfatin levels may have contributed to IR and GDM.

The association between serum visfatin and GDM was further studied by Tsiotra et al[103] in Athens, Greece in 2018. Tsiotra et al[103] evaluated the expression of visfatin by the visceral and subcutaneous adipose tissues and placenta in 15 obese and nonobese women with GDM, compared to a control group that consisted of 23 obese and nonobese women with standard glucose tolerance. The study revealed a lower circulating visfatin level in obese women with GDM than in nonobese women with normal glucose tolerance. The study reported comparable visfatin mRNA expression in all tissues.

In Egypt in 2018, the association between serum visfatin with IR and proinflammatory cytokines in patients with T2DM was studied by Hetta and co-researchers[104]. The case-control study involved the assessment of anthropometric measurements, blood pressure, and serum levels of visfatin, CRP, IL-6, TNF-α and HOMA-IR in 80 people with diabetes in comparison to a control group of 40 healthy participants. The study reported significantly higher levels of visfatin, CRP, IL-6 and TNF-α in the diabetic group compared with the healthy control group. Serum visfatin was also shown to be positively correlated with BMI, WC, HOMA-IR and proinflammatory markers[104]. The study results provided evidence of the potential role of serum levels of visfatin in the pathogenesis of IR, an effect that the activation of the proinflammatory cytokines could mediate.

In addition to assessing the association between serum levels of visfatin and IR, the interest in the use of saliva as an alternative tool to serum for the measurement of biomarkers has been developed. The use of salivary levels of visfatin as a biomarker for T2DM was investigated in a study conducted by Srinivasan et al[105] in the USA and published in 2018. The study involved measuring levels of visfatin, TNF-α, IL-6, resistin and ghrelin in unstimulated fasting saliva samples collected from 40 subjects (20 diabetics and 20 healthy controls). It revealed significantly higher salivary levels of visfatin in patients with T2DM than in the control group, supporting the potential use of salivary visfatin as a biomarker for T2DM[105].

Compared with blood sampling, saliva sampling is simple, safe and noninvasive. The use of saliva as a diagnostic tool is evolving not only due to the rapid advances that are being made in the fields of nanotechnology and molecular diagnostics but also because saliva contains biomarkers that are ideal for early detection and monitoring of oral as well as systemic diseases including biomarkers for IR such as resistin, TNF-α, leptin, visfatin, adiponectin, IL-6 and CRP[106].

The association between serum levels of visfatin and GDM was further investigated in a study conducted by Souvannavong-Vilivong et al[107] in Bangkok, Thailand, and published in 2019. The study involved the measurement of serum visfatin among a sample of pregnant women with GDM class A1 (n = 37) compared with a control group with normal pregnancy (n = 37). The results reported significantly higher levels of serum visfatin and plasma glucose levels in women with GDM class A1. This was associated with a negative correlation between serum levels of visfatin with neonatal weight and length, thus supporting the use of serum visfatin level as a biomarker for GDB and prediction of pregnancy outcomes in patients with GDM[107].

The usefulness of serum visfatin as a biomarker for GDM was further investigated by Bawah et al[108] in Ghana and published in 2019. The study examined the alterations of serum levels of visfatin with GDM in a case-control study that included 140 women in their first trimester (70 with GDM and 70 without GDM). In addition to BMI measurement, serum levels of visfatin, resistin and leptin, and lipid
profile were assessed. The study reported significantly higher serum visfatin levels in patients with GDM compared with the controls. It also showed a significant positive correlation between serum levels of visfatin with age, total cholesterol, triglycerides, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and leptin, and a negative correlation with high-density lipoprotein cholesterol [108].

Additional evidence of the increased serum visfatin in women with GDM was provided in a study conducted by Manoharan et al.[109] in India and published in 2019. The study involved measuring cord plasma levels of visfatin, insulin, HOMA-IR, insulin sensitivity, and beta-cell function. The pregnancy outcomes such as birth weight were also assessed. Forty pregnant women were recruited for the study (n = 20 with GDM and n = 20 with normal pregnancy). The results revealed significantly higher cord plasma insulin, visfatin, and HOMA-IR levels in women with GDM than in the control group[109].

The association between serum visfatin and IR among obese children was evaluated in a study conducted by Yin et al.[110] in China and published in 2019. A total of 244 children (160 obese and 84 lean) were recruited. The study involved assessing serum levels of visfatin, high-sensitivity CRP (hs-CRP), TNF-α, IL-6, angiotensin-2, vascular cellular adhesion molecule (VCAM)-1, E-selectin levels, anthropometric measurements, insulin, glucose, and lipid profile. The study reported significantly higher levels of visfatin in obese children compared with controls. There was a positive correlation between serum visfatin with each of the following: BMI, WC, hs-CRP, TNF-α, IL-6, angiotensin-2, VCAM-1, and E-selectin levels, thus supporting the role of elevated serum visfatin in prompting inflammation and IR in obese children[110].

A more recent study on the association between serum visfatin and IR in patients with Alzheimer’s disease (AD) was conducted by Sharifipour et al.[111] in Iran and published in 2020. The study involved the measurement of serum visfatin, blood glucose levels, HOMA-IR, and BMI among 60 subjects divided into two groups: 34 subjects with AD and 26 normal subjects. The study reported a significant increase in HOMA-IR and decrease in serum visfatin levels in patients with AD compared with the control group, with no significant change in BMI or serum insulin levels among the two groups. The results reported a negative correlation between serum visfatin and HOMA-IR, providing evidence of systemic IR and lower serum visfatin in nonobese, non-overweight AD patients[111].

The effect of obesity on serum levels of visfatin in patients with PCOS was further evaluated by Abdul-Maksoud et al.[112] in a recent study conducted in Egypt and published in 2020. The study involved measuring serum levels of visfatin, insulin and HOMA-IR in 210 women (70 healthy women: 35 obese, and 35 nonobese + 140 with PCOS: 70 nonobese and 70 obese). There was upregulation of visfatin expression in PCOS, thus supporting the use of serum visfatin as a biomarker for PCOS[112].

A recent cross-sectional study was published in 2020 on the correlation between serum visfatin levels and IR in obese women. The study was conducted by Alnowihi et al.[113] in Saudi Arabia, where 83 women were recruited for the study between January 2014 and 2016, divided into three groups according to their BMI (35 obese, 15 overweight and 33 lean). The study involved the evaluation of anthropometric measurements, serum levels of visfatin, insulin, lipid profile, and HOMA-IR. The study reported significantly higher levels of visfatin, insulin, IR, and glucose in the obese group when compared with the lean and overweight groups. The study also reported a positive correlation between serum visfatin levels and BMI, WC, HC, insulin, and HOMA-IR[113].

A study on the use of salivary visfatin as a biomarker for diabetes was published in 2021. This was a case–control study conducted by Eroglu Içli and Bildaci in Turkey. It involved the collection of saliva samples from 91 pregnant women between 24 and 28 weeks’ gestation. Salivary levels of visfatin were measured using ELISA. Classification of the patients was based on their OGTT results into two groups: the GDM group, which consisted of 18 patients, and a control group comprising 73 patients with normal OGTT. The study reported a positive correlation between salivary visfatin levels and 1-h glucose levels in the GDM group, a cut-off value of 13.5 ng/mL for the expected levels of salivary visfatin, a sensitivity of 72% and a specificity of 63% of saliva visfatin as a screening test for GDM[114].

CONCLUSION

Visfatin is important in glucose homeostasis because of its insulin-like actions mediated by NAD biosynthesis. Increased visfatin levels in obesity may indicate a regulatory response to keep blood glucose levels stable. However, exceeding a threshold level appears to be associated with an increase in inflammation, which may contribute to the development of IR, T2DM, and their associated complications, such as cardiovascular and renal diseases. The available evidence supports the potential use of visfatin serum levels as a biomarker for T2DM, including GDM. Salivary visfatin levels appear to be a potential biomarker for IR. However, the number of studies assessing visfatin in saliva in relation to diabetes and related complications is still limited.
FOOTNOTES

Author contributions: Abdalla MMI collected the data and wrote the paper.

Conflict-of-interest statement: The author declares no conflict of interest for this article.

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S-Editor: Chen YL
L-Editor: Kerr C
P-Editor: Chen YL

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Hyperthermic intraperitoneal chemotherapy and colorectal cancer: From physiology to surgery

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Scoring:

- Specialty type: Surgery
- Provenance and peer review: Unsolicited article; Externally peer reviewed.
- Peer-review model: Single blind
- Peer-review report’s scientific quality classification
  - Grade A (Excellent): 0
  - Grade B (Very good): B
  - Grade C (Good): C
  - Grade D (Fair): D
  - Grade E (Poor): 0
- P-Reviewer: Ding L, China; Farouk S, Egypt; Serban ED, Romania
- Received: January 13, 2022
- Peer-review started: January 13, 2022
- First decision: June 15, 2022
- Revised: June 23, 2022
- Accepted: August 13, 2022
- Article in press: August 13, 2022
- Published online: October 26, 2022

Abstract

The pursuit of this paper is to collect principal reviews and systematic reviews about hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) used in colorectal cancer (CRC). We focus on principal biological aspects of CRC, hyperthermia effects, and surgical procedures. We searched PubMed/MEDLINE for the principal reviews and systematic reviews published from 2010 to 2021 regarding the bimodal treatment (CRS + HIPEC) against local and advanced CRC. In the literature, from several studies, it seems that the efficacy of bimodal treatment with an accurate CRS can extend overall survival. Despite these studies, there are not still any straight guidelines more detailed and scheduled about the use of combined treatment in patients with CRC. Even if the concept is still not very clear and shared, after a careful evaluation of the published data, and after some technical and pathophysiological descriptions, we concluded that it is possible to improve the overall survival and quality of life and
to reduce the tumor relapse in patients affected by locally advanced (pT4) CRC with peritoneal metastases.

**Key Words:** Hyperthermic intraperitoneal chemotherapy; Colorectal cancer; Peritoneum; Cytoreductive surgery

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**Core Tip:** The purpose of this review is to summarize the most relevant evidence on the use of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer and to specify the main properties of HIPEC and its application.

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**URL:** https://www.wjgnet.com/2307-8960/full/v10/i30/10852.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i30.10852

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**INTRODUCTION**

The synergistic anti-tumor effects of heat and intraperitoneal chemotherapy, have been known to be effective since decades and is now well known as hyperthermic intraperitoneal chemotherapy (HIPEC); this strategy is based on both hyperthermia and high intraperitoneal concentration of chemotherapy (IP).

Originally, hyperthermia was introduced by Spratt et al[1] who demonstrated the benefit of heated IP perfusion in canine models; furthermore, the first prototype IP therapy filtration system was designed and tested by Palta et al[2].

HIPEC is based on the physiological effect of the 'peritoneal-plasma barrier': While peritoneal surface malignancies (PSM) cannot be effectively reached by intravenous chemotherapy[3], these tumors can benefit from intraperitoneal administration of high-dose cytotoxic drugs in direct contact with tumor cells, combining the effect of hyperthermia and minimizing the systemic toxic effects of drug reabsorption.

The first use of HIPEC was described in 1979 for the treatment of recurrent peritoneal pseudomyxoma (PMP) after previous cytoreductive surgery (CRS)[4]; subsequently, Sugarbaker et al[5,6] compared the use of 5-fluorouracil IP with systemic therapy for colorectal cancer (CRC) and appendiceal cancer to show the benefits of IP therapy[7-10]. During the years, HIPEC became a new option of care for different tumors with peritoneal metastases (PMs): CRC, appendiceal cancer, ovarian cancer (OC), gastric cancer (GC), and peritoneal mesothelioma[11,12].

Later, HIPEC was also applied in the treatment of PSM from GC and OC: In 1988, Fujimoto et al[9] reported the effects of HIPEC in patients with PMs from GC and in 1996, Yonemura et al[13] showed a 5-year survival of 11% in a cohort of 83 patients who underwent CRS and HIPEC for GC; moreover, in 1989, HIPEC was used for peritoneal lesions from OC[14].

Since the 1990s, CRS combined with HIPEC has been a treatment option for PSM; today, CRS and HIPEC represent the standard of care for PMP and peritoneal mesothelioma[15]. In particular, regarding the combination of CRS plus HIPEC in CRC, there were several clinical trials about this specific combined treatment; nevertheless, this option of treatment remains a debated topic. Ceelen[16] first described the efficacy of CRS + HIPEC in peritoneal carcinomatosis arising from CRC. Later, numerous studies have been conducted until nowadays, reaching a better use of the bimodal treatment. For instance, Birgisson et al[17] studied the use of the peritoneal cancer index (PCI) as a prognostic factor in patients affected by PMs from CRC and treated with CRS + HIPEC.

Rosa et al[18] showed the clinical outcomes in 67 patients affected by CRC, focusing on the complete cytoreduction of PMs and calculating the median overall and disease-free survival.

Moreover, Elias et al[19] showed the results of HIPEC plus second look surgery in selected patients, increasing their 5-year overall survival to 90%.

However, despite several studies on this topic, there is still no consensus on the indication of CRS combined with HIPEC in CRC.

The purpose of this review is to summarize the most relevant evidence on the use of HIPEC in CRC and to specify the main properties of HIPEC and its application.
Ammerata G et al. HIPEC and CRC

MATERIAL AND METHODS
In this narrative review, we searched PubMed, a free online biomedical database developed by the National Center for Biotechnology Information at the National Library of Medicine, using the following keywords: “Colorectal Tumor” and “HIPEC”, “Colorectal Cancer” and “HIPEC”, “HIPEC”, “Hyperthermic Intra-peritoneal Chemotherapy”, “Hyperthermia and HSPs”, “Hyperthermia and Tumor”, and “Hyperthermia and Cancer” (Figure 1). We collected the reviews and systematic reviews published from 2010 to 2021 and analyzed the principal clinical studies about the management of PMs arising from CRC (Table 1; Figure 2). This current work focuses the attention on HIPEC, from its first uses to now, looking at principal uses in different tumors like gastric, ovarian, and colorectal. Moreover, the review explains in detail the biologic effects of HIPEC on tumoral cells and the latest clinical trials regarding locally advanced colorectal cancer by describing CRS technique step by step.

HIPEC AND CRC
CRC is a big killer, representing the third most commonly diagnosed malignancy worldwide; it represents the third most common cancer in men (746000 cases; 10 % of the total) and the second in women (614000 cases; 9.2 % of the total)[20]. Surgery represents the elective therapy for resectable CRC (to gain R0 resection); instead, chemotherapy, radiotherapy, and the combination of both have indications for neoadjuvant and adjuvant purposes[21].

CRC most frequently metastasizes to the liver and peritoneum. PMs from CRC are tumoral deposits on the peritoneal surface, originating from the primitive cancer. PMs originated from CRC can cause several and severe complications like bowel and ureteral obstruction, and malignant ascites[22-24].

There are a variety of chemohyperthermia protocols in the literature, but in general they consist of intraperitoneal infusion of different drugs at a particular range of temperature and pression for a definite time at the end of surgery to eradicate the residual microscopic tumor tissue[25,26].

Today, HIPEC after CRS is still considered an investigational treatment for CRC-originated PMs, but its role is not yet defined.

HIPEC AND PHYSIOLOGICAL MECHANISM
HIPEC for PMs from CRC has some technical specific parameters like temperature, drugs, and pressure.

Mitomycin-C (MMC) is administered as monotherapy in a large majority of protocols[11,27-29] or in combination with cisplatin[30-34]. The second most commonly used drug in monotherapy is oxaliplatin or also in combination with irinotecan. MMC gives higher efficacy as a single agent administered at a dose of 35 mg/m²[35-40], although the dose of MMC can be modified from 10 to 40 mg/m²[41].

Establishing the drug dose is the cornerstone for even distribution of chemotherapy; some institutions use an approach called body surface area-based and others use a concentration-based approach. These approaches have some limitations such as gender and the presence of malignant ascites, but both attempt to find a conventional dose[42].

High temperature is a key issue; there are three temperature ranges that classify the type of hyperthermia: Fever hyperthermia (39-40 °C), mild hyperthermia (heat shock temperature 41-43 °C), and thermal ablation (cytotoxic temperature, > 43 °C).

Focusing attention on biological aspects, it is necessary to discuss about hyperthermia effects on tumor tissue. Hyperthermia has an important role in different paths like apoptosis regulation, neoangiogenesis, and immune status of the tumor. For example, hyperthermia induces DNA damage response by activating single strand break, double strand break, histone H3AX with phosphorylated C-terminal serine (γ-H3AX) site formation, and ataxia-telangiectasia mutated protein phosphorylation, and by decreasing DNA replication and repair.

Indirectly, hyperthermia activates DNA damage response and induces tumor suppressor alternative reading frame by starting reactive oxygen species (ROS) production, cell cycle arrest, cell cycle checkpoint arrest, and cell death; in addition, hyperthermia decelerates DNA replication.

Hyperthermia can also damage cancer stem cells exceeding conventional therapeutic regimens, so it is used in combination with chemotherapy or radiation to result in non-reversible damage to tumor cellular DNA[43].

Specifically, fever range hyperthermia can alter cell membrane fluidity and stability, changing cell shape and affecting intracellular sodium-calcium levels[44]; moreover, it recruits heat shock proteins (HSPs) and endoplasmic reticulum (ER) stress (type II) at the same time[45].

ER stress and ROS (type I) activate immunogenic cell death (ICD) and promote, through specific signals “eat me” and “enabler”, the recruitment of immune cells. Definitively, hyperthermia can be considered an inducer of ICD and a powerful change of tumor microenvironment (TME)[46-48].
Table 1 List of clinical studies with phases, correlated institutions and principal investigators (Clinicaltrials.gov or clinicaltrialsregister.eu; the list below describes the brief titles of the ended clinical trials)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Institution/Group</th>
<th>Country</th>
<th>Author/ClinicalTrials.gov ID</th>
<th>Year beginning</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Fudan University</td>
<td>China</td>
<td>Guoxiang Cai/NCT02965248</td>
<td>November 2016</td>
</tr>
<tr>
<td>III</td>
<td>Zhejiang University</td>
<td>China</td>
<td>Ding Ke-Feng/NCT02179489</td>
<td>October 2014</td>
</tr>
<tr>
<td>II</td>
<td>Wuhan University</td>
<td>China</td>
<td>Bin Xiong/NCT02830139¹</td>
<td>July 2016</td>
</tr>
<tr>
<td>II/III</td>
<td>Catharina, Ziekenhuis, Eindhoven</td>
<td>Netherlands</td>
<td>Koen Rovers/NCT02758951</td>
<td>June 2017</td>
</tr>
<tr>
<td>III</td>
<td>Academisch Medisch Centrum-Universiteit van Amsterdam</td>
<td>Netherlands</td>
<td>P.J. Tanis/NCT02231086</td>
<td>March 2015</td>
</tr>
<tr>
<td>III</td>
<td>Universitair Medisch Centrum Groningen</td>
<td>Netherlands</td>
<td>NACHO trial /2010-020787-37</td>
<td>January 2013</td>
</tr>
<tr>
<td>II</td>
<td>University Hospital, Ghent</td>
<td>Belgium</td>
<td>Wim P Ceelen/NCT02399410</td>
<td>December 2015</td>
</tr>
<tr>
<td>II</td>
<td>University Hospital, Ghent</td>
<td>Belgium</td>
<td>Trial Bureau/2012-000701-77²</td>
<td>May 2012</td>
</tr>
<tr>
<td>II</td>
<td>University Hospital, Ghent</td>
<td>Belgium</td>
<td>Bimeta Clinics/2014-000882-34¹</td>
<td>June 2014</td>
</tr>
<tr>
<td>III</td>
<td>Gustav Roussy, Cancer Campus, Grand Paris</td>
<td>France</td>
<td>Diane GOERE/NCT01226394</td>
<td>April 2010</td>
</tr>
<tr>
<td>I/II</td>
<td>Hospices Civils de Lyon</td>
<td>France</td>
<td>Benoit You/NCT02866905⁴</td>
<td>May 2017</td>
</tr>
<tr>
<td>III</td>
<td>UNICANCER</td>
<td>France/Spain</td>
<td>BEATA JUZYNA/2006-000175-20</td>
<td>December 2012</td>
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<tr>
<td>III</td>
<td>University of Roma La Sapienza</td>
<td>Italy</td>
<td>P.Sammartino/NCT02874536</td>
<td>March 2019</td>
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<tr>
<td>III</td>
<td>Maimonides Biomedical Research Institute of Cordoba</td>
<td>Spain</td>
<td>Alvaro Arjona Sanchez /NCT02614534</td>
<td>November 2015</td>
</tr>
</tbody>
</table>

¹Radical colorectal resection and hyperthermic intraperitoneal chemotherapy in locally advanced colorectal cancer.
²Cytoreduction followed by normothermic vs hyperthermic intraperitoneal intraoperative chemoperfusion: A phase II study in peritoneal carcinomatosis.
³Catheter based adjuvant intraperitoneal chemotherapy for carcinomatosis.
⁴IPOXA, phase I/II dose escalation trial aiming to evaluate the safety of intraperitoneal oxaliplatin in association with systemic FOLFIRI bevacizumab chemotherapy in patients with peritoneal carcinosis of colorectal origin and uncertain resectability.

A range of heat shock temperature recruits different molecules like L-selectin, P-selectin, and intracellular cell adhesion molecule-1 in the vessel wall, and causes the production of pro-inflammatory cytokines and chemokines [interleukin (IL)-1β, IL-6, IL-8, IL-10, and C-C class chemokines 22][49-52]. These cytokines “storm” facilitates the infiltration of lymphocytes in the TME and triggers an immune cascade against solid tumor.

Many HSPs are expressed on the surface of different types of solid and haematological tumors, a high concentration of mHSPs is associated with tumor progression and resistance to anti-tumor therapies, but under stress (for example anoxia and hyperthermia), HSPs can modify their relationship with tumor. Hyperthermia, in this sense, becomes an inducer of HSPs; it rapidly regulates different heat shock factors in tumor cells and activates HSPs, and in particular leads the translocation of HSPs to the

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Figure 1 Flowchart of all studies found in PubMed search.
nucleus and their synthesis by an autocrine loop[53].

HSPs constitute a large family of proteins, acting as molecular chaperones; they reside in three intracellular compartments such as the cytosol, nucleus, and plasma membrane or in the extracellular space. For example, HSP70, localized on the plasma membrane of tumor cells in CRC[54], facilitates cross-presentation of antigenic peptides via major histocompatibility complex class I molecules and determines the consecutive induction of a CD8+ T cell-mediated immune response. CD8+ T cell differentiation and their cytotoxicity against pathogens are both temperature sensitive, in fact hyperthermia can promote antigen-specific naive CD8+ T cell differentiation and increase cytotoxic potential of T cells and memory stem T cell generation. Moreover, chaperones of HSP70 family can activate the proliferation of natural killer cells even without immunogenic peptides[55].

There is no univocal standard on the temperature to be used during HIPEC: A range from 38.5 °C to 44 °C is reported in the abdomen with an average value that is usually considered close to 42 °C. However, it is essential that the temperature does not exceed thermal ablation to avoid systemic toxic effects.

**CRS: STEP BY STEP**

CRS has a curative intent and consists of a complex series of steps, aiming to achieve a radical visceral and parietal peritonectomy to eliminate the macroscopic visible tumor nodules, leaving a most microscopic residual tumor tissue. It is important to consider cancer histopathology, radiological imaging, and PCI to plan the best surgery[56-58].

The patient is placed in the lithotomic position, supine with legs extended and laid on St. Mark’s holders and arms beneath the torso.

The tools used in CRS are based on electrosurgery and electro-evaporation, specifically it is usual to use ball-tipped electrosurgical handpiece to minimize blood lost.

The median incision is the from the xiphi-sternal junction to the pubis; at this point, if tumor nodules are visible, the surgeon can start with parietal peritonectomy or rather separating parietal peritoneum from the inferior surface of the anterior abdominal wall. The dissection of visceral peritoneum starts generally from bottom to top.

Omentectomy is often necessary and sometimes mandatory in order to better explore the peritoneal cavity.

CRS continues with dissection of the left hypochondrium: We start by dissecting the peritoneum behind the rectus muscle to the left diaphragmatic dome and mobilizing the left colic flexure, thus exposing the diaphragm with its vessels and exposing the spleen, which can be removed, if it is infiltrated by neoplastic tissue.

The approach to the right side is mirrored by the contralateral; it is essential to totally mobilize the liver from its peritoneal attachment, particularly the right and left triangular ligament, the falciform ligament, and the teres hepatic ligament; sometimes, the Glisson’s capsule must be fulgurated if cancerous deposits are present.

As for the small intestine and its mesentery, it is important to free them and completely inspect them because if they are involved by the tumor, the surgeon will remove the affected part. The colon is another elective situs of peritoneal carcinomatosis, particularly the fusion layer between the parietal and visceral peritoneum of the right colon. Sometimes, it is necessary to proceed to partial or total...
colectomy.

The pelvic peritonectomy is another important step in CRS. Two anatomic structures represent the polar star in this part of pelvic dissection: Posteriorly the ureters and anteriorly the muscular portion of bladder. The right and left ureters are identified and preserved, in the woman the ovarian vessels are ligated at the lower pole of the kidney, otherwise in men, the testicular vessels are avoided from the surgical field. After these procedures, it is usual to execute in woman hysterectomy with colic resection and in men an anterior resection of the rectum. If there are some visceral resection, the surgeon will restore intestinal functions with anastomoses or stomas[59].

PROTOCOLS OF HIPEC FOR CRC

Nowadays there are two attitudes to execute HIPEC: In closed or in open abdominal cavity (also defined coliseum technique)[60,61].

Close technique implies the insertion of two inflow drains under the left and right diaphragmatic cupola and an outflow drain in the pouch of Douglas. Temperature probes are also inserted within the abdominal cavity (behind the liver pedicle and near the first jejunal loop). Other temperature probes are set up outside the abdominal cavity on the inflow and outflow drains and inside the bladder within a Foley catheter. As a final step, there is a closure of laparotomy incision and the inflow and outflow drains are connected to a closed sterile circuit. Also, in this case there is no specific evidence that suggests which technique is better than other, and probably closed technique reduces risks of exposure of drugs to the personnel[62].

The intraperitoneal chemotherapy after cytoreductive surgery trial compared the benefit of HIPEC with early, postoperative, normothermic IP chemotherapy (EPIC) in patients affected by colorectal cancer and undergoing optimal CRS.

Enrolment began in March 2013 with completion date of March 2018 at Memorial Sloan Kettering Cancer Center and was given MMC in HIPEC and fluoruridine in IPEC.

The outcome measure of the study is disease-free survival, within 3 years, though secondary measures were used to monitor surgical and chemotherapy–related toxicities up to 60 d postoperatively [63].

The PRODIGE7 study, a randomized, multicentre, phase III trial at the Institut di Cancer Val d’Aurelle (Montpellier, France), started to evaluate the benefit of HIPEC to complete CRS.

The recruitment of 270 patients with CRC and limited peritoneal dissemination was completed in 2013. Patients undergoing CRS were randomized withinoperatively to receive HIPEC or saline lavage only. In this study, oxaliplatin (460 mg/m²) in 2 L/m² of dextrose 5% over 30 min at a temperature of 42 °C was used. One hour before the HIPEC, 20 mg/m² of leucovarin and 400 mg/m² of 5-fluorouracil were given intravenously in the HIPEC arm[64].

The CAIRO-6 study, similarly to the previous study, focused on the role of perioperative systemic therapy on survival in patients undergoing CRS and HIPEC for CRC. This phase II/III study randomized patients to undergo neoadjuvant therapy intravenously with 5-fluorouracil, leucovarin, and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX) with bevacizumab followed by CRS and HIPEC, then adjuvant systemic therapy with FOLFOX and CAPOX[65].

The control arm is represented by CRS and HIPEC only. Both the studies confirm the importance of full CRS in patients that received systemic chemotherapy.

The ProphiloCHIP-PRODIGE 15 (France) study started the recruitment of 150 patients in 2010. This is a multicentre, randomized, phase III study to demonstrate the role of HIPEC as a prophylactic measure in initial treatment and in the adjuvant setting in patients with high risk of developing colorectal peritoneal metastases[66].

The COLOPEC (Netherlands) study, enrolled 204 patients, aged from 18 to 75 years, between 2014 and 2017. The patients had CRC at T4N0-M0 stage, and the treatment consisted of intravenous injection of fluorouracil (400 mg/m²) and leucovarin (20 mg/m²), then, during the surgery, the use of oxaliplatin (460 mg/m²) for 30 min. COLOPEC demonstrated an absolute risk reduction of 15% in PMs[67].

CONCLUSION

In CRCs, PMs are underestimated and they are correlated with a poor prognosis. Despite the fact that the secondary localizations of tumor are visible in the chest or in the liver, during the execution of full-body computed tomography for tumor staging, PMs cannot be identified easily. Moreover, a failed treatment of PMs determines a median survival of 5 mo; on the contrary, a palliative systematic therapy increases the median survival from 5 to 15 mo. Unfortunately, the survival remains worse in respect to non-peritoneal metastases.

Furthermore, CRC affects in higher percentage the young ages, so it becomes necessary to discuss about a protocol of treatment to prevent the principal complications (malignant ascites and obstruction) of colorectal tumors, eliminate macroscopic malignancies on peritoneal surface, and increase the median
survival.

In light of the main studies collected regarding CRS plus HIPEC in CRC, it is still no very clear and shared the indications and technique used in PMs arising from CRC.

However, looking at the clinical trials and physiologic principles, CRS (open or laparoscopic) plus HIPEC can be a valid treatment especially in young patients (< 50 years) affected by locally advanced (pT4) CRC with PMs. In this way, it is possible to improve the overall survival and quality of life and reduce the tumor relapse.

**ACKNOWLEDGEMENTS**

This work was supported by Dr. Thom Douglas for the English language review.

**FOOTNOTES**

**Author contributions:** Ammerata G and Ammendola M contributed to the study design; Filippo R, Memeo R, Laface C, and Solaini L contributed to the data collection and statistical analysis; Cavaliere D and Navarra G contributed to drafting and revising the manuscript critically; Ranieri G, Curro G, and Ammendola M contributed to the final approval of the version submitted.

**Conflict-of-interest statement:** The authors have nothing to disclose.

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S-Editor: Zhang H
L-Editor: Wang TQ
P-Editor: Zhang H

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New-onset diabetes secondary to acute pancreatitis: An update

Xian-Qiang Yu, Qian Zhu

Abstract

Diabetes is a condition of persistent hyperglycemia caused by the endocrine disorder of the pancreas. Therefore, all pancreatic diseases have the risk of diabetes. In particular, increasing attention has been paid recently to new-onset diabetes secondary to acute pancreatitis (AP). The complications of secondary diabetes have caused a lot of trouble for patients and have garnered increasing attention. At present, the pathophysiological mechanism of new-onset diabetes caused by AP is not clear. This review summarizes the current understanding of new-onset diabetes secondary to AP.

Key Words: Acute pancreatitis; New-onset diabetes; β-cell; Hyperglycemia

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Core Tip: Increasing attention has been paid recently to new-onset diabetes secondary to acute pancreatitis (AP). The complications of secondary diabetes have caused a lot of trouble to patients and have garnered increasing attention. This review summarizes the current understanding of new-onset diabetes secondary to AP.

Citation: Yu XQ, Zhu Q. New-onset diabetes secondary to acute pancreatitis: An update. World J Clin Cases 2022; 10(30): 10862-10866

URL: https://www.wjgnet.com/2307-8960/full/v10/i30/10862.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.10862
INTRODUCTION

At present, new-onset diabetes secondary to acute pancreatitis (AP) is considered to be the most common type of pancreatogenic diabetes [1-3]. Structural or functional disorders of blood glucose caused by pancreatogenic factors are the main pathophysiological mechanisms, including AP and chronic pancreatitis, pancreatic trauma, and surgery. The pancreas is the largest exocrine gland of the digestive tract. Although the volume of pancreatic islet B cells is very limited, the insulin secreted by the pancreas plays a key role in maintaining the stability of endocrine blood glucose [4]. In short, any cause of pancreatic damage can lead to diabetes. In recent years, reports on pancreatogenic diabetes have garnered increasing attention.

AP is a common acute abdomen and the number one cause of acute digestive system hospitalizations in the United States [5,6]. Most patients have mild AP and can recover and be discharged after 3 to 5 d of conservative treatment. However, about 20% of patients still develop severe AP, which leads to systemic inflammatory response syndrome and multiple organ dysfunction syndromes, leading to poor prognosis [7,8]. The risk factors for triggering pancreatic endocrine insufficiency in AP include age (>45 years), obesity, hypertriglyceridemia, family history of diabetes, and recurrent pancreatitis [9]. But these factors do not affect the severity of endocrine function. In addition, some studies have shown that the severity of AP is not associated with the incidence of new-onset diabetes [10-13]. However, Chinese scholars suggest that pancreatic necrosis (PN) and persistent organ failure are risk factors for a high incidence of new-onset diabetes secondary to AP [14]. These results suggested that further studies should be conducted to determine the impact of PN on secondary diabetes. There have been few reports on the incidence of new-onset diabetes after pancreatitis, with one meta-analysis showing a prevalence of 23% [15]. Therefore, the current clinical understanding of the characteristics of new-onset diabetes secondary to AP is not exact.

DIAGNOSTIC CRITERIA AND DEFINITIONS

The diagnostic criteria for pancreatogenic diabetes include: no previous history of diabetes, definite abnormalities of glucose metabolism caused by benign and malignant diseases of the pancreas, and the criteria for diabetes diagnosis. Diabetes including impaired glucose tolerance was defined according to the 1999 World Health Organization standard. The American Diabetes Association classifies it as type 3 diabetes [2]. Its main causes include AP, pancreatic cancer, and cystic fibrosis [16,17]. Among them, new-onset diabetes secondary to AP is caused by AP, which occurs based on impaired pancreatic exocrine function. In addition to the similar clinical manifestations, complications, and prognosis of type 2 diabetes, glucose fragility is an obvious clinical characteristic of this disease. Multiple episodes of hypoglycemia can further deteriorate pancreatic islet function and greatly increase the risk of pancreatic cancer [18-21]. Therefore, standardized and individualized treatment and management of pancreatic diabetes are more necessary.

Diabetes is diagnosed by typical diabetes symptoms with any of the following parameters (Tables 1 and 2).

PATHOPHYSIOLOGY OF NEW-ONSET DIABETES SECONDARY TO AP

The main functions of the pancreas include exocrine and endocrine parts. The exocrine part consists of the acinar and duct, secreting pancreatic juice containing a large amount of bicarbonate and a variety of digestive enzymes, involved in the digestion of food. The endocrine part of the pancreas, namely the islet, is composed of A, B, D, and PP cells, which can secrete insulin, glucagon, somatostatin, and pancreatic polypeptide, respectively. The pancreas as a whole cannot be separated from its exocrine and endocrine functions. The exocrine and endocrine secretory parts of the pancreas interact and influence each other in pancreatic physiology and disease. AP is often accompanied by elevated blood glucose [22], which may be related to the following factors: (1) Under stress, insulin can reverse regulate the secretion of the hormone, while insulin secretion is relatively reduced, which leads to the enhancement of lipolysis and proteolysis, and the increase of liver glucose production; (2) Acute inflammation of the pancreas, pancreatic tissue swelling, ischemia, and microcirculation disorders affect the secretion and excretion of insulin, when a large number of pancreatic cells undergo necrosis in a short period time, which can lead to a serious shortage of endogenous insulin secretion; (3) Sympathetic nervous system excitatory catecholamine secretion increases, accelerates liver glycogen decomposition and inhibits pancreatic B cell secretion, increases blood glucose, and further aggravates endogenous insulin secretion deficiency; and (4) AP may be accompanied by insulin resistance. This high blood glucose state is AP glands, exocrine function in the performance of the different degree of damage, AP early hyperglycemia, and the correlation between the severity of AP has been recognized and valued. However, in the past, blood glucose metabolism disorder was considered a transient manifestation of the disease, so the monitoring and management of blood glucose after discharge did not receive enough attention.
Table 1 Diagnosis of diabetes: Typical diabetes symptoms and any of the following

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value of number</th>
</tr>
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<tbody>
<tr>
<td>FPG</td>
<td>≥ 7.0 mmol/L</td>
</tr>
<tr>
<td>Random glucose</td>
<td>≥ 11.1 mmol/L</td>
</tr>
<tr>
<td>OGTT</td>
<td>2hPG &gt; 11.1 mmol/L after a 75-g OGTT</td>
</tr>
<tr>
<td>HbA1c</td>
<td>≥ 6.5% mmol/L</td>
</tr>
</tbody>
</table>

FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; OGTT: Oral glucose tolerance test.

Table 2 Diabetes can be diagnosed by any of the following parameters if without classical diabetes symptoms

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value of number</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>&gt; 7.0 mmol/L for 2 times</td>
</tr>
<tr>
<td>OGTT</td>
<td>2hPG ≥ 11.1 mmol/L for 2 times</td>
</tr>
<tr>
<td>IGT</td>
<td>FPG &lt; 7.0 mmol/L and 7.8 mmol/L &lt; 2hPG &lt; 11.1 mmol/L after a 75-g OGTT</td>
</tr>
<tr>
<td>HbA1c</td>
<td>≥ 6.5% mmol/L</td>
</tr>
</tbody>
</table>

FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; IGT: Impaired glucose tolerance; OGTT: Oral glucose tolerance test.

In AP, there is usually simultaneous pancreatic and exocrine dysfunction, and the disorder of blood glucose metabolism, as a common clinical manifestation of AP in the early stage, has gradually attracted attention. However, the pathophysiology of onset diabetes secondary to AP remains unclear[23]. But its occurrence may be related to some factors of AP, including islet cell damage associated with AP, pancreatic autoimmunity induced by AP, and insulin secretion disorder induced by the inflammatory response, etc. At present, basic and clinical studies on the pathogenesis of diabetes are still insufficient. Defining mechanisms is essential to guide clinical interventions.

It is important to emphasize that diabetes and hyperglycemia levels themselves can increase the severity of AP, mortality, and complications, and in turn increase the severity of diabetes[24,25]. However, higher body mass index and other factors are often closely associated with the development of diabetes[26]. Therefore, attention should be paid to the risk of new-onset diabetes in patients with AP caused by weight and other related indicators.

MANAGEMENT OF NEW-ONSET DIABETES SECONDARY TO AP

Currently, there is no detailed standard for the management of new-onset diabetes secondary to AP. However, as a special type of diabetes, in addition to its general clinical manifestations, complications, and prognosis, blood glucose fragility is a significant clinical feature of new-onset diabetes secondary to AP. Such fluctuations in blood glucose can lead to dysfunction in the pancreas, further increasing the risk of pancreatic cancer[19,20]. Therefore, it is necessary to pay attention to the changes in blood glucose in time and select an individualized treatment plan.

Based on the current clinical data, the management of new-onset diabetes secondary to AP mainly includes prevention, screening, and treatment. From a prevention perspective, it is important to guide the population to avoid risk factors or lifestyles that contribute to AP and diabetes, such as timely control of obesity and hyperlipidemia. In terms of treatment, despite the lack of clinical trial evidence and relevant evidence-based guidelines, type 2 diabetes-based control strategies can still be used for new-onset diabetes secondary to AP. It is important to clarify the pathogenesis and inducement of diabetes secondary to AP for precise treatment. Regarding follow-up screening, given the potential risk of pancreatic cancer after new-onset diabetes secondary to AP, regular follow-up is necessary for standard assessment of pancreatic endocrine function.

CONCLUSION

New-onset diabetes secondary to AP is increasingly recognized as a sequela of AP. The few studies to date show that the severity of AP does not indicate the risk of developing secondary diabetes. Further
elucidation of the risk factors and pathogenesis of new-onset diabetes secondary to AP will facilitate more effective early treatment. Early warning, screening, and follow-up findings will benefit new-onset diabetes secondary to AP patients. At the same time, worldwide evidence-based studies will help to enrich the in-depth understanding of the disease.

FOOTNOTES

Author contributions: Yu XQ and Zhu Q completed the design and writing of the paper; Yu XQ participated in the overall design and revision of the paper.

Conflict-of-interest statement: All authors have no conflicts of interest to declare.

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S-Editor: Liu JH
L-Editor: Filipodia
P-Editor: Liu JH

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Ketosis-prone diabetes mellitus: A phenotype that hospitalists need to understand

Sydney Boike, Mikael Mir, Ibtisam Rauf, Abbas B Jama, Shaleen Sunesara, Hisham Mushtaq, Anwar Khedr, Jain Nitesh, Salim Surani, Syed A Khan

**Abstract**

Diabetes has been classified mainly into types 1 and 2. Some type 2 diabetes patients, when developing ketosis, have been labeled as having atypical diabetes. Lately, syndromes of ketosis-prone diabetes, primarily in patients who we previously classified as type 2 diabetics, have emerged, and calls are being made to even reclassify diabetes. This mini-review will extensively deal with the historical, molecular, phenotypical, and clinical basis of why ketosis-prone diabetes is different than the traditional principles of type 1 and 2 diabetes and should be classified as such. Clinicians, especially those who are not diabetologists or endocrinologists, as well as hospitalists, intensivists, and primary care providers, will greatly benefit from this review.

**Key Words:** Diabetic ketoacidosis; Diabetes; Diabetes prone ketosis; Ketosis; Acidosis
Core Tip: Diabetes is one of the most common chronic diseases globally. Ketosis-prone diabetes is now being increasingly recognized. The majority of patients with ketosis-prone diabetes are being diagnosed at the time of their presentation as diabetic ketoacidosis. Its presentation is unique, and it has components of both type 1 and type 2 diabetes. This article helps the clinician understand the pathophysiology of this phenotype.

Citation: Boike S, Mir M, Rauf I, Jama AB, Sunesara S, Mushtaq H, Khedr A, Nitesh J, Surani S, Khan SA. Ketosis-prone diabetes mellitus: A phenotype that hospitalists need to understand. World J Clin Cases 2022; 10(30): 10867-10872
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/10867.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.10867

INTRODUCTION

The earliest record of diabetes was described on the Ebers Papyrus. An Egyptian document is believed to be from approximately 1500 before Christ (BC)[1]. At present, diabetes is estimated to affect over 420 million people worldwide, with expectations that this number will rise to over 500 million by the end of this decade. According to the Report of the global Diabetes Summit, co-hosted by the World Health Organization and the Government of Canada[2-4].

Diabetes is broadly categorized as diabetes mellitus, diabetes insipidus, and gestational diabetes, with diabetes mellitus and diabetes insipidus having further subcategorizations of type 1 and type 2. Gestational diabetes is defined as glucose intolerance that is first discovered during pregnancy. It affects 2%-5% of pregnant women and risk factors include a strong family history of diabetes and obesity. Diabetic ketoacidosis (DKA) can develop as a life-threatening complication for both the mother and the fetus. The incidence of occurrence of DKA ranges from 0.5%-10.0% in gestational diabetes. Its pathophysiology can be characterized by insulin resistance and respiratory alkalosis. Considered a physiologic mechanism to preserve glucose for the fetus, insulin sensitivity for the mother is decreased. Furthermore, increased alveolar ventilation in the mother results in respiratory alkalosis that is offset by increased bicarbonate secretion which can lead to ketoacidosis. Additionally, the fetus uses a significant amount of maternal glucose, which leads to decreased fasting glucose of the mother, which in relation to the insulin deficiency leads to increased production of free fatty acids that are converted to ketones in the liver[5].

Different forms of diabetes have been increasingly recognized in the last few decades. Some published work includes the characterization of ketosis-prone diabetes (KPD), also called ketosis-prone type 2 diabetes mellitus (KPDM), Flatbush diabetes, idiopathic type 1 diabetes, or atypical diabetes[6,7]. KPD is unique in that its presentation and the clinical course contain elements of both types 1 and 2 diabetes mellitus[6].

Here we aim to review the contemporary literature and outline the background, molecular, phenotype, and clinical basis of why this ketosis-prone diabetes is different and must be classified as so to benefit clinicians. This review provides the current understanding of KPD with recent literature and can serve as a resource for medical professionals during their clinical decision-making.

BACKGROUND AND HISTORY OF KPD

KPD, commonly known as “Flatbush Diabetes”, refers to a hybrid form of diabetes that has various characteristics of type 1 diabetes and type 2 diabetes[8]. Type 1 diabetes is caused by the autoimmune loss of insulin-producing beta cells in the pancreas. Patients become dependent on insulin as a result of this, and the lack of natural insulin makes patients vulnerable to DKA. On the other hand, type 2 diabetes differs from type 1 diabetes because it is caused by insulin resistance in the body in elderly patients, which leads to beta-cell burnout over time[5]. KPD is a type 2 diabetes-like illness that involves DKA but occurs later in life and can regain beta cell activity, similar to type 2 diabetes. KPD has similar biochemical and acid-base parameters to type 1 diabetes[5].

KPD has been recognized as a medical condition since 1984. Most of the early studies were focused on African American individuals but have shifted to sub-Saharan African, Hispanic, and Asian populations in recent years. Studies show that Blacks and Hispanics account for 20%-50% of KPD patients in the United States[8]. KPD predominantly affects African men who are overweight, have a family history of KPD, and have a low prevalence of autoimmune markers[8].

KPD is believed to commence with ketoacidosis in people who lack autoimmune markers, islet cell antibodies, and glutamic acid decarboxylase (GAD) autoantibodies[9]. People dealing with these conditions require insulin replacement, but it may be possible for them to end insulin treatment in the
future, depending on the progress of treatment and the condition of the individual. This unusual condition that does not fit traditional categories is described as KPD[9]. Furthermore, at the initial stage of diagnosis, many individuals will have impaired insulin secretion in addition to complications such as ketosis or DKA[10]. Studies have found that up to 75% of people who have KPD had DKA at the diagnosis level. The classification of KPD is dependent on testing for GAD, anti-islet cell antibodies, and fasting C-peptide levels[8].

**PATHOPHYSIOLOGY**

KPD departs from the classical presentations of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Whereas T1DM is the autoimmune destruction of pancreatic B-cells, and T2DM is characterized by insulin resistance and B-cell dysfunction, KPD has unique pathogenesis. It lacks the immunologic markers to distinguish it as T1DM but also lacks the insulin requirements to be considered T2DM. Considered the third type of diabetes, there are four classifications for KPD: The American Diabetes Association (ADA) classification, the modified ADA system, the BMI system, and the Aß system[11]. The Aß system distinguishes four subgroups based on the presence/absence of autoantibodies and B cell function. The four subgroups include autoantibodies present beta-cell function absent (A+ß-), autoantibodies present beta-cell function present (A+ß+), autoantibodies absent beta-cell function absent (A-ß-), and autoantibodies absent beta-cell function present (A-ß+) (Table 1).

Differentiating A+ß+ from A+ß+ KPD allows exploration into autoimmune pathways that lead to distinct patterns of beta-cell loss. The more moderate clinical course of A+ß+ KPD patients compared with A+ß- KPD patients may be related in part to epitope-specific antibodies to the 65-kDa isoform of glutamic acid decarboxylase (GAD65)[12]. Furthermore, a specific amino-terminal epitope defined by monoclonal antibody DPD is correlated with a higher beta-cell functional reserve and was associated with the milder A+ß+[13]. However, the mechanisms that create the autoantibody specificity and result in variable beta-cell functional reserve remains to be known. In healthy individuals, GAD65 antibodies (GAD65Ab) are present in the sera but are masked by anti-idiotypic antibodies[13]. Masked GAD65Ab specific for the epitope DPD is strongly associated with preserved beta-cell function among patients with KPD[13]. Additionally, circulating insulin DNA is a biomarker for A+ß+ KPD patients, though absent in A+ß- KPD patients[14].

A-ß- KPD is characterized by beta cell failure and undetectable autoimmunity. Some A-ß- KPD patients may be misclassified as “A-” because of a decline in autoantibody titers over time though a decline in antibody titer is less likely as GAD autoantibodies are reportedly durable[11]. Most A-ß- KPD patients have relatives with a strong family history of diabetes, which suggests a familial trait and defects in genes responsible for beta-cell development and function[15]. Significant variants in the genes encoding the key beta-cell transcription factors hepatocyte nuclear factor-1-alpha (HNF1a), PAX-4, pancreas-duodenum homeobox-1 (PDX-1), TCF1, PAX-4, PDX-1, are enhanced in A-ß- KPD which may contribute to a monogenic etiology for some patients with the A-ß- phenotype[15].

Finally, the A+ß+ phenotype is characterized by partially reversible beta-cell dysfunction, which may be due to metabolic, genetic, or viral etiologies[16]. Dysfunctional pathways of branch chain amino acid (BCAA) and arginine/citrulline metabolism in A+ß+ patients were discovered by a plasma metabolomics survey[10]. A+ß+ patients had impaired ketone oxidation and fatty acid oxidation, resulting in increased leucine catabolism which highlights an aberrant mechanism for energy production and ketosis in A+ß+ KPD[10]. It was also found that A+ß+ patients in acute episodes of DKA had impaired catabolism and accelerated fatty acid conversion of ketones, similar to the T1DM patients [17].

**CLINICAL PRESENTATION**

The clinical presentation of KPD follows a similar constellation of symptoms across those affected. The majority affected are considered to be of middle age, are classified as obese, and have recently received a diagnosis of diabetes mellitus[18]. These individuals present acutely with DKA and classically follow a similar history prior to presentation (increased urination, increased thirst, and associated weight loss), with a predilection of men vs women being affected by the condition[18]. Of those who present with KPD, they classically do not have the standard phenotypic expression of autoimmune type I diabetes, which is what one may expect in a patient presenting with DKA. That is, many present with features similar to type 2 diabetes, including the previously listed symptoms of obesity and diagnosis of diabetes in middle age, in addition to strong family history, hypertension, and beta-cell functional reserve[19]. Regarding findings obtained in labs, these individuals present with severe hyperglycemia, ketosis +/- acidosis, and will commonly have negative panels for autoantibodies against beta-cell antigens[20], further distinguishing this pathology from type 1 or type 2 diabetes mellitus. Certain ethnicities are more commonly associated with KPD as well. In a 2004 study performed by Maldonado et al[21], 321 patients were interviewed over a span of 3.5 years, in which information was collected to analyze group
**Table 1 Aβ system for four ketosis-prone diabetes subgroups based on the presence/absence of autoantibodies and β cell function**

<table>
<thead>
<tr>
<th>A+: Autoantibodies present, β cell function present</th>
<th>A-: Autoantibodies absent, β cell function present</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+β+: Fasting serum C-peptide concentration greater than or equal to 1 ng/mL (0.33 nmol/L) or a peak serum C-peptide response to glucagon greater than or equal to 1.5 ng/mL (0.5 nmol/L)</td>
<td>A-β+: Fasting serum C-peptide concentration less than 1 ng/mL (0.33 nmol/L) or a peak serum C-peptide response to glucagon less than 1.5 ng/mL (0.5 nmol/L)</td>
</tr>
<tr>
<td>A+β+: Fasting serum C-peptide concentration greater than or equal to 1 ng/mL (0.33 nmol/L) or a peak serum C-peptide response to glucagon greater than or equal to 1.5 ng/mL (0.5 nmol/L)</td>
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</tr>
</tbody>
</table>

GAD65: Glutamic acid decarboxylase; IA-2: Anti-islet tyrosine phosphatase 2.

**CLINICAL MANAGEMENT OF KPD**

Management of KPD is divided into three stages: acute management of DKA, evaluation of the KPD subgroup after DKA resolution, and long-term health maintenance. KPD patients who present with DKA should be managed according to standard care methods for DKA, regardless of subtype. These inpatient protocols include aggressive fluid replacement to restore circulatory volume, regular IV insulin therapy, evaluation and treatment of precipitating factors, correcting the hyperglycemia, stabilizing the electrolyte disorders, and alleviating ketoacidosis. This treatment plan should be followed with a transition from IV insulin therapy to subcutaneous regimens. Additionally, all KPD patients should be given a discharge plan that provides 24-h insulin coverage. Insulin may be discontinued only after a thorough evaluation and accurate classification of the KPD subtype and assessing the patient’s predictive factors. This evaluation should be performed at the first outpatient visit following discharge from the hospital, preferably after 1-3 wk.

Evaluation of the KPD subgroup is performed via assessment of beta-cell secretory reserve and beta-cell immunology. This evaluation is usually performed at least 1-3 wk after the resolution of DKA to minimize the effects of glucose toxicity and beta-cell desensitization on the diagnostic parameters. The beta-cell secretory reserve is measured with C-peptide levels during a fasted state or after glucagon stimulation, and it is a strong predictor of long-term glycemic control and insulin discontinuation. Patients are classified as A+ if they have adequate beta-cell reserve with a fasting serum C-peptide concentration greater than or equal to 1 ng/mL (0.33 nmol/L) or a peak serum C-peptide response to glucagon greater than or equal to 1.5 ng/mL (0.5 nmol/L). Patients are classified as A- if they have inadequate beta-cell reserve with a fasting serum C-peptide concentration less than 1 ng/mL (0.33 nmol/L) or a peak serum C-peptide response to glucagon less than 1.5 ng/mL (0.5 nmol/L). This classification scheme is used due to its high accuracy and predictive value.

Quantitative assessment of beta-cell auto-antibodies is also valuable for this clinical evaluation, especially in patients with the A+K+ KPD phenotype. The serum autoantibodies measured include anti-glutamic acid decarboxylase (GAD65) and anti-islet tyrosine phosphatase 2 (IA-2), and increased accuracy of this classification is also often done by measuring serum titers of autoantibodies to the zinc transporter 8 (ZnT8) antigen. Patients are then classified as A+ or A- based on the presence of a significant number of autoantibodies.

Once the patient has been classified with a KPD subtype, began on appropriate therapy, and been assessed for risk factors for subsequent ketotic episodes, the standard protocol for diabetes management should be followed for long-term management of KPD. In addition to other forms of diabetes mellitus,
all subtypes of KPD should be managed with lifestyle changes, including appropriate diet and adequate exercise. A registered dietician is recommended, along with a diabetic educator as needed. Additional measures include weight loss in obese patients, smoking cessation, if applicable, and physical activity multiple times a week\[27\]. Insulin discontinuation in B+ can be achieved by evaluating for factors such as new diagnosis of diabetes, older age at onset, and high beta-cell secretory reserve. The presence of beta-cell autoantibodies can also be used to determine beta-cell function in the future and insulin discontinuation. Although KPD patients with autoantibodies tend to have a lower beta-cell function at the time of diagnosis and at follow-up, approximately 50% of A+B+ KPD patients maintain a long-term beta-cell secretory reserve\[28\]. Due to the unpredictability of beta-cell reserve, A+B+ KPD patients can also come off insulin therapy initially but require close monitoring for at least two years. HLA subtyping is useful in predicting long-term outcomes because it can elucidate those patients who will most likely have a more severe experience.

CONCLUSION

 Syndromes of ketosis-prone diabetes have been described in the literature, and much has been learned about the condition. However, much is still unknown about the etiology, treatment, and why it affects certain ethnicities more than others. The wide range of presentations and classifications poses an obstacle to proper preventative and clinical management of KPD since the pathophysiology of each subtype is different. The role of genetics and genotyping in KPD has yet to be elucidated, but further understanding of both the etiology and risk factors of KPD will guide clinicians in determining the most effective therapies for the management of the condition and the prevention of ketosis.

FOOTNOTES

Author contributions: Boike S, Mir M, Rauf I, and Jama AB contributed to conceptualization, drafting, reviewing, final editing, and agreeing to the accuracy of the work; Mushtaq H, Khedr A, and Nitesh J contributed to literature search and review of the manuscript; Surani S and Khan SA contributed to supervision, critical revision of the manuscript, editing, reviewing, and agreeing to the final accuracy of the work.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

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Boike S et al. Ketosis prone diabetes
2022 Monkeypox outbreak: Why is it a public health emergency of international concern? What can we do to control it?

Shi-Yan Ren, Jing Li, Rong-Ding Gao

Abstract

The World Health Organization (WHO) called the recent monkeypox (MPX) outbreak a Public Health Emergency of International Concern on July 23, 2022. The United States of America (US) alarmed the recent MPX outbreak as the US public health emergency on August 4, 2022. Since early May 2022, more than 35000 MPX cases and 12 deaths had been reported to WHO from 92 countries and territories by August 17, 2022, and MPX cases continue rising rapidly with improved surveillance, access to diagnosis, and continuous virus spreading globally. Approximately 99% MPX cases are men, of which 95% cases are men who have sex with man. No evidence of MPX being sexually transmitted infections (STIs) is found; however, a high percentage (25%) of concurrent STIs and frequent anogenital symptoms suggest transmission through local inoculation during close intimate contact or sexual activity. Many approaches including a comprehensive international vaccination strategy and adequate supplies are mandatory to prevent MPX pandemic. Education, vaccination, MPX scrutiny and careful monitoring, and crossborder collaborations with international sectors are practical strategy to contain MPX outbreaks. People are educated to reduce the risk of exposure and to reduce the number of sexual partners especially new ones, to avoid contacting travelers from epidemic regions or animals that may carry MPX virus, and avoid traveling to endemic areas.

Key Words: Monkeypox; Outbreak; Public Health Emergency of International Concern vaccination; Infectivity; Transmission; Man who have sex with man

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Core Tip: The World Health Organization called the current monkeypox (MPX) outbreak a Public Health Emergency of International Concern on 23 July, 2022. United States (US) alarmed the recent MPX outbreak as the US public health emergency on August 4, 2022. Despite MPX cases continue to rise rapidly with improved surveillance, as MPX outbreaks is primarily contained in adult men, it should be manageable, and will be controlled by education, MPX surveillance, careful monitoring, vaccination, and crossborder collaborations with international sectors.

INTRODUCTION

The World Health Organization (WHO) announced the recent global outbreak of monkeypox (MPX) a public health emergency on July 23, 2022[1-3]. Since May, 2022, more than 35000 MPX cases and 12 deaths had been reported to WHO, from 92 countries and territories by August 17, 2022[4], where the MPX virus is not endemic. Previous cases of MPX found in non-endemic regions were usually related with travel to Central or West Africa, however, cases in recent outbreak appear to have no link with endemic areas that suggests community transmission[3]. It is timely to know the transmissibility and available preventive approaches to obtain the outbreak of MPX.

SEARCH METHODS

The references were systematically searched and reviewed on the Internet homepage of the National Library of Medicine, web of science without language limitations. The search covered all years available on the internet. The search terms were applied as follows: Monkeypox, outbreak, Public Health Emergency of International Concern vaccination, Infectivity, Transmission, and Man who have sex with man. The citations in each article found during the main search were researched for potential relevance. Published articles were included and reviewed, the related results were extracted given they provided original data on monkeypox.

WHAT IS MONKEYPOX?

MPX is a rare zoonotic disease in humans, induced by the MPX virus that is alike to other orthopoxvirus, particularly smallpox and relates to the Poxviridae family, chordopoxvirinae subfamily, and orthopoxvirus genus[1]. The MPX was named after the original detection of the virus in monkeys in a Danish laboratory in 1958 when monkeys transferred from Singapore to Denmark for study had a vesicular illness[1,5]. Both the West African virus and Central African viruses cause a comparable clinical syndrome[1]. A 9-month-old baby boy is the first MPX patient diagnosed in August 1970 in Zaire, nowadays the Democratic Republic of the Congo[3].

HOW DOES IT SPREAD?

The natural hosts of MPX virus are rodents such as squirrels and giant pouched rats, which stand for the largest animal reservoirs for the virus[1]. MPX usually spreads through intimate touch with infected skin or mucosal lesions, body fluids and blood, and polluted personal clothes[3,6-10]. Outbreaks occur occasionally in sub-Saharan Africa after contacting with an infected wild animal. Outside of Africa, the largest known outbreak in the United States (US) happened in 2003, when 47 cases were infected by pet prairie dogs that had contaminated the virus from rodents imported from Ghana[1,9]. In Belgium, many MPX cases were related to a gay festival in Antwerp. The virus can be detected in semen[10,11], most MPS cases have lesions exclusively perigenital, perianal, and around the mouth[10,12].

Recent epidemiologic study shows that the main mode of transmission is through skin-to-skin and sexual contact, rather than contact with polluted clothes. Currently, US and most of the European (EU) countries are epidemic countries[3,6-8]. Reported cases in recent outbreak have mainly but not exclusively been identified among men who have sex with men (MSM), particularly those with new or
multiple partners, and bisexual men between the ages of 20-59 years, 99% cases are men, of which 95% cases are MSM[13,14].

Whether monkeypox is STIs, infected from person to person through blood, semen or other bodily fluids during sex, is unclear yet. But several studies indicate that DNA from MPX virus is present in semen for weeks after infection. Infectious viruses were isolated from semen six days after their symptoms appeared. In United Kingdom (UK)[10], all 54 men being confirmed MPX infection were identifying as MSM, with a median age of 41 years, and 13 (24%) were living with human immunodeficiency virus (HIV)[10]. In Spain, 147 specimens were picked up from 12 patients and tested by real-time polymerase chain reaction (PCR). MPX DNA was identified in saliva, rectal swab, nasopharyngeal swab, semen, urine and faeces[15]. In Italy, four PMX cases of young adult men informing condomless sexual intercourse are healthy necessitating no specific antiviral therapy, MPX DNA were tested positive in seminal fluid[16]. In Germany, first two human MPX patients demonstrate clinical and virological findings, revealing MPX DNA in blood and semen[17]. The close contact during sexual activity may spread virus easier, it is most likely a accidental introduction of MPX which then spread among MSM[10]. Now there is not enough evidence to call PMX a STI. The possibility of sexual transmission of MPX virus needs to be confirmed[16].

**HOW SERIOUS IS MONKEYPOX?**

MPX has an incubation time ranging from 5 to 21 d, most cases develop symptoms 6-13 d after the first contact[1,9]. MPX is generally a self-limited febrile rash of limited severity, and most patients are mild, and recover within a few weeks, usually have fever, chills, headaches fatigue, muscle pain, and enlargement of lymph node followed by an eruption of pus-filled blisters. Within 5 d after fever, a variety of sizes of rashes build up from the face to the trunk and extremities. The rashes often come out on the palms and soles of the feet with size of 0.5-1 cm in diameter, resolving into crusts then falling off[1,9]. The median time between symptom onset and diagnosis was 7 d[13].

More serious cases can be found in children, elderly, pregnant women and immunocompromised patients[17], who may have many complications, such as respiratory disorders and encephalitis. Death usually occurs within the second week of the infection[17,18].

The MPX genome has more than 200000 base pairs, is approximately seven times the size of severe acute respiratory coronavirus 2 (SARS-CoV-2)'s and more than 20 times longer than HIV’s. As MPX virus is a DNA virus, MPX has far better genetic repair mechanisms than RNA viruses such as HIV and SARS-CoV-2, which hints at it evolves more slowly[6,10]. Although smallpox viruses belong to the genus orthopoxvirus, but the infectivity and pathogenicity of MPX virus are weaker than smallpox virus. The fatality rate of smallpox can reach 30%, the fatality rate of MPX in Central Africa (the Congo Basin strain) is about 10.6%, and that in West Africa is around 3.6%. The mortality rate of MPX cases reported worldwide in 2022 was about 0.03%, and the eight reported deaths were all in Africa. As of May 2022, the Democratic Republic of the Congo was the country with the highest number of cases and deaths with 1284 verified cases between January 1, 2022 and May 8, 2022, including 58 deaths[19].

More than 35000 MPX cases and 12 deaths had been informed to WHO from 92 countries and territories by August 17, 2022[3,6-9,14,20].

**HOW THE DIAGNOSIS OF MPX IS MADE?**

Symptoms do not have any specific characteristics, but help establish the suspicion of MPX. The enlarged lymph nodes are uncommon signal of smallpox, but occur in 90% of MPX distributed in the neck, the groin and submandibular areas[1,18]. They are considered a distinctive hallmark indicating MPX. Diagnosis is made initially with a pan-orthopox PCR then by a specific MPX PCR test and genome sequencing[10]. IgM is more useful in diagnosing newly infectious cases, while IgG itself cannot provide a definitive diagnosis for a patient infected with orthopoxvirus[21]. As the symptoms are various and non-specific, many disorders can be included in a differential diagnosis of MPX, e.g. sexual transmitted infections (STIs), chickenpox, syphilis, water warts, red measles, drug reactions, staphylococcus skin infections, bacillus anthracis, and itch mites[6,9]. Community transmission happened several times globally without recognition may be misdiagnosis of MPX as STIs especially as it showed with atypical genital and peri-anal lesions, mild or asymptomatic cases, non-reporting of cases, and a dearth of active surveillance. Another reason is the population’s withdrawing protection from smallpox vaccines. Smallpox, being in the same family as MPX, was eradicated in the 1980s through mass vaccination. The lack of immunity in young people allows them easier to get MPX[9,10].
WHY DOES MONKEYPOX EPIDEMIC CONSTITUTE A “PUBLIC HEALTH EMERGENCY OF INTERNATIONAL CONCERN”?

A disease outbreak is endemic when it is consistently present but limited to a particular geographic area or region. WHO classified some African countries such as Cameroon, the Central African Republic, the Democratic Republic of the Congo, and Nigeria, as MPX endemic. Previous MPX cases in non-endemic regions were usually related with travel to Central or West Africa[18]. But, since early May 2022 an unique outbreak of MPX from non-endemic countries has been reported to WHO globally (Figure 1), US and most EU become endemic, global spread is clearly a concern, and requires collaborative international efforts[9].

May 6, 2022 an outbreak of MPX was proved in the UK, coming from a British resident who had travelled to Nigeria, the endemic area, inducing the index case of the outbreak into the UK[3,5]. As of May 22, 2022, 92 cases from 15 non-endemic countries have been confirmed worldwide[9]. As of May 26, the number increased to 334[19] (Figure 2).

MPX is endemic to some African countries and usually came up outside this region only when related to travelers. The current outbreak, mostly in some Western countries, has no evidence of travel history to endemic areas suggesting community transmission[14]. The countries reporting the highest number of confirmed cases were the UK, Portugal, and Canada. Figure 3 shows the number of confirmed and suspected cases of MPX in non-endemic countries that had been reported to the WHO between May 13, 2022 and 26, 2022[19].

On the afternoon of June 23, 2022, 3040 cases had been reported in 47 countries and regions, the WHO emergency committee held an expert meeting to evaluate the risk of MPX outbreaks in the world, only three members were for declaring a “public health emergency of international concern” (PHEIC) and 11 were opposed, therefore, the alarm of PHEIC was not sounding[22]. As of August 10, 2022, 41 countries across Europe had reported confirmed MPX cases, 5162 cases in Spain, while 2982 cases in the UK (Figure 4).

On the afternoon of July 21, 2022, 75 countries and regions, mainly in non-endemic area such as Europe and North America had reported more than 16000 cases including 5 deaths, the WHO emergency committee held another expert meeting to assess the MPX epidemic, the panel did not formally vote, six members agreed with declaring a PHEIC, nine were against. Nevertheless, considering the outbreak is an extraordinary event and the MPX disease is a global public-health risk, and needs collaborative international efforts. The WHO director-general Tedros Adhanom Ghebreyesus stated MPX had constituted the PHEIC on July 23, 2022 that places a risk to multiple countries, and requires a coordinated international response[12].

The worldwide number of MPX cases has risen to 21099 as of July 29, 2022 according to data by global.health, while mortality is not a concern yet (Figure 5). A total of 19429 cases of MPX have been found from 43 countries and areas throughout the European region through The European Surveillance System (TESSy), up to August 16, 2022[13]. The majority of cases were between 31 and 40 years-old (40%) and male (98.9%). Among cases with known HIV status, 38% (2749/7322) were HIV-positive. The majority of cases have rash (77.1%) and systemic symptoms such as fever, fatigue, muscle pain, chills, or headache (65%). 505 cases were hospitalized (5.8%), of which 179 cases demanded clinical care. Three cases died of MPX later[15]. On August 4, 2022, a total of 26800 cases of MPX had been documented globally, at least 7100 cases of MPX were identified in US, the largest number of confirmed cases in the world.

HOW TO PREVENT MPX?

Education, MPX surveillance, diligent monitoring, vaccination, and crossborder collaborations with international sectors are practical strategy to contain MPX outbreaks. People are educated to reduce the risk of exposure and to reduce the number of sexual partners especially new ones, to avoid close contacting travelers from epidemic areas or animals that may carry MPX virus. Virus spreading among MSM populations can be broken through aggressive public health measures, including increased vaccination and investigative testing and extensive education campaigns aimed at high risk persons and reducing social stigma[23-25].

It is critical to educate people and to identify, isolate and treat cases early and to shot vaccine for high risk persons. In case of rash and other symptoms, one should consult with a doctor and inform the travel history. To promptly recognize MPX cases and avoid further transmission, medical workers should be alert of the travel or contact history of the cases with similar symptoms[26].
MPX virus is closely related to smallpox virus. Due to cross immunization, smallpox vaccination with vaccinia virus was about 85% protective against MPX[9]. Nevertheless, the vaccine called vaccinia contains a natural pox virus cultured in labs. Vaccinia replicates inside the recipient and sometimes induced severe side effects, even one death in 1 million vaccinated people[3].

As to date no specific treatment for MPX is available. Since most cases of MPX are mild and self-limited disease, and can be treated with supportive care[9]. The vaccination was key to the success of the smallpox eradication campaign. Centers for Disease Control and Prevention recommends giving the smallpox vaccine within 4 d of exposure which may avoid the MPX disease, and within 2 wk to minimize symptoms[9]. Currently available vaccines for preexposure prophylaxis against orthopoxvirus infection among persons at risk include ACAM2000® (live, replication competent vaccinia virus), JYNNEOS (live, replication incompetent vaccinia virus) in US and EU, IMVAMUNE in Canada, IMVANEX in Europe, CJ-50300 in Korea, and LC16M8 in Japan. The two-dose MVA-BN JYNNEOS marked in US is same product of IMVANEX in Europe and IMVAMUNE in Canada that all manufactured by Bavarian Nordics[9].

Bavarian Nordic JYNNEOS smallpox (Monkeypox) vaccine is established on a live, attenuated vaccinia virus, modified vaccinia ankara that is cultured in chicken embryo fibroblast cells and a serum-free medium, it cannot replicate in the human body, and can elicit a potent immune response. The US Food and Drug Administration (FDA) explicitly approved JYNNEOS vaccine for both smallpox and MPX in adults 18 years of age and older verified to be at high risk for infection. JYNNEOS cannot replicate in the human, it needs two doses given 4 wk apart, it is efficient and safe in people infected.
Figure 3 Confirmed and suspected cases of monkeypox in non-endemic countries reported to the World Health Organization from May 13, 2022 to May 26, 2022. Source: https://www.statista.com/statistics/1310714/monkeypox-cases-in-non-endemic-countries-reported-to-who.

Figure 4 Number of confirmed monkeypox cases in Europe as of August 10, 2022, by country. Source: https://www.statista.com/statistics/1311194/monkeypox-reported-cases-in-europe.

with HIV or atopic dermatitis[9]. Exactly how well modified vaccinia virus ankara protects against monkeypox and for how long is unknown. Nor is it clear how much protection is lost by administering only a single dose rather than the suggested two doses, because some regions are short of vaccine supply, or how much protection a vaccine given after exposure can provide[9].

The ACAM2000 vaccine is licensed by the US FDA for smallpox and permitted to prevent MPX on an expanded access basis (“compassionate use” for an investigational drug use). ACAM2000, or LC16M8, is live, competent vaccinia virus and can replicated in immunocompromised patients, thereby cause adverse side effects that stimulates developing new vaccines like JYNNEOS.

Antivirals (e.g. tecovirimat, brincidofovir, cidofovir) and vaccinia immune globulin intravenous are indicated to use in severe disease, immunocompromised patients, pediatrics, pregnant and breastfeeding women, complicated lesions, and lesions around the mouth, eyes, and genitals[23]. Tecovirimat, in 2018 became the first ever approved by FDA to treat smallpox after it proved safe in human trials and
The worldwide number of monkeypox cases has risen to 21099 as of July 29, 2022 while mortality is not a concern yet. Source: global.health.

Effective in animals administered closely related viruses. FDA approved Smallpox antivirals tecovirimat to treat MPX[9]. One patient had taken 600 mg tecovirimat orally twice per day for 2 wk and was hospitalized for 10 d with no adverse effects except a shorter time of viral shedding[25]. In 2021, FDA approved a second drug for smallpox, brincidofovir, although it showed promising results against the virus in animal studies[25], three patients had 200 mg brincidofovir per week orally, all of them had elevated liver enzymes leading to stop this treatment[25]. Brincidofovir shows a better clinical effect than tecovirimat based on the limited data.

CONCLUSION

The World Health Organization called the current MPX outbreak a Public Health Emergency of International Concern on July 23, 2022. Cases of MPX continue to rise rapidly with improved surveillance, access to diagnosis, and continuing spreading of infection globally. JYNNEOS is the only FDA-approved non-replicating smallpox and monkeypox vaccine with less side effects. MPX has a much less serious threat of a massive global pandemic than COVID-19. As MPX outbreaks is primarily contained in adult men, it should be manageable, and will be controlled by education, MPX surveillance, diligent monitoring, vaccination, and crossborder collaborations with international sectors.

FOOTNOTES

Author contributions: Ren SY searched and studied the references, designed, wrote, revised, and submitted the manuscript; Li J and Gao RD searched, studied the references, and discussed the manuscript; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH
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10880
October 26, 2022 | Volume 10 | Issue 30
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Clinical characteristics and prognosis of non-small cell lung cancer patients with liver metastasis: A population-based study

Jun-Feng Wang, Hong-Di Lu, Ying Wang, Rui Zhang, Xiang Li, Sheng Wang

BACKGROUND
The presence of liver metastasis (LM) is an independent prognostic factor for shorter survival in non-small cell lung cancer (NSCLC) patients. The median overall survival of patients with involvement of the liver is less than 5 mo. At present, identifying prognostic factors and constructing survival prediction nomogram for NSCLC patients with LM (NSCLC-LM) are highly desirable.

AIM
To build a forecasting model to predict the survival time of NSCLC-LM patients.

METHODS
Data on NSCLC-LM patients were collected from the Surveillance, Epidemiology, and End Results database between 2010 and 2018. Joinpoint analysis was used to estimate the incidence trend of NSCLC-LM. Kaplan-Meier curves were constructed to assess survival time. Cox regression was applied to select the independent prognostic predictors of cancer-specific survival (CSS). A nomogram was established and its prognostic performance was evaluated.

RESULTS
The age-adjusted incidence of NSCLC-LM increased from 22.7 per 1000000 in 2010 to 25.2 in 2013, and then declined to 22.1 in 2018. According to the multivariable Cox regression analysis of the training set, age, marital status, sex, race, histological type, T stage, metastatic pattern, and whether the patient received chemotherapy or not were identified as independent prognostic factors for CSS (P < 0.05) and were further used to construct a nomogram. The C-indices of the training and validation sets were 0.726 and 0.722, respectively. The results of decision curve analyses (DCAs) and calibration curves showed that the nomo-
gram was well-discriminated and had great clinical utility.

**CONCLUSION**

We designed a nomogram model and further constructed a novel risk classification system based on easily accessible clinical factors which demonstrated excellent performance to predict the individual CSS of NSCLC-LM patients.

**Key Words:** Non-small cell lung cancer; Liver metastasis; Nomogram; Risk classification system

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**Core Tip:** Metastatic disease to distant organs from non-small cell lung cancer (NSCLC) is the main reason for poor survival. The liver is one of the most commonly involved extra-pulmonary sites of metastasis in NSCLC patients. The presence of liver metastasis (LM) is an independent prognostic factor for shorter survival in NSCLC patients. The median overall survival of patients with involvement of the liver is less than 5 mo. At present, identifying prognostic factors and constructing survival prediction nomogram for NSCLC patients with LM (NSCLC-LM) are highly desirable. We aimed to identify independent predictors and further build a novel risk stratification system to predict cancer-specific survival (CSS) of NSCLC-LM patients. To the best of our knowledge, our study was the first Surveillance, Epidemiology, and End Results (SEER)-based study to determine prognostic factors affecting CSS in NSCLC patients with liver involvement.

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i30/10882.htm
**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i30.10882

**INTRODUCTION**

Lung cancer is the leading cause of cancer morbidity and mortality worldwide, with more than 2.0 million new cases diagnosed (more than 10% of the diagnosed cancers) and approximately 1.8 million deaths (close to 20% of the cancer-related deaths) in 2020[1]. Approximately 85% of all lung cancers belong to the non-small cell lung cancer (NSCLC) type[2]. Patients presenting with distant organ involvement account for 40% to 65% of the diagnosed NSCLC cases[3]. Their five-year survival rate is as low as 5%[4,5]. Bone, brain, liver, and the adrenal glands are commonly affected extrapulmonary sites of metastasis in NSCLC patients[3]. Liver involvement accounts for 17% of the NSCLC cases with distant organ metastases and most of those patients have involvement of another extra-hepatic organ[3,6,7]. Recent reports have shown an association between specific organ metastases of NSCLC and survival time, and the presence of liver metastasis (LM) is associated with the worst prognosis. The median overall survival is approximately 4 mo and only a few patients have long lifespans[6,8]. A growing number of researchers have realized that the individual survival disparities are caused by differences in clinicopathological characteristics, such as marital status, age, sex, tumor site, tumor stage, and treatment methods. However, studies focusing on how to stratify the prognosis of NSCLC patients with liver involvement are relatively rare. Therefore, development of a risk classification system with technical feasibility and easy accessibility to predict the survival of NSCLC patients with LM (NSCLC-LM) is highly desirable.

Nomogram has been regarded as a practical and convenient clinical tool to estimate an individual’s clinical outcome by utilizing several clinicopathological variables[9]. A nomographic chart transforms complex patient information into a visual graph, which is characterized by its excellent predictive accuracy and definite reliability when generally applied to decision-making by clinicians.

The purpose of our retrospective study was to determine the demographic information and clinicopathological characteristics correlating with the prognosis of NSCLC-LM and further construct and validate a nomogram predictive model using the SEER database. Then, the novel risk classification system based on the nomogram scores was refined.
MATERIALS AND METHODS

Data source and study design
The SEER database established by the National Cancer Institute is recognized as one of the most authoritative sources of follow-up data for cancer patients in the world. The clinicopathological information of millions of patients in 18 cancer registries of the United States has been recorded in detail over the past 40 years.

We identified and collected the data of all the NSCLC-LM cases diagnosed between 2010 and 2018. The selection criterion was primary and microscopically confirmed NSCLC-LM. Patients with multiple primary cancers and incomplete data regarding distant metastatic sites or survival were excluded. Clinical variables for each case included age (< 65 and ≥ 65 years old), marital status (married and unmarried), sex (female and male), race (black, white, and other), primary site (upper lobe, middle lobe, lower lobe, main bronchus, and other), histological type (adenocarcinoma, squamous cell carcinoma, and other NSCLCs), T stage (T1, T2, T3, and T4), N stage (N0, N1, N2, and N3), metastatic pattern (liver only; liver and bone; liver and brain; liver, bone, and brain), radiotherapy (yes and no/unknown), and chemotherapy (yes and no/unknown). The primary endpoint of the study was cancer-specific survival (CSS) which was defined as the length of time from the initial diagnosis of NSCLC-LM to the time of death from NSCLC-LM.

Statistical analysis
All cases were randomly divided into a training cohort and a validation cohort at a 7:3 ratio. The training cohort was used to establish the nomogram model, and the validation cohort was used to test the model. Categorical variables are shown as frequencies and proportions. The training and validation sets were compared using the chi-squared test.

The independent prognostic variables were first analyzed using the Kaplan-Meier method and the log-rank test. Significant variables screened by univariate analysis were then entered into a multivariate regression analysis, yielding hazard ratios (HR). Finally, those independent predictors were used to construct a nomogram for predicting 3-, 6-, and 12-mo CSS. The predictive ability of the nomogram was assessed by the concordance index (C-index), calibration curves, and decision curve analyses (DCAs)[10, 11]. DCAs were constructed to estimate the clinical applicability of the survival prediction model[12]. In addition, a novel risk stratification system was introduced based on an individual’s nomogram scores and was used to divide the training cohort into three risk groups with similar numbers of cases in the low-, intermediate-, and high-risk groups. Joinpoint analysis was used to estimate the incidence trend of NSCLC-LM.

All statistical analyses were performed using SPSS 24.0 (IBM Corporation, Armonk, NY, United States) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). All data were extracted using SEER*Stat Software version 8.3.9 (Information Management Services, Inc., Calverton, MD, United States). Two-sided P values of < 0.05 were considered statistically significant.

RESULTS

Incidence and survival of NSCLC-LM
Overall, the incidence rate of NSCLC-LM could be divided into two stages (stage 1: 2010-2013 and stage 2: 2013-2018). The age-adjusted incidence (AAI) of NSCLC-LM increased from 22.7 cases per 1000000 in 2010 to 25.2 cases in 2013, and then declined to 22.1 cases in 2018. The annual percentage change (APC) was 4.19% and -2.63% (P < 0.05), respectively (Figure 1A). The median CSS of patients with NSCLC-LM (12 mo) was significantly shorter than patients with bone (16 mo) or brain (14 mo) metastasis (P < 0.001) (Figure 1B).

Patient characteristics
Overall, a total of 4475 NSCLC-LM patients meeting the eligibility criteria were divided into the training (3135, 70%) and validation cohorts (1340, 30%). Table 1 shows the demographic and clinicopathological characteristics of the NSCLC-LM patients. In all cohorts, the median age at diagnosis was 67 years (range: 23-96 years). More than half of the patients were married (2463, 55.0%) and male (2537, 56.7%). The majority of patients in all sets were white (3517, 78.6%) and had adenocarcinomas (2967, 66.3%). The most common primary site of NSCLC was the upper lobe (2452, 54.8%). In terms of metastatic patterns, more than one-third of the cases presented with liver and bone metastases (1701, 38.0%) and liver involvement only (1598, 35.7%). The majority of patients (2417, 54.0%) received chemotherapy and 1871 (41.8%) received radiotherapy. The median age of the training cohort was 67 years (range: 23-96 years). More than half of the patients were married (2463, 55.0%) and male (2537, 56.7%).
### Table 1 Baseline characteristics of the overall, training, and validation cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall cohort (n = 4475)</th>
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<th>Validation cohort (n = 1340)</th>
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<td>&lt; 65</td>
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Wang JF et al. NSCLC patients with liver metastasis

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<td>1458 (46.5)</td>
<td>600 (44.8)</td>
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1Other only includes American Indian/Alaskan Native and Asian/Pacific Islander.

Figure 1 Incidence and survival of non-small cell lung cancer-liver metastasis. A: The age-adjusted incidence of non-small cell lung cancer patients with liver metastasis between 2010 and 2018; B: Kaplan-Meier curves showing cancer-specific survival of patients with liver, bone, and brain metastasis.

Independent predictors of NSCLC-LM

The Cox proportional hazards regression model was performed in the training cohort to identify independent prognostic factors of CSS. Age, sex, race, pathological type, T stage, metastatic pattern, and chemotherapy were significantly associated with CSS in univariate analysis, and all of those variables were further proved to be independent predictors of CSS by multivariate analysis (Table 2).

Nomogram construction and validation

Based on the independent variables above, a nomogram was constructed to predict 3-, 6-, and 12-mo CSS (Figure 2). The nomogram also generated corresponding scores for each predictive variable (Table 3). The probability of an individual’s CSS can be easily calculated by adding the corresponding nomogram points for the patient. The forecasting model also indicated that chemotherapy made the greatest contribution to a patient’s CSS. For each predictor, a vertical line is drawn downward to determine the nomogram points, and the points are added together to obtain the patient’s total nomogram points. A vertical line is drawn from the location of the total point axis down to the survival axes. The number on this line indicates the predicted 3- (78%), 6- (64%), and 12-mo (48%) CSS. For example, a 65-year-old (score of 20), married (score of 0), black woman (score of 31.7) had squamous-cell lung carcinoma (score of 12.9). The tumor size was 2 cm (T1 stage, score of 0) but had metastasized to the liver (score of 0). She received chemotherapy (score of 0). The total nomogram score of this patient was 64.6, and a line was drawn down to the survival axes to determine the 3- (78%), 6- (64%), and 12-mo (48%) CSS probabilities.

The nomogram was validated internally and externally in the training and validation cohorts, respectively. The C-indices were 0.726 (95%CI: 0.708-0.744) and 0.722 (95%CI: 0.692-0.751), respectively. Both the internal (Figure 3A) and external (Figure 3B) calibration curves showed a good correlation between the actual and predicted probabilities of 3-, 6-, and 12-mo CSS. In addition, DCAs demonstrated that the predictive model yielded preferable net benefits among an extremely wide field
Table 2 Univariate and multivariate analyses of cancer-specific survival in the training cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI of HR</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65 vs &lt; 65</td>
<td>1.312</td>
<td>1.221-1.411</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried vs Married</td>
<td>1.245</td>
<td>1.158-1.338</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs Female</td>
<td>1.219</td>
<td>1.134-1.311</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White vs Black</td>
<td>1.128</td>
<td>1.043-1.221</td>
</tr>
<tr>
<td>Other vs Black</td>
<td>0.781</td>
<td>0.714-0.855</td>
</tr>
<tr>
<td>Pathological type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC vs SCC</td>
<td>0.814</td>
<td>0.749-0.884</td>
</tr>
<tr>
<td>Other NSCLCs vs SCC</td>
<td>0.786</td>
<td>0.677-0.913</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 vs T1</td>
<td>1.195</td>
<td>1.052-1.357</td>
</tr>
<tr>
<td>T3 vs T1</td>
<td>1.277</td>
<td>1.124-1.451</td>
</tr>
<tr>
<td>T4 vs T1</td>
<td>1.358</td>
<td>1.201-1.536</td>
</tr>
<tr>
<td>N stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1 vs N0</td>
<td>1.050</td>
<td>0.901-1.225</td>
</tr>
<tr>
<td>N2 vs N0</td>
<td>1.019</td>
<td>0.925-1.122</td>
</tr>
<tr>
<td>N3 vs N0</td>
<td>0.988</td>
<td>0.883-1.105</td>
</tr>
<tr>
<td>Metastatic pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver + bone vs Liver only</td>
<td>1.181</td>
<td>1.086-1.285</td>
</tr>
<tr>
<td>Liver + brain vs Liver only</td>
<td>1.328</td>
<td>1.166-1.512</td>
</tr>
<tr>
<td>Liver + bone+ brain vs liver only</td>
<td>1.244</td>
<td>1.121-1.381</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs No/unknown</td>
<td>0.967</td>
<td>0.900-1.040</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs No/unknown</td>
<td>0.346</td>
<td>0.321-0.373</td>
</tr>
</tbody>
</table>

1 Other only includes American Indian/Alaskan Native and Asian/Pacific Islander.

HR: Hazard ratio; CI: Confidence interval; ADC: Adenocarcinoma; SCC: Squamous cell carcinoma; NSCLC: Non-small cell lung cancer.

of threshold probabilities, suggesting the substantial clinical benefit of the formulated model (Figure 4).

**Novel risk classification system construction**

A novel risk classification system for CSS was also established to classify all patients based on their individual total scores generated by the formulated nomogram scale. The system classified the patients into three risk groups of nearly equal numbers. According to the risk stratification system, the patients in the training cohort were divided into low-risk (1007/3136, 32.1%; score 0-119.9), intermediate-risk (1102/3136, 35.1%; score 120.0-199.9), and high-risk groups (1026/3136, 32.7%; score 200.0-267.0). In the training cohort, the median CSS rate of patients in the low-, intermediate-, and high-risk groups was 9.0 mo (95%CI: 8.3-9.7), 4.0 mo (95%CI: 3.7-4.3), and 1.0 mo (95%CI: 0.9-1.1), respectively (Figure 5).
Table 3 Corresponding nomogram scores of each variable

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nomogram score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>0</td>
</tr>
<tr>
<td>≥ 65</td>
<td>20.09207</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>0</td>
</tr>
<tr>
<td>Unmarried</td>
<td>9.018027</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>16.9568</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>31.70234</td>
</tr>
<tr>
<td>White</td>
<td>37.39893</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>2.971477</td>
</tr>
<tr>
<td>SCC</td>
<td>12.914657</td>
</tr>
<tr>
<td>Other NSCLCs</td>
<td>0</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>16.23500</td>
</tr>
<tr>
<td>T3</td>
<td>21.12835</td>
</tr>
<tr>
<td>T4</td>
<td>27.17024</td>
</tr>
<tr>
<td>Metastatic pattern</td>
<td></td>
</tr>
<tr>
<td>Liver only</td>
<td>0</td>
</tr>
<tr>
<td>Liver + bone</td>
<td>23.05159</td>
</tr>
<tr>
<td>Liver + brain</td>
<td>41.91404</td>
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<tr>
<td>Liver + bone + brain</td>
<td>43.49717</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No/unknown</td>
<td>100</td>
</tr>
</tbody>
</table>

Other only includes American Indian/Alaskan Native and Asian/Pacific Islander.
ADC: Adenocarcinoma; SCC: Squamous cell carcinoma.

DISCUSSION

Distant metastasis, particularly to the liver, is an important negative prognostic factor for NSCLC patients and leads to a reduction in health-related quality of life and a significant increase in cancer-related mortality. Despite recent advances in various treatment strategies, such as tyrosine kinase inhibitors and immune checkpoint blockade therapy, to prolong patient survival compared to traditional chemotherapy, NSCLC patients who present with LM are still regarded as belonging to a special subgroup whose odds of survival is slim beyond the first 8 mo after diagnosis[6,13-16]. Therefore, investigations into the prognostic factors associated with survival and the construction of feasible risk stratifications for NSCLC-LM is critical for treatment selection and prognosis assessment.

The nomogram model is a statistical tool which consists of several significant variables to estimate an individual’s prognosis in the form of a graphic display. Several nomograms for NSCLC have already
Wang JF et al. NSCLC patients with liver metastasis

Figure 2 Nomogram for predicting 3-, 6-, and 12-mo cancer-specific survival of patients presenting with liver metastases at the initial diagnosis of non-small cell lung cancer.

Figure 3 Calibration curves for predictions of cancer-specific survival at 3, 6, and 12 mo. A: Training cohort; B: Validation cohort. CSS: Cancer-specific survival.

been formulated in previous studies[17,18]. As far as we know, this is the first survival prediction nomogram developed using the data from an extensive number of NSCLC-LM from a large contemporary population-based cohort database. All predictors integrated into the model were common patient clinical variables which are readily available to clinicians. This nomogram also stratified patients into different risk subgroups, which might be meaningful and informative for individual treatments. Furthermore, these survival prediction models may be helpful for designers of clinical trials to formulate appropriate inclusion and exclusion criteria and arrange reasonable patient groups. In addition, the SEER database includes 18 registries and covers 28% of the US population, which makes our results more representative and more generalizable than other single-center studies.
In this retrospective study, we primarily explored independent prognostic factors for the CSS of NSCLC-LM patients. Several clinicopathological features, including age, sex, race, pathological type, T stage, metastatic pattern, and chemotherapy were identified that could independently affect the CSS. First, this retrospective study showed that the metastatic pattern was an important prognostic factor which independently affected the CSS of NSCLC-LM patients. In our study, the most common metastatic pattern was liver and bone, followed by liver only, liver, bone, and brain, and liver and brain. The metastatic pattern of liver, bone, and brain had a significantly higher HR for death compared to other clinicopathological variables by multivariate regression analysis (HR = 1.562, 95%CI: 1.400-1.742, \( P < 0.001 \)). Several studies have explored the association between the number of metastatic sites and the prognosis of NSCLC patients and reported that multiple organ involvement was significantly associated with poorer survival\(^5,19\). Therefore, we further divided multiple organ involvement into different metastatic patterns, and then investigated the effect of the metastatic patterns on survival time.

This study also showed that patients of younger ages (< 65 years old) had survival advantages over older patients, which was similar to previous studies. Wu et al.\(^{20}\) also found that age \( \geq 65 \) years was an independent factor affecting the survival of stage I-IIIA NSCLC patients. Two other studies explored the outcomes of immunotherapy for different age groups and found that older patients had a significantly higher HR for death than younger patients\(^{21,22}\). Subramanian et al.\(^{23}\) attributed the age-related prognostic differences to differences in the clinical characteristics, including sex, pathology, and diagnosis stage, between the younger and older patients. The organ function of the younger patients was in a relatively balanced state, which was significantly different from that of the elderly patients.
Figure 5 Kaplan–Meier curves of cancer-specific survival for patients in the training cohort according to the novel risk stratification. Low risk vs intermediate risk, \( P < 0.001 \); low risk vs high risk, \( P < 0.001 \); intermediate risk vs high risk, \( P < 0.001 \).

This also made a significant contribution to the different prognoses[24,25]. As for gender, this study revealed that female gender was a favorable prognostic factor in NSCLC, which was consistent with the results of many previous studies[26-28]. Yoshida et al[26] explained that women were prone to early-stage disease, contributing to longer survival times compared to men. Similarly, Hanagiri et al[28] also reported that 69% of the female patients were found to have NSCLC through medical tests for other diseases and 45% of the male patients were diagnosed with lung cancer-related symptoms, so there were more late male NSCLC patients than female. Interestingly, a previous study suggested that most lung adenocarcinomas occurred in the non-smoking population, whereas most of the women were non-smokers. Furthermore, the survival advantage of women with NSCLC disappeared after adjustment for the confounding factor of smoking. Thus, the main factors affecting the prognosis of lung cancer were smoking and pathological types, rather than sex[29]. We also explored the effect of marital status on the CSS of NSCLC-LM patients and found that unmarried patients were at significantly higher risk for poorer prognoses. Wu et al[30] retrospectively analyzed more than 70000 NSCLC patients and concluded that unmarried patients had shorter survival time compared to married patients, regardless of the stage of the disease. The living conditions of married patients are more stable and the interaction with and caretaking of a spouse play important roles in the physiology and psychology of patients with cancer. Most married patients receive care and support from their spouses in life and have high compliance with medical treatment and regular examinations. As for the study, our treatment revealed that the CSS was better in the chemotherapy cohort than in the non-chemotherapy cohort. We believe that this is because chemotherapy and radiotherapy were the cornerstone of lung cancer treatment strategy for advanced NSCLC before the era of molecular targeted therapy and immunotherapy and only three therapeutic measures, including surgery, chemotherapy, and radiotherapy, are included in the SEER database. However, we found that radiotherapy did not improve the survival of NSCLC-LM. This may be because most of the patients in our study had multiple organ metastases. Previous studies showed that extrahepatic metastasis, as well as the size and number of liver lesions, significantly affected the outcome of radiotherapy in NSCLC-LM[31]. Considering the stage, we found that higher T stages were significantly associated with poorer survival, whereas the N stage did not affect the prognosis, which was consistent with two previous studies[6,32]. Those studies reported that lymph node involvement was associated with a poor prognosis for patients with lung cancer, but that effect was not seen in the prognosis of NSCLC-LM, a finding not explained by clinical experience[6,32]. Multivariate analysis also demonstrated that race and histological type were independent predictors, which was also consistent with the results reported by previous studies[33-35]. Deng et al[36] demonstrated that the survival of adenocarcinoma patients was superior to that of patients with other histological types in metastatic NSCLC patients, but that study did not directly compare the survival rates of squamous cell carcinoma and adenocarcinoma patients. Wang et al[33] found that squamous cell carcinoma was a risk factor for poor prognosis compared to adenocarcinoma in localized and regional metastatic NSCLC patients, but no significant difference was found in patients with distant metastases. Interestingly, the present study showed that squamous cell carcinoma was the worst prognostic factor among histological types in NSCLC-LM. With regard to race, Lathan et al[37] reported that black patients who underwent surgical staging, but did not receive resection, had a better prognosis than their white counterparts. In our study, white patients had an inferior prognosis to black patients among those with liver involvement. The primary cause of such obvious differences between our study and those of...
others might be differences in the inclusion criteria and sample size. That is, our study indicated that the clinicopathological characteristics had different influences on the prognosis of patients with liver metastasis. All the risk factor information is easily available and deserves close attention in clinical work. Moreover, more active treatment measures should be provided to patients with these risk factors. In addition, several clinicopathological characteristics were poor indicators for patients with hepatic metastasis from NSCLC. These characteristics might be good prognostic indicators for patients with other organ involvement, which suggests that clinicians should personally evaluate the potential survival of each of their NSCLC patients.

Based on the risk factors extracted by the Cox proportional hazards model, a prognostic nomogram for predicting 3-, 6-, and 12-mo CSS in NSCLC-LM was constructed. High C-indices in the internal and external validation demonstrated perfect discrimination ability of the new model and the calibration plots revealed that the nomogram prediction agreed well with observed rates. In addition, the DCAs showed good clinical applicability of the model. All these factors ensured that the formulated model could conveniently and accurately predict patient prognosis, facilitating the formulation of effective treatment strategies or interventions. Finally, using the corresponding nomogram scores, a novel risk classification system was formulated to stratify all patients into low-, intermediate-, and high-risk groups. High-risk patient populations should receive closer attention and more rigorous follow-up in order to monitor carefully for any progression or reoccurrence and adjust treatment plan in a timely manner as changes in their condition occur. In addition, by identifying high-risk patients, palliative care, like spiritual guidance or psychological support, can be given sooner and their participation in clinical trials of anti-cancer drugs can be encouraged.

Our study was innovative and superior to other risk models and generated a reliable tool that clinicians can easily use by gathering and entering clinicopathological variables to assign patient risk and predict survival. Nonetheless, several limitations deserve attention and need to be improved. One of the main limitations resulted from the SEER dataset itself. For example, the specific clinical information of certain patients, such as chemotherapy and radiation therapy, was not always given clearly and was labeled as “no/unknown”. This did not reflect the real situation and reliable conclusions could not be drawn after statistical analysis. In addition, the absence of therapeutic regimens, including molecular targeted therapy and immunotherapy, could reduce the long-term significance of the prognostic model. Besides, the types of data accessible through the SEER program were limited. For example, there is a lack of data on changes in tumor size during the course of the disease, type of gene mutations, performance status, and the sequence of treatments. These factors might have a major impact on the prognosis of NSCLC-LM patients. Furthermore, as a retrospective study, inherent selection biases were inevitable. Finally, the constructed nomogram was validated in a subgroup of patients that met the inclusion criteria, but the strictest external validation based an independent large sample size needs to be performed.

CONCLUSION
A nomogram was constructed using several key variables and was validated as a convenient and reliable instrument for survival prediction in NSCLC-LM. Based on the prognostic nomogram, a novel risk classification system was developed and effectively identified a high-risk population, which could aid in guiding treatment strategies and prognostic evaluation for clinicians.

ARTICLE HIGHLIGHTS

Research background
The risk factors affecting the cancer-specific survival (CSS) of non-small cell lung cancer (NSCLC) patients with liver metastasis (LM) (NSCLC-LM) are not well known.

Research motivation
A nomographic chart transforms complex patient information into a visual graph, which is characterized by its excellent predictive accuracy and definite reliability when generally applied to decision-making by clinicians.

Research objectives
To build a forecasting model to predict the survival time of NSCLC-LM patients.

Research methods
Joinpoint analysis was used to estimate the incidence trend of NSCLC-LM. Cox regression was applied to identify the independent prognostic predictors of CSS. A survival prediction model was constructed
for predicting 3-, 6-, and 12-mo CSS. The predictive ability of the nomogram was estimated using calibration curves and decision curve analyses (DCAs).

**Research results**

Clinical variables including age, marital status, sex, race, histological type, T stage, metastatic pattern, and whether the patient received chemotherapy or were identified as independent prognostic factors for CSS ($P < 0.05$) and were further used to construct a nomogram. The results of DCAs and calibration curves showed that the nomogram was well-discriminated and had great clinical utility.

**Research conclusions**

A convenient and credible nomogram model was constructed, which could aid in guiding treatment strategies and prognostic evaluation for clinicians.

**Research perspectives**

Our study may serve as a reference for clinicians to identify high-risk populations for providing individualized therapy.

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**FOOTNOTES**

**Author contributions:** Wang JF and Wang S designed the study; Wang JF and Lu HD wrote the manuscript; Wang Y and Zheng R contributed to the data collection; Wang JF, Li X, and Wang S performed the statistical analysis; Li X revised the manuscript; all authors read and approved the final manuscript.

**Institutional review board statement:** The study was reviewed and approved by the Ethics Committee of the Jilin Province Tumor Hospital.

**Conflict-of-interest statement:** We have no financial relationships to disclose for this article.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Prevalence and risk factors for *Candida* esophagitis among human immunodeficiency virus-negative individuals

Yan-Hua Chen, Tzu-Ming Jao, Yow-Ling Shiue, I-Jung Feng, Ping-I Hsu

**Abstract**

**BACKGROUND**

*Candida* esophagitis (CE) is among the commonest esophageal infections and is known as an opportunistic fungal infection mostly affecting people living with the human immunodeficiency virus (HIV). However, some medical conditions might predispose HIV-negative individuals to esophageal candidiasis. The epidemiology and associated endoscopic findings of CE among people without HIV have rarely been reported.

**AIM**

To investigate the prevalence of CE among HIV-negative persons, and determine risk factors predicting CE.

**METHODS**

Between January 2015 and December 2018, all consecutive outpatients who under-
went routine esophagogastroduodenoscopy as part of health check-ups at their own expense at the Health Check-up Center of the Kaohsiung Veterans General Hospital, Taiwan, were recruited in this study. Those with positive HIV serology results were excluded. Sociodemographic and clinical characteristics including age, gender, economic status, smoking history, alcohol consumption, tea and coffee consumption, underlying diseases, body fat percentage, body mass index, endoscopic findings, and *Helicobacter pylori* infection status were carefully reviewed. CE was confirmed by endoscopic biopsy and pathological assessment with hematoxylin and eosin and periodic acid-Schiff staining. To evaluate independent factors predicting the development of CE, we conducted a univariate analysis of clinical characteristics. The variables found to be significant via univariate analysis were subsequently included in a multivariable analysis of potential risk factors for CE development.

**RESULTS**

A total of 11802 participants were included in this study. Forty-seven (0.4%) were confirmed as having CE by pathological examination. Univariate analysis identified older age, the presence of chronic kidney disease, alcohol consumption, and steroid use (\(P = 0.023, < 0.001, 0.033, \) and \(0.004, \) respectively) as significantly associated with CE. Multivariable analysis revealed older age [adjusted odds ratio (OR) = 1.027; 95%CI: 1.001-1.053; \(P = 0.045\)], chronic kidney disease (adjusted OR = 13.470; 95%CI: 4.574-39.673; \(P < 0.001\)), alcohol consumption (adjusted OR = 2.103; 95%CI: 1.151-3.844; \(P = 0.016\)), and steroid use (adjusted OR = 24.255; 95%CI: 5.343-110.115; \(P < 0.001\)) as independent risk factors for CE development. The presence of dysphagia was associated with severe CE (\(P = 0.021\)).

**CONCLUSION**

The prevalence of CE among HIV-negative persons was 0.4% in Taiwan. Independent risk factors for CE were older age, chronic kidney disease, alcohol consumption, and steroid use.

**Key Words:** *Candida* esophagitis; Prevalence; Risk factors; Human immunodeficiency virus

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**Core Tip:** *Candida* esophagitis (CE) is not only an opportunistic fungal infection affecting people living with the human immunodeficiency virus (HIV) but has also been identified in HIV-negative individuals. The prevalence of CE in Taiwan has reached 0.4% in general population, higher than previous reports. Significant risk factors include older age, chronic kidney disease, alcohol consumption, and steroid use. It is among the etiologies causing dysphagia in the general population, and esophagogastroduodenoscopy combined with histopathological examination are essential for accurate diagnosis.

**Citation:** Chen YH, Jao TM, Shieu YL, Feng IJ, Hsu PI. Prevalence and risk factors for *Candida* esophagitis among human immunodeficiency virus-negative individuals. *World J Clin Cases* 2022; 10(30): 10896-10905

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i30/10896.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i30.10896

**INTRODUCTION**

*Candida* esophagitis (CE) is a fungal infection of the esophagus caused by *Candida* species. It is one of the most common esophageal infections and is known as an opportunistic infection associated with human immunodeficiency virus (HIV) infection[1-5]. *Candida albicans* is the causative agent in most cases. Infections caused by other species such as *C. glabrata*, *C. dubliniensis*, *C. tropicalis*, *C. stellatoidea* and *C. krusei* have been reported[6,7]. In HIV-negative individuals, the prevalence of CE ranges from 0.3%-10.5%[8-11].

Some medical conditions and treatments, including the presence of malignancies, diabetes mellitus, steroids, radiation therapy, antimicrobial therapy, liver cirrhosis, acid suppression therapy, and dentures, have been associated with CE development[9,12,13]. Upper endoscopy is a sensitive and reliable method for diagnosing CE[14]. The typical endoscopic findings of CE are elevated white plaques coating the esophageal mucosa with either a nodular, linear, or confluent pattern. An endoscopic severity grading for CE has been proposed by Kodsi et al[15], Asayama et al[16] and Takahashi et al[17].
Currently, the prevalence of CE among HIV-negative individuals remains unknown in Taiwan. We aimed to investigate the prevalence of CE among HIV-negative individuals in Taiwan and determine independent risk factors for CE development in the general population.

**MATERIALS AND METHODS**

**Patients**

Between January 2015 and December 2018, all consecutive outpatients who underwent routine esophagogastroduodenoscopy (EGD) as part of health check-ups at their own expense at the Health Check-up Center of the Kaohsiung Veterans General Hospital, Taiwan, were recruited in this study. Most of these individuals were physically healthy without medical illness or signs of immunodeficiency and underwent health check-ups to rule out physical disorders, particularly malignancy. Other participants either had routine physical check-ups arranged by their employers or sought medical consultations to evaluate physical symptoms. An HIV serologic test was performed in 81% of the population. The exclusion criteria were: (1) Age < 20 years; (2) Refused biopsy for suspicious gastrointestinal tract lesions; and (3) A positive HIV serology result.

**Questionnaire**

As a routine practice at our physical examination center, every outpatient was instructed to fill out a questionnaire detailing their personal history, demographic data, medical history, as well as their history of smoking, alcohol consumption, and coffee and tea consumption. The questionnaire was designed with a mainly dichotomous manner, and the questions were divided in detail according to different functional systems of the human body. The questionnaire also captured self-reported gastrointestinal discomfort or symptoms, including acid reflux symptoms, epigastric pain, dysphagia, odynophagia, and dyspepsia.

**Study design**

Clinical data including personal information from the questionnaire, laboratory data, body weight, body mass index (BMI), body fat percentage, endoscopic findings, and histopathologic findings were collected by retrospective chart review. The endoscopy devices used for examinations from January 2015 through August 2015 were the GIF-XP260N, GIF-XQ260, GIF-Q260, and GIF-H260Z systems (Tokyo, Japan). New endoscopy systems, the GIF-H290Z and GIF-HQ290, were introduced to our department and used for endoscopic examinations from September 2015 onward. All endoscopic examinations throughout the entire study period were performed by five experienced endoscopists. Most of the endoscopic procedures were performed under conscious sedation with the administration of intravenous sedative agents by anesthesiologists. Some patients did not undergo conscious sedation because of advanced age, high risk of anesthesia complications due to underlying medical conditions, or personal reasons. If a participant underwent more than one endoscopic examination during the study period, only the results of the first examination were included in the analysis. CE was suspected when we endoscopically identified white plaques coating the esophageal mucosa that could not be washed away [18]. The endoscopic CE severity was graded according to the classification proposed by Kodsi et al [15]. The diagnosis was confirmed by endoscopic biopsy for histopathologic assessment with hematoxylin and eosin and periodic acid-Schiff staining.

**Statistical analysis**

The primary endpoint was the presence of histopathologically-confirmed CE. To identify risk factors for CE, we conducted univariate analysis with the chi-square test or Fisher’s exact test for categorical variables and two sample t test for continuous variables, to individually investigate the associations between 29 clinical variables and the presence of CE. These variables included age; gender; smoking history; alcohol consumption history; coffee, tea, and betel nuts use; underlying disease status; surgical history; systemic steroid use; Helicobacter pylori infection status; waist circumference (normal: < 90 cm for males and < 80 cm for females; obese: ≥ 90 cm for males and ≥ 80 cm for females); body fat percentage (normal: < 25% for males and < 30% for females; obese: ≥ 25% for males and ≥ 30% for females); BMI (normal: < 24; overweight: 24 ≤ BMI < 27; obese: ≥ 27); and endoscopic findings. The variables found to be statistically significant in the univariate analysis were subsequently assessed by multivariable logistic regression analysis to identify independent factors predicting CE. All statistical analyses were performed using the SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, United States). P-values less than 0.05 were considered statistically significant. The statistical methods in this study were reviewed by Dr. I-Jung Feng, Associate Professor of Biostatistics in National Sun Yat-sen University, Kaohsiung City, Taiwan.
RESULTS

Participant characteristics and endoscopic findings
During the study period, a total of 11805 participants were enrolled. Most of these individuals \((n = 7968, 67.5\% )\) were physically healthy and underwent their health check-ups to rule out physical disorders, particularly malignancies. The remaining individuals either underwent employment-related check-ups \((n = 2691, 22.8\% )\) or had sought medical consultations to evaluate physical symptoms \((n = 1146, 9.7\% )\). Of these, we excluded two participants who refused biopsy sample collection and one with a positive HIV serology result. Finally, the data of 11802 individuals \((\text{mean age}, 51.29 \pm 11.58 \text{ years}; 55.7\% \text{ male})\) were included in the analyses.

Endoscopically suspected CE was observed in 71 \((0.6\% )\) individuals, and 47 participants were confirmed to have CE \(\text{via biopsy examination}. Therefore, the overall prevalence of CE was 0.4\%. The histopathologic diagnoses of the remaining 24 participants were normal esophageal mucosa \((n = 3)\), chronic esophagitis \((n = 18)\), and glycogenic acanthosis \((n = 3)\). No dysplasia or adenocarcinoma was detected. Among the included 11802 individuals, a total of 9560 participants received HIV serology testing, and the results were negative. The prevalence of CE in the participants with negative results of HIV serology was 0.5\%.

Univariate analysis of clinical characteristics associated with CE
Table 1 shows the clinical characteristics of the subjects with and without CE. The mean age was significantly higher among individuals with CE than among those without CE. Alcohol consumption, chronic kidney disease (CKD), and steroid use were more common among participants with CE. Although men and obese individuals (defined by a high body fat percentage) were more likely to have CE than women and participants with normal body fat percentages, respectively, these differences were not statistically significant.

Multivariable analysis of independent factors predicting the development of CE
Multivariable analysis revealed older age \([\text{adjusted odds ratio (OR)} = 1.027; 95\% \text{CI}: 1.001-1.053; P = 0.045]\), CKD \((\text{adjusted OR} = 13.470; 95\% \text{CI}: 4.574-39.673; P < 0.001)\), steroid use \((\text{adjusted OR} = 24.255; 95\% \text{CI}: 5.343-110.115; P < 0.001)\), and alcohol consumption \((\text{adjusted OR} = 2.103; 95\% \text{CI}: 1.151-3.844; P = 0.016)\) as significant risk factors for CE development (Table 2).

Clinical symptoms predicting endoscopic severity
The endoscopic appearance of CE was classified as grade I to grade IV according to the Kodsi system [15]. Table 3 summarizes the association between the endoscopic severity of CE and clinical symptoms. Most of the participants were classified as grade II \((n = 29)\). Of the 47 participants with histopathologically-confirmed CE, seven had chest pain, three had abdominal pain, and one had dysphagia. None of the patients complained of globus, acid reflux, or odynophagia. The presence of dysphagia was associated with severe CE \((P = 0.021)\).

DISCUSSION

CE is the most common opportunistic gastrointestinal disorder among people living with HIV, and a low CD4+ cell count (< 200 cells/mL) is one of the most important risk factors for CE in this population [19]. However, in the HIV-negative population, CE is occasionally identified accidentally during EGD for other indications. In this study, 47 otherwise healthy subjects undergoing routine health check-ups in Taiwan were confirmed to have CE, reflecting an overall prevalence of 0.4\%. Our study also demonstrated older age, CKD, steroid use, and alcohol consumption as independent risk factors predicting the presence of CE.

The previously reported prevalence of CE in HIV-negative populations ranges from 0.3%-10.5%; these rates have tended to increase over time [17]. However, the prevalence of CE in the general population is rarely discussed. Choi et al [8] conducted a retrospective study from July 2005 through April 2011 to evaluate the prevalence of incidentally identified CE among healthy individuals in Korea, diagnosed endoscopically or histologically; they found a prevalence of 0.32\%. Another retrospective study conducted in Korea by Kim et al [9] revealed a 0.35\% prevalence of histology proven CE in a health check-up population. Recently, Ou et al [13] determined a prevalence of 0.39\% among patients undergoing EGD for various medical conditions in Taipei, Taiwan. However, most of their patients with CE were diagnosed by endoscopic findings and not confirmed histopathologically. In our study, all CE diagnoses were confirmed by histopathologic examination. The results estimate the prevalence of CE in the Taiwanese general population to be 0.4\%. We also identified older age, steroid use, alcohol consumption, and CKD as independent risk factors for CE development.

Candida albicans commonly colonizes the human gastrointestinal tract, with a variety of adhesins facilitating attachment to epithelial and endothelial surfaces [20]. Whether or not mucocutaneous
Table 1: Univariate analysis of clinical characteristics associated with *Candida esophagitis*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Yes (n = 47)</th>
<th>No (n = 11755)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (mean ± SD)</td>
<td>55.13 ± 11.73</td>
<td>51.27 ± 11.58</td>
<td>0.023</td>
</tr>
<tr>
<td>Male gender</td>
<td>32 (68.1)</td>
<td>6541 (55.6)</td>
<td>0.087</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (19.1)</td>
<td>1979 (16.8)</td>
<td>0.672</td>
</tr>
<tr>
<td>Consumption of alcohol</td>
<td>30 (63.8)</td>
<td>5674 (48.3)</td>
<td>0.033</td>
</tr>
<tr>
<td>Consumption of betel nuts</td>
<td>3 (6.4)</td>
<td>400 (3.4)</td>
<td>0.216</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>5 (10.6)</td>
<td>1520 (12.9)</td>
<td>0.640</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>3 (6.4)</td>
<td>542 (4.6)</td>
<td>0.478</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (8.5)</td>
<td>845 (7.2)</td>
<td>0.579</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>6 (12.8)</td>
<td>975 (8.3)</td>
<td>0.281</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0 (0)</td>
<td>224 (1.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>6 (12.8)</td>
<td>1376 (11.7)</td>
<td>0.821</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>4 (8.5)</td>
<td>70 (0.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Steroid use</td>
<td>2 (4.3)</td>
<td>21 (0.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Previous gastric surgery</td>
<td>0 (0)</td>
<td>3 (&lt; 0.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid reflux</td>
<td>0 (0)</td>
<td>344 (2.9)</td>
<td>0.648</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7 (14.9)</td>
<td>1549 (13.2)</td>
<td>0.729</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>0 (0)</td>
<td>200 (1.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (6.4)</td>
<td>1264 (10.8)</td>
<td>0.334</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1 (2.1)</td>
<td>134 (1.1)</td>
<td>0.525</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>0 (0)</td>
<td>7 (0.1)</td>
<td>0.867</td>
</tr>
<tr>
<td>Globus</td>
<td>0 (0)</td>
<td>25 (0.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Waist</td>
<td></td>
<td></td>
<td>0.182</td>
</tr>
<tr>
<td>Normal (&lt; 90 cm for males, &lt; 80 cm for females)</td>
<td>26 (55.3)</td>
<td>7600 (64.7)</td>
<td></td>
</tr>
<tr>
<td>Obese (≥ 90 cm for males, ≥ 80 cm for females)</td>
<td>21 (44.7)</td>
<td>4155 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Body fat percentage</td>
<td></td>
<td></td>
<td>0.081</td>
</tr>
<tr>
<td>Normal (&lt; 25% for males, &lt; 30% for females)</td>
<td>28 (59.6)</td>
<td>8347 (71.1)</td>
<td></td>
</tr>
<tr>
<td>Obese (≥ 25% for males, ≥ 30% for females)</td>
<td>19 (40.4)</td>
<td>3387 (28.9)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td>0.463</td>
</tr>
<tr>
<td>Normal (BMI &lt; 24)</td>
<td>22 (46.8)</td>
<td>6523 (55.5)</td>
<td></td>
</tr>
<tr>
<td>Overweight (24 ≤ BMI &lt; 27)</td>
<td>15 (31.9)</td>
<td>3293 (28.0)</td>
<td></td>
</tr>
<tr>
<td>Obese (27 ≥ BMI)</td>
<td>10 (21.3)</td>
<td>1939 (16.5)</td>
<td></td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td>9 (19.1)</td>
<td>2047 (17.4)</td>
<td>0.754</td>
</tr>
<tr>
<td>Endoscopic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflux esophagitis</td>
<td>7 (14.9)</td>
<td>2940 (25.0)</td>
<td>0.110</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>20 (42.6)</td>
<td>5302 (45.1)</td>
<td>0.726</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>23 (48.9)</td>
<td>4896 (41.7)</td>
<td>0.312</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>2 (4.3)</td>
<td>850 (7.2)</td>
<td>0.580</td>
</tr>
<tr>
<td>Gastric and duodenal ulcer</td>
<td>23 (48.9)</td>
<td>5179 (44.1)</td>
<td>0.501</td>
</tr>
</tbody>
</table>
Table 2 Multivariable analysis of risk factors predicting Candida esophagitis

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>Odds ratio (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.026</td>
<td>0.013</td>
<td>1.027 (1.001-1.053)</td>
<td>0.045</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2.600</td>
<td>0.551</td>
<td>13.470 (4.574-39.673)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Steroid use</td>
<td>3.189</td>
<td>0.772</td>
<td>24.255 (5.343-110.115)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.743</td>
<td>0.308</td>
<td>2.103 (1.151-3.844)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

BMI: Body mass index; ESEM: Endoscopically suspected esophageal metaplasia.

Table 3 The relationship between endoscopic severity of Candida esophagitis and clinical symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Severity (%)</th>
<th>Grade 1 (n = 11)</th>
<th>Grade 2 (n = 29)</th>
<th>Grade 3 (n = 6)</th>
<th>Grade 4 (n = 1)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td></td>
<td>3 (27.3)</td>
<td>4 (13.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.564</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>1 (9.1)</td>
<td>2 (6.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0.021</td>
</tr>
<tr>
<td>Globus</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Acid reflux</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Odynophagia</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A: Not applicable.

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invasion or systemic infection occurs depends on host and fungal factors[21]. Oral or aerosolized corticotherapy is a well-known risk factor associated with CE[22-24]. The prevalence of CE among inhaled corticosteroid users has been reported to be as high as 37%[25].

We are not the first to report alcohol consumption as an independent risk factor for CE development. Choi et al[8] and Zillessen et al[26] also identified alcohol consumption as a significant predisposing factor for CE. Recently, a retrospective study conducted at the endoscopy unit of a tertiary hospital in Mwanza, Tanzania, by Mushi et al[27] also identified that individuals with a history of alcohol consumption were at high risk of developing CE. According to previous reports, the amount of gastric acid output may be influenced by different alcohol concentrations; beverages with low ethanol content, such as beer and wine, are stimulants of gastric acid secretion, while beverages with higher ethanol concentrations, such as spirits, do not stimulate and even may decrease gastric acid secretion[28,29]. Moreover, the stomach’s adaptive capacity may change its response to alcohol in association with chronic alcoholism. Atrophic gastritis and superficial gastritis, with or without associated hyposecretion of gastric acid or achlorhydria, are more often associated with chronic alcoholism[28]. In addition, the parietal cells, which are responsible for acid secretion, decrease in number with increasing alcohol exposure[29]. Given that acid suppression therapy probably facilitating colonization of the esophagus by oral bacteria and yeast due to elevated gastric pH may contribute to the development of CE, heavy alcohol consumption may also increase the risk of CE via the same mechanism[28,30-32].

In the present study, older age was another independent risk factor associated with CE development. This finding was consistent with previous findings by Takahashi et al[17], who demonstrated advanced age as a risk factor for CE among HIV-negative patients[20]. Indeed, the aging process may attenuate the host’s ability to mount a robust or effective immune response. The underlying mechanism of impaired immunity may be associated with defects in hematopoietic bone marrow and peripheral lymphocyte migration, maturation, and function[33].

The present study also revealed CKD as an independent risk factor for CE development. This important finding has rarely been reported. Thorman et al[34] reported that oral fungal infection was significantly more prevalent among patients with end-stage renal disease (ESRD). In addition, lymphocyte numbers and the CD4/CD8 ratio are diminished in patients with ESRD. In fact, both the quantity and quality of T-cell activation are impaired in the context of chronic renal failure[35].
Furthermore, cellular mechanisms are essential in host responses to fungal infections and candidiasis at the gastrointestinal surface. Dysfunction of T-lymphocytes and a reduction in their number are typically observed in patients with mycotic diseases. Reductions in T-lymphocyte number and in the ratio of T-helper to T-suppressor cells are of critical importance for explaining diminished IgA production and enhanced adhesion of fungal cells to the surface of host cells, as well as for facilitating the intrusion of fungi throughout the skin and mucous membranes[20]. Therefore, it is reasonable to expect CKD as a risk factor for CE.

Common symptoms associated with CE include dysphagia, odynophagia, retrosternal chest pain, epigastric pain, and acid reflux symptoms[16,22]. A cross-sectional study conducted by Takahashi et al [10] found dysphagia and odynophagia as the only two symptoms predicting CE among individuals without HIV. In our study, the presenting symptoms among participants with CE were chest pain ($n = 7, 14.9\%$), abdominal pain ($n = 3, 6.4\%$) and dysphagia ($n = 1, 2.1\%$), similar to the findings mentioned above. However, none of these symptoms were significantly associated with CE according to the multivariable analysis.

The association between clinical symptoms and the endoscopic severity of CE graded by Kodsi’s classification has been investigated before. Asayama et al[16] reported that the presence of odynophagia was significantly associated with grade III and grade IV CE. In our study, none of the participants with CE presented with odynophagia. Although none of the patients with grade I to grade III CE presented with dysphagia, dysphagia was a presenting complaint in the one patient with grade IV CE.

This study has several limitations. First, its retrospective observational design means that it was subject to confounding by unmeasured variables. Second, in real-world clinical practice, some situational factors can influence the CE detection rate, such as the foregoing of endoscopic biopsy examination because of overlooked low-grade CE or misdiagnoses of CE as foreign body reactions or glycogenic acanthosis. Third, there were relatively few CE cases, making it difficult to definitively confirm associations between clinical symptoms and the endoscopic severity of CE.

CONCLUSION
In conclusion, the prevalence of CE among HIV-negative participants in this single-center cohort in Taiwan was 0.4% from 2015 through 2018. Older age, CKD, alcohol consumption, and steroid use were independent risk factors for CE development.

ARTICLE HIGHLIGHTS
Research background
Candida esophagitis (CE) is an opportunistic esophageal fungal infection mostly affecting human immunodeficiency virus (HIV)-positive people. However, some HIV-negative individuals are prone to esophageal candidiasis under certain medical conditions.

Research motivation
The definite diagnosis of CE relies on both endoscopic and histopathological findings. However, the epidemiology of CE diagnosed with strict histopathological confirmation among the general population without HIV in Taiwan has rarely been reported.

Research objectives
To update the prevalence of CE among HIV-negative persons, and identify independent risk factors predicting CE in Taiwan.

Research methods
HIV-negative outpatients who underwent routine esophagogastroduodenoscopy at the Health Check-up Center of the Kaohsiung Veterans General Hospital, Taiwan, between January 2015 and December 2018 were recruited. Sociodemographic status, clinical characteristics, and endoscopic findings were carefully reviewed. CE was confirmed by endoscopic biopsy and pathological assessment. A univariate analysis of clinical characteristics was conducted to evaluate independent factors predicting CE. Significant variables found via univariate analysis were subsequently included in a multivariable analysis of potential risk factors for CE development.

Research results
A total of 11802 participants were included in this study. The prevalence of CE confirmed by pathological examination was 0.4%. Multivariable analysis revealed older age [adjusted odds ratio (OR) = 1.027; 95%CI: 1.001-1.053; $P = 0.045$], chronic kidney disease (adjusted OR = 13.470; 95%CI: 4.574-
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39.673; \( P < 0.001 \), alcohol consumption (adjusted OR = 2.103; 95%CI: 1.151-3.844; \( P = 0.016 \), and steroid use (adjusted OR = 24.255; 95%CI: 5.343-110.115; \( P < 0.001 \) as independent risk factors for CE development.

Research conclusions
The prevalence of CE among HIV-negative population in Taiwan has reached 0.4%. Older age, chronic kidney disease, alcohol consumption, and steroid use were independent risk factors for CE.

Research perspectives
CE is not an uncommon esophageal disease among the HIV-negative population in Taiwan. Chronic kidney disease was an independent risk factor for the development of CE, which was a unique finding in our study.

FOOTNOTES

Author contributions: All authors helped to perform the research; Chen YH and Hsu PI designed the study and drafted the manuscript; Chen YH, Jao TM, Shiue YL and Feng IJ collected the data; Chen YH, Jao TM, Shiue YL and Feng IJ performed statistical analyses; Chen YH, Jao TM, Shiue YL, Feng IJ and Hsu PI revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

Supported by the In-Hospital Research Project Funding of Kaohsiung Veterans General Hospital, No. VGHKSI08-042; and An Nan Hospital, China Medical University, No. ANHRF109-38.

Institutional review board statement: This study was reviewed and approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (VGHKSI18-CT10-11).

Informed consent statement: Patients were not required to give informed consent to the study as the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

Data sharing statement: No additional data are available.

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S-Editor: Zhang H
L-Editor: Webster JR
P-Editor: Zhang H

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Retrospective Study

Prognostic impact of number of examined lymph nodes on survival of patients with appendiceal neuroendocrine tumors

Rui Du, Jiang-Wei Xiao

**Abstract**

**BACKGROUND**
The prognosis of patients with appendiceal neuroendocrine tumors (ANETs) is related to lymph node (LN) metastasis and other factors. However, it is unclear how the number of examined LNs (ELNs) impact on survival.

**AIM**
To determine the factors affecting the cancer-specific survival (CSS) of patients with ANET and to evaluate the impact of the number of ELNs on survival.

**METHODS**
A total of 4583 ANET patients were analyzed in the Surveillance, Epidemiology, and End Results database. Univariate survival analysis was used to identify factors related to survival and the optimal number of ELNs and lymph node ratio (LNR) were determined by the Kaplan–Meier method. The survival difference was determined by CSS.

**RESULTS**
Except for sex, the other factors, such as age, year, race, grade, histological type, stage, tumor size, ELNs, LNR, and surgery type, were associated with prognosis. The 3-, 5-, and 10-year CSS rates of ANET patients were 91.2%, 87.5, and 81.7%, respectively (median follow-up period of 31 mo and range of 0-499 mo). There was no survival difference between the two surgery types, namely, local resection and colectomy or greater, in both stratifications of tumor size ≥ 2 cm ($P = 0.523$) and < 2 cm ($P = 0.068$). In contrast to patients with a tumor size < 2 cm, those with a tumor size ≥ 2 cm were more likely to have LN metastasis ($\chi^2 = 378.16, P < 0.001$).

The optimal number of ELNs was more than 11, 7, and 18 for all patients, node-negative patients, and node-positive patients, respectively. CSS rates of patients with a larger number of ELNs were significantly improved ($\leq 10$ vs $\geq 11$, $\chi^2 = 20.303, P < 0.001$; $\leq 6$ vs $\geq 7$, $\chi^2 = 11.569, P < 0.001$; $\leq 17$ vs $\geq 18$, $\chi^2 = 21.990, P < 0.001$;
ANET patients with an LNR value ≤ 0.16 were more likely to have better survival than those with values of 0.17-0.48 (χ² = 48.243, P < 0.001) and 0.49-1 (χ² = 168.485, P < 0.001).

CONCLUSION
ANET ≥ 2 cm are more likely to develop LN metastasis. At least 11 ELNs are required to better evaluate the prognosis. For patients with positive LN metastasis, 18 or more LNs need to be detected and lower LNR values (LNR ≤ 0.16) indicate a better survival prognosis.

Key Words: Appendiceal neoplasm; Neuroendocrine tumors; Carcinoid tumor; Lymph node dissection; Lymph node ratio; Survival analysis

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Core Tip: This study aimed to explore factors that have an influence on survival of patients with appendiceal neuroendocrine tumors. We identified the optimal number of examined lymph nodes that could achieve the best survival for patients with appendiceal neuroendocrine tumors with different lymph node statuses. Furthermore, lymph node ratio takes both examined lymph nodes and positive lymph nodes into account. We also identified the optimal value of lymph node ratio that could achieve the best survival for node-positive patients.

Citation: Du R, Xiao JW. Prognostic impact of number of examined lymph nodes on survival of patients with appendiceal neuroendocrine tumors. World J Clin Cases 2022; 10(30): 10906-10920
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/10906.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.10906

INTRODUCTION
Carcinoid tumors were first described by some researchers[1] in 1907, and neuroendocrine tumors (NETs) were first described by some researchers[2] in 1888. NETs, historically known as carcinoid tumors, are mainly found in the gastrointestinal tract, but they can occur in multiple sites throughout the body[3]. Gastrointestinal NETs are most common in the stomach, small intestine, and pancreas, and their incidence has been reported to be steadily increasing in recent years[4]. The Surveillance Epidemiology and End Results (SEER) database estimates 3.56 cases of gastrointestinal NETs per 100,000 individuals each year[5]. Appendiceal neuroendocrine tumors (ANETs), belonging to appendiceal carcinoids, are considered a subtype of midgut NET[6], which account for almost 60% of all appendiceal tumors[7,8]. Most ANETs are found via pathological examination after appendectomy. According to a retrospective study, 29 (0.2%) of 13,863 appendectomy specimens in 10 years were histopathologically confirmed to have NETs[7]. Another study revealed that 17 (0.27%) of the 6,369 patients who underwent appendectomy had ANETs[9].

For prognosis, a previous study has shown that the 5-year overall survival (OS) of all gastrointestinal NETs is 67.2% in a cohort of 73,782 patients[10]. Another study has shown that the median survival duration is 41 mo for patients with gastrointestinal NETs, and 5- and 10-year OS rates are 39.4% and 18.1%, respectively[11]. In comparison, ANETs had a better prognosis than gastrointestinal NETs[12]. The 10-year OS has been reported to be as high as 95% (53 of 56)[13]. The survival of ANET patients is primarily determined by tumor grade and stage[14]. In 2001, an analysis of 619 cases with ANETs using Cox multivariate regression showed that age, stage, sex, and primary appendix localization are independent predictors of survival[15]. A retrospective study has shown that the lymph node (LN) status of ANET patients is related to survival[16]. However, it remains unclear whether the number of LNs detected and the positive rate are related to the prognosis.

So far, there has not detailed survival rate of patients with ANET, especially the survival rates related to different disease stages. Further, there are clinical cases diagnosed with ANETs preoperatively. The issue is what type of surgery should be chosen and how many LNs should be resected for optimal survival in this situation. The purpose of the present study was to determine the related factors that affect the cancer-specific survival (CSS) of ANET patients and the impact of the number and positive rate of LNs detected on survival and prognosis. This study also investigated whether the survival prognosis is related to tumor size, scope of resection, and other factors.
MATERIALS AND METHODS

Patients and data collection
Data were collected from the SEER database. A total of 14920 cases of appendectomy were extracted by anatomical site, and 5808 cases of NETs or carcinoid tumors were identified according to the 3rd edition of the International Classification of Diseases for Oncology. A total of 1002 cases of nonprimary and nonfirst primary appendiceal tumors were excluded. Ultimately, 4583 cases with ANETs were included.

Variables
The following variables were reviewed: Age (age at diagnosis), year (year at diagnosis), race, sex, grade (well differentiated, moderately differentiated, poorly differentiated, and undifferentiated), histological type (9 categories), tumor size (reclassified into ≤ 2 cm and > 2 cm), and stage (patients were restaged according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. “T stage” included Tx, Tis, T1 (T1a and T1b), T2, T3, and T4 (T4a, T4b, and T4). The data variables (N0, N1, N2, and Nx) of the N status were reclassified into N0 and N1. The M status in the database was transformed into the standard “M stage” by the 7th edition of AJCC, and the M0 and M1 (M1a, M1b, and M1) data variables were reclassified into M0 and M1 categories. The stage status of the disease was modified to stages I-IV. Surgery types were reclassified into local resection and colectomy or greater. Examined lymph nodes (ELN) is the exact number of LNs detected. Lymph node ratio (LNR) is the lymph node positive rate, which was calculated as the number of positive LNs divided by the number of ELNs. Survival duration was defined as the interval from the date of diagnosis to the date of death. CSS was the primary vital status (death attributable to the cancer) in this study.

Statistical analysis
Data were entered into Excel datasheets from the SEER database and then analyzed with SPSS 18.0 (IBM, Armonk, NY, United States) statistics software for Windows. Figures were created using GraphPad Prism software version 7.00 (San Diego, CA, United States). Continuous variables are expressed as the mean ± SD. Categorical data are expressed as absolute values or fractions. The Cox proportional hazards model was applied to assess the prognostic factors associated with survival, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The CSS survival curves were plotted using the Kaplan-Meier method and compared by the log-rank test. P < 0.05 was considered statistically significant. Continuous variables were also converted into categorical variables. X-tile software version 3.6.1 (Yale University, New Haven, CT, United States) was used to determine the optimal cutoff points of ELNs and LNR[17].

RESULTS

Demographic and clinicopathologic characteristics
As shown in Table 1, 4583 patients were included from 1975 to 2016, of which 57% were female, with a mean age of 44.59 years. White people were the majority race. There were four histopathological grades according to the degrees of differentiation, and 72.6% of cases were well differentiated. The mean tumor size was 17.56 mm. Most patients were at an earlier stage in terms of T, N, and M stages, and 57.36% were at stage I. On average, 16.5 LNs were examined, and the mean LNR was 0.26. The mean interval from diagnosis to the resection date was 64.57 mo.

Univariate analysis using Cox proportional hazard model
The continuous variables were transformed into classified variables. In particular, age, LNR, and number of ELNs were divided into subsections by the cutoff values determined with X-tile software [17]. Age was divided into three levels as follows: ≤ 40 years old, 41-65 years old, and ≥ 66 years old. Patients were divided into two groups according to the ELN cutoff points. All node-positive patients were divided into three levels according to LNR cutoff points as: 0 < LNR ≤ 0.16, 0.17 ≤ LNR ≤ 0.48, and 0.49 ≤ LNR ≤ 1. Histological types in few patients were ignored. For the stage and grade, we clustered them into a dichotomy as: Grade 1/2 and grade 3/4; and stage I/II and stage III/IV. CSS was significantly different between the groups for each variable by the log-rank test.

In the univariate analysis, age ≥ 66 years (HR = 16.14, 95%CI: 11.08-23.52, P < 0.001; reference: ≤ 40 years), diagnosis in 1991-2000 (HR = 4.72, 95%CI: 2.51-8.85, P < 0.001; reference: 1975-1980), Black people (HR = 1.58, 95%CI: 1.20-2.08, P = 0.02; reference: White people), female gender (HR = 1.02, 95%CI: 0.85-1.23, P = 0.80; reference: Male), grade 3/4 (HR = 19.14, 95%CI: 13.63-26.87, P < 0.001; reference: Grade 1/2), large cell neuroendocrine carcinoma (HR = 14.45, 95%CI: 10.30-20.27, P < 0.001; reference: Carcinoid tumor), tumor size > 2 cm (HR = 8.54, 95%CI: 5.99-12.17, P < 0.001; reference: ≤ 2 cm), stage III/IV (HR = 17.12, 95%CI: 11.78-24.87, P < 0.001; reference: Stage I/II), number of ELN ≤ 10 (HR = 1.75, 95%CI: 1.37-2.13, P < 0.001; reference: ≥ 11), LNR = 0.49-1 (HR = 7.70, 95%CI: 5.38-11.01, P < 0.001; reference: 0-0.16), and surgery of colectomy or greater (HR = 3.47, 95%CI: 1.95-6.17, P < 0.001; reference:...
Table 1 Demographics and clinicopathologic characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>mean ± SD/n (%)</th>
</tr>
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<td>mean ± SD, yr</td>
<td>44.59 ± 18.15</td>
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<td></td>
<td>1991-2000</td>
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<tr>
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<tr>
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<td>1972 (43)</td>
</tr>
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<td>2611 (57)</td>
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<td>Grade</td>
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<td>1857 (72.59)</td>
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<tr>
<td></td>
<td>Grade 2</td>
<td>408 (15.96)</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>248 (9.69)</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
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<td>Goblet cell carcinoid</td>
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<td>Adenocarcinoid tumor</td>
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<tr>
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<td>Neuroendocrine carcinoma</td>
<td>419 (9.14)</td>
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<td>Atypical carcinoid tumor</td>
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<td>Tumor size</td>
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<td></td>
<td>II</td>
<td>504 (23.70)</td>
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<td></td>
<td>III</td>
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<td></td>
<td>IV</td>
<td>133 (6.25)</td>
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<td>Tis</td>
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<td></td>
<td>T2</td>
<td>194 (8.70)</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>446 (20.01)</td>
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<tr>
<td></td>
<td>T4</td>
<td>204 (9.15)</td>
</tr>
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<td>M0</td>
<td>2094 (94.07)</td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>132 (5.93)</td>
</tr>
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<td>N1</td>
<td>569 (18.24)</td>
</tr>
<tr>
<td>Surgery</td>
<td>Local resection</td>
<td>405 (10.34)</td>
</tr>
<tr>
<td></td>
<td>Colectomy or greater</td>
<td>3513 (89.66)</td>
</tr>
</tbody>
</table>
ELNs: Examined lymph nodes; LNR: Lymph node ratio (the ratio of positive lymph nodes to the total lymph nodes examined).

Local resection) were predictors of poor CSS. The results are shown in Table 2.

Survival analysis of ANET patients at different disease stages
For the whole cohort, the median follow-up time was 31 mo (range, 0-499 mo), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 91.2%, 87.5%, and 81.7%, respectively. We calculated the 3-, 5-, and 10-year CSS rates of patients at each stage, and the rate decreased as the stage increased as shown in Table 3. The 10-year CSS rates and most median CSS times were unknown. We also plotted the survival curve for all patients (Figure 1A) and curves based on the four stages (Figure 1B).

Impact of tumor size and surgery on survival of ANET patients
Tumor size > 2 cm is generally considered to be an important prognostic factor for patients with ANETs, and it may also affect the choice of surgery. According to the North American Neuroendocrine Tumor Society (NANET) guidelines, > 2 cm is one of the criteria for right hemicolectomy (RHC) for ANET patients.[18] The European Neuroendocrine Tumor Society (ENETS) guidelines also recommend aggressive surgery for ANET patients with tumors > 2 cm due to the risk of recurrence and metastasis. In addition, tumor stratification is partly according to tumor size.[19] In the present study, we divided the tumor size and surgery into two categories. Univariate analysis suggested that there was a significant survival difference between tumor sizes and different surgeries by the log-rank test ($P < 0.001$). The survival curves are shown in Figure 2. Patients with tumors ≤ 2 cm and who underwent local resection had better survival compared to the other categories. To determine whether survival differences exist between surgical methods in patients with different tumor sizes, we also conducted a survival analysis of two surgeries but divided the patients into two stratifications by tumor size. There were 225 patients undergoing local resection and 1468 patients undergoing colectomy or greater with tumor size ≤ 2 cm, while there were 21 patients undergoing local resection and 584 patients undergoing colectomy or greater with tumor size > 2 cm (Figure 3A). The log-rank test showed that there was no significant difference in both tumor size between the two surgeries ($P = 0.068$, Figure 3B; $P = 0.523$, Figure 3C). The data analysis showed that when the tumor size was less than 2 cm, there was no survival benefit due to expansion surgery (Figure 3B). Therefore, for ANETs less than 2 cm, right hemicolectomy should be carefully selected. According to our analysis results, when tumors were larger than 2 cm, the two different surgical methods did not show the expected survival difference (Figure 3C), but only 21 patients with tumors larger than 2 cm chose local resection, which may have produced statistical bias.

LN invasion associated with tumor size
Small ANETs are generally considered to be benign, and LN metastasis is rarely reported for tumors smaller than 2 cm.[18] There is a clearly increased risk of LN metastasis for ANETs > 2 cm,[19] and the risk is up to 40%.[20] In addition, a tumor diameter of 2 cm has been suggested to be associated with LN metastasis. To confirm this in our cohort, 2202 patients were divided into two categories according to both tumor sizes and LN status (Table 4). There were a total of 1837 (85.1%) node-negative patients and 329 (14.9%) node-positive patients. For all 1613 patients with tumor size ≤ 2 cm, there were 1516 (94.0%) node-negative patients and only 97 (6.0%) node-positive patients. For all 589 patients with tumor size > 2 cm, there were 357 (60.6%) node-negative patients and 232 (39.4%) node-positive patients. The chi-squared test showed that there was a significant difference in LN metastasis between patients with different tumor sizes ($\chi^2 = 378.16, P < 0.001$). Patients with tumor size > 2 cm were more likely to be susceptible to LN metastasis (Figure 4).

Impact of number of ELNs on survival
We used X-tile software to identify the optimal number of ELNs that generated the greatest survival difference. For the entire cohort, 11 LNs was the optimal number of ELNs that generated the greatest survival difference ($\chi^2 = 20.303, P < 0.001$). The cutoff point was 7 LNs ($\chi^2 = 11.569, P = 0.001$) for node-negative patients and 18 LNs ($\chi^2 = 21.990, P < 0.001$) for node-positive patients. We further calculated the 3-, 5-, and 10-year CSS rates for patients based on LN status and different numbers of ELNs (Table 5).

Survival analysis of optimal number of ELNs for all patients
For two categories divided by the ELN cutoff point of all patients, the median follow-up of patients with
### Table 2 Univariate analysis using Cox proportional hazard model

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>HR</th>
<th>95% CI</th>
<th>Log-rank P value</th>
</tr>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
<td></td>
<td>41-65 yr</td>
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<td>5.09-10.32</td>
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</tr>
<tr>
<td></td>
<td>≥ 66 yr</td>
<td>16.14</td>
<td>11.08-23.52</td>
<td></td>
</tr>
<tr>
<td>Year</td>
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<td>-</td>
<td>-</td>
<td><em>P &lt; 0.001</em></td>
</tr>
<tr>
<td></td>
<td>1981-1990</td>
<td>3.06</td>
<td>1.56-6.01</td>
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<tr>
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<td>1991-2000</td>
<td>4.72</td>
<td>2.51-8.85</td>
<td></td>
</tr>
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<td>2001-2010</td>
<td>3.83</td>
<td>2.09-7.02</td>
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<td>2011-2016</td>
<td>1.84</td>
<td>0.98-3.43</td>
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<td>-</td>
<td><em>P = 0.02</em></td>
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<td></td>
<td>Other</td>
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<td>0.73-1.83</td>
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<td></td>
<td>Black</td>
<td>1.58</td>
<td>1.20-2.08</td>
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<tr>
<td>Sex</td>
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<td>-</td>
<td>-</td>
<td><em>P = 0.80</em></td>
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<td>Female</td>
<td>1.02</td>
<td>0.85-1.23</td>
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</tr>
<tr>
<td>Grade</td>
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<td>-</td>
<td><em>P &lt; 0.001</em></td>
</tr>
<tr>
<td></td>
<td>Grade 3/4</td>
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<td>13.63-26.87</td>
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<tr>
<td>Histological type</td>
<td>Carcinoid tumor</td>
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<td>-</td>
<td><em>P &lt; 0.001</em></td>
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<tr>
<td></td>
<td>Neuroendocrine carcinoma</td>
<td>2.36</td>
<td>1.44-3.88</td>
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<td></td>
<td>Goblet cell carcinoid</td>
<td>4.98</td>
<td>3.61-6.87</td>
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<td>Adenocarcinoid tumor</td>
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<td>4.89-9.64</td>
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<td>Tumor size</td>
<td>≤ 2 cm</td>
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<td>-</td>
<td><em>P &lt; 0.001</em></td>
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<tr>
<td></td>
<td>&gt; 2 cm</td>
<td>8.54</td>
<td>5.99-12.17</td>
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<tr>
<td>Stage</td>
<td>I/II</td>
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<td>III/IV</td>
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<td>11.78-24.87</td>
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<td>-</td>
<td><em>P &lt; 0.001</em></td>
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<tr>
<td></td>
<td>T2</td>
<td>5.16</td>
<td>1.29-20.64</td>
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<td>T3</td>
<td>17.25</td>
<td>6.09-48.81</td>
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<td>T4</td>
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<td>43.03-320.55</td>
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<tr>
<td>M stage</td>
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<td>-</td>
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</tr>
<tr>
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<td>M1</td>
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<td>N stage</td>
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<td>-</td>
<td>-</td>
<td><em>P &lt; 0.001</em></td>
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<tr>
<td></td>
<td>N1</td>
<td>8.44</td>
<td>6.69-10.65</td>
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<tr>
<td>Surgery</td>
<td>Local resection</td>
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<td>Colectomy or greater</td>
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<td>ELNs</td>
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<td>≤ 10</td>
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<td>2.25-4.64</td>
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<td>0.49-1</td>
<td>7.70</td>
<td>5.38-11.01</td>
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ELNs: Examined lymph nodes; LNR: Lymph node ratio (the ratio of positive lymph nodes to the total lymph nodes examined).
### Table 3 The 3-, 5-, and 10-yr cancer-specific survival rates for patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>3-yr, %</th>
<th>5-yr, %</th>
<th>10-yr, %</th>
<th>Follow-up, mo</th>
<th>Median follow-up, mo</th>
<th>Median survival time, mo</th>
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<td>87.5</td>
<td>81.7</td>
<td>0-499</td>
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<td>-</td>
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<td>99.7</td>
<td>-</td>
<td>0-83</td>
<td>23</td>
<td>-</td>
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<td>Stage II</td>
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<td>95.5</td>
<td>-</td>
<td>0-83</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>Stage III</td>
<td>89.0</td>
<td>82.0</td>
<td>-</td>
<td>0-82</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>Stage IV</td>
<td>42.0</td>
<td>25.1</td>
<td>-</td>
<td>0-83</td>
<td>23</td>
<td>30</td>
</tr>
</tbody>
</table>

Median survival is unavailable when there were not half patients dead at the cutoff date.

### Table 4 Fourfold contingency table of tumor size and lymph node status

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>LN status</th>
<th>N0</th>
<th>N1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 cm</td>
<td></td>
<td>1516 (94.0)</td>
<td>97 (6.0)</td>
<td>1613 (100)</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
<td></td>
<td>357 (60.6)</td>
<td>232 (39.4)</td>
<td>589 (100)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1873 (85.1)</td>
<td>329 (14.9)</td>
<td>2202 (100)</td>
</tr>
</tbody>
</table>

LN: Lymph node.

### Table 5 The 3-, 5-, and 10-yr cancer-specific survival rates by lymph node status and cutoff points of examined lymph nodes

<table>
<thead>
<tr>
<th>Patients</th>
<th>ELNs</th>
<th>3-yr, %</th>
<th>5-yr, %</th>
<th>10-yr, %</th>
<th>Follow-up, mo</th>
<th>Median follow-up, mo</th>
<th>Median survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>≤ 10</td>
<td>83.2</td>
<td>76.1</td>
<td>67.9</td>
<td>0-306</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>≥ 11</td>
<td>90.3</td>
<td>85.5</td>
<td>79.1</td>
<td>0-347</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>Node-negative</td>
<td>≤ 6</td>
<td>94.9</td>
<td>86.5</td>
<td>79.3</td>
<td>0-306</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>≥ 7</td>
<td>98.1</td>
<td>95.4</td>
<td>90.1</td>
<td>0-326</td>
<td>43</td>
<td>-</td>
</tr>
<tr>
<td>Node-positive</td>
<td>≤ 17</td>
<td>60.7</td>
<td>50.0</td>
<td>40.6</td>
<td>0-345</td>
<td>31</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>≥ 18</td>
<td>78.4</td>
<td>71.5</td>
<td>61.4</td>
<td>0-347</td>
<td>35</td>
<td>-</td>
</tr>
</tbody>
</table>

Median survival is unavailable when there were not half patients dead at the cutoff date. ELNs: Examined lymph nodes.

≤ 10 ELNs was 36 mo (range, 0-306 mo), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 83.2%, 76.1%, and 67.9%, respectively. For patients with ≥ 11 ELNs, the median follow-up was 38 mo (range, 0-347 mo), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 90.3%, 85.5%, and 79.1%, respectively. The Kaplan–Meier survival curve based on ELN cutoff points was plotted (Figure 5A). Among all patients, patients with ≥ 11 ELNs had a better CSS than patients with ELNs ≤ 10 (χ² = 20.303, P < 0.001). The results suggested that the number of LNs detected should be greater than or equal to 11 for a better survival and prognosis.

**Survival analysis of optimal number of ELNs for node-negative patients**

Considering node-negative patients, patients with ELNs ≤ 6 had a median follow-up of 28 mo (range, 0-306 mo), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 94.9%, 86.5%, and 79.3%, respectively. For patients with ELNs ≥ 7, the median follow-up was 43 mo (range, 0-326 mo), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 98.1%, 95.4%, and 90.1%, respectively. We plotted survival curves based on ELN cutoff points of ≤ 6 and ≥ 7 for node-negative patients (Figure 5B). Patients with ELNs ≥ 7 had a better CSS (χ² = 11.569, P < 0.001). The results suggested that the number of LNs detected in node-negative ANET patients is preferably greater than or equal to 7 for a better survival.
Survival analysis of optimal number of ELNs for node-positive patients

For the node-positive patients, patients with ELNs ≤ 17 had a median follow-up of 31 mo (range, 0-345 mo), and the median CSS time was 60 mo. The 3-, 5-, and 10-year CSS rates were 60.7%, 50.0%, and 40.6%, respectively. For patients with ELNs ≥ 18, the median follow-up was 35 mo (range, 0-347 mo), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 78.4%, 71.5%, and 61.4%, respectively. Kaplan–Meier survival curves based on ELN cutoff points for node-positive patients were plotted (Figure 5C). Patients with ELNs ≥ 18 had a better CSS than patients with ELNs ≤ 17 ($\chi^2 = 24.464$, $P < 0.001$). The results suggested that the number of LNs detected in node-positive ANET patients is preferably greater than or equal to 18 for a better survival and prognosis.

Survival analysis of optimal LNR

We found that 0.16 was the optimal cutoff point of LNR that generated the greatest survival difference for node-positive patients. The log-rank test showed that there were survival differences among the three stratifications divided by two cutoff values of LNR ($\chi^2 = 160.406$, $P < 0.001$). We calculated the 3-, 5-, and 10-year CSS rates for all node-positive patients by different LNRs (Table 6). For all node-positive patients, the median follow-up was 33 mo (range, 0-347 mo), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 67.3%, 58.4%, and 48.9%, respectively. For the three stratifications divided by the LNR cutoff points, the median follow-up of patients with an LNR ≤ 0.16 was 45 mo (range, 0-347 mo), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 88.5%, 80.8%, and 68.9%, respectively. For patients with an LNR between 0.17 and 0.48, the median follow-up was 32 mo (range, 1-345 mo), and the median CSS time was 46 mo. The 3-, 5-, and 10-year CSS rates were 59.7%, 46.2%, and 37.4%, respectively. For patients with an LNR ≥ 0.49, the median follow-up was 16 mo (range, 0-203 mo), and the median CSS time was 18 mo. The 3-, 5- and 10-year CSS rates were 24.7%, 17.7%, and 14.2%, respectively.

LNR ≤ 0.16 was associated with a better CSS. Kaplan–Meier survival curves based on the LNR cutoff points were plotted (Figure 6). Survival differences existed between patients with an LNR ≤ 0.16 and those with an LNR between 0.17 and 0.48 ($\chi^2 = 48.243$, $P < 0.001$), between patients with an LNR between

Figure 1 Survival curves for all patients and patients at different disease stages. A: Survival for all patients; B: Survival for patients at different stages.

Figure 2 Survival curves by tumor size and surgery type. A: Survival by tumor size; B: Survival by different surgeries.
### Table 6 The 3-, 5-, and 10-yr cancer-specific survival rates for node-positive patients based on lymph node ratio cutoff points

<table>
<thead>
<tr>
<th>LNR</th>
<th>3-yr, %</th>
<th>5-yr, %</th>
<th>10-yr, %</th>
<th>Follow-up, mo</th>
<th>Median follow-up, mo</th>
<th>Median survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>67.3</td>
<td>58.4</td>
<td>48.9</td>
<td>0-347</td>
<td>33</td>
<td>-</td>
</tr>
<tr>
<td>0.016</td>
<td>88.5</td>
<td>80.8</td>
<td>68.9</td>
<td>0-347</td>
<td>45</td>
<td>-</td>
</tr>
<tr>
<td>0.17-0.48</td>
<td>59.7</td>
<td>46.2</td>
<td>37.4</td>
<td>1-345</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>0.49-1</td>
<td>24.7</td>
<td>17.7</td>
<td>14.2</td>
<td>0-203</td>
<td>16</td>
<td>18</td>
</tr>
</tbody>
</table>

Median survival is unavailable when there were not half patients dead at the cutoff date. LNR: Lymph node ratio (the ratio of positive lymph nodes to the total lymph nodes examined).

#### DISCUSSION

ANETs are mostly discovered coincidentally during appendectomy and usually have a benign clinical course. As the major form of appendiceal neoplasms, ANETs are rare appendiceal neoplasms[21]. These tumors are generally confirmed by pathological examination in appendectomy specimens[22]. In the ENETS guidelines, tumor size (including T class), localization within the appendix, extent of invasion into the mesoappendix, and vascular invasion are the main prognostic features. Tumor size, mesoappendiceal invasion, tumor grade, tumor location, and angioinvasion or lymphatic invasion are considered as risk factors that may be associated with disease course and therapy methods[20]. Under

0.17 and 0.48 and those with an LNR ≥ 0.49 ($\chi^2 = 26.908, P < 0.001$), as well as between patients with an LNR ≤ 0.16 and those with an LNR ≥ 0.49 ($\chi^2 = 168.485, P < 0.001$). Compared to patients with an LNR ≥ 0.17, patients with an LNR ≤ 0.16 were more likely to have a better survival. Thus, LNR ≤ 0.16 may be the critical point for determining the better survival prognosis of ANET patients.
Du R et al. ELN impact on survival of ANET patients

Figure 4 Lymph node status according to tumor size. The chi-squared test showed significant difference ($\chi^2 = 378.16, P < 0.001$).

Figure 5 Survival curves by cutoff points of examined lymph nodes. A: All patients; B: Node-negative patients; C: Node-positive patients. ELN: Examined lymph nodes.

some circumstances, RHC should be considered as an additional operation after appendectomy in 3 mo [19,23,24]. The NANET and ENETS guidelines show that tumor size is closely related to the survival, and the prognosis of patients with tumors ≥ 2 cm is worse. Moreover, deep invasion, regional metastasis, and LN metastasis are also related to tumor size [18]. Abdelaal et al [12] reviewed 32 appendectomy specimens that were histologically confirmed as NETs and indicated that appendectomy is an adequate surgical method for patients with tumors smaller than 2 cm with negative pathological margins. Bamboat and Berger [25] reported on five patients with tumors greater than 2 cm and four of the patients were treated by secondary RHC following appendectomy, and they were all alive with a mean follow-up of 10 years (range, 1-15 years). Moertel et al [26] studied 150 patients with ANETs; LN metastasis was observed in 7 (30.43%) of 23 patients with tumors ≥ 2 cm, while no LN metastasis was observed in 123 patients with tumors < 2 cm. Mullen et al [27] reported that LN metastases were present in 44 of 89 patients (49%), including 4 of 27 patients (15%) with tumors ≤ 1.0 cm, 16 of 34 patients (47%) with tumors between 1.0 cm and 2.0 cm, and 24 of 28 patients (86%) with tumors > 2.0 cm, and they
concluded that increasing tumor size predicts LN involvement.

Tumor size > 2 cm is the most accepted risk factor, but it remains controversial. According to published data, the cutoff value of tumor size related to LN involvement is 1.55 cm [28]. Rault-Petit et al. [29] suggested that 1.95 cm is the optimal cutoff value of tumor size to predict LN status of ANETs. Mehrvarz Sarshkeheh et al. [16] suggested that 1 cm is a more appropriate cutoff than 2 cm for predicting LN metastasis. Kleiman et al. [30] performed a retrospective study of 79 patients and noted that tumors < 2 cm with small-vessel invasion had similar metastatic potential as those ≥ 2 cm. Except, histology is also a significant LN metastasis predictor [31]. Pawa et al. [32] suggested that the differentiation grade may be associated with LN metastasis because all G2 and G3 patients have regional LN metastasis. Brighi et al. [28] reported that G2 and lymphovascular infiltration are related to LN involvement other than tumor size > 1.55 cm. Carr et al. [33] suggested that patients with tumors ≥ 2 cm but with subserosa or mesoappendix invasion, lymphovascular invasion, or increased mitotic activity (> 2 mitoses per 50 high-power fields) are at risk for LN or distant metastasis in some cases. For tumor size and LN metastasis in the present study, patients with tumors > 2 cm had a LN metastasis rate of 39.4% compared to the rate of 6.0% in patients with tumors ≤ 2 cm. The χ² test showed that there was statistical significance, indicating that tumor size > 2 cm is a factor associated with LN metastasis. At present, there is no factor or rule that completely and accurately predicts LN metastasis. Until additional evidence becomes available, our data analysis combined with the results of most research suggest that tumor larger than 2 cm is still considered to be an important risk factor for LN metastasis.

In terms of treatment, the ENETS guidelines recommended that patients with a tumor diameter > 2 cm should be treated by RHC [20]. However, a substantial number of patients may not receive appropriate surgical resection despite the current treatment recommendations. A population-based retrospective study has suggested that 28% of ANET patients with tumors > 2 cm do not undergo RHC, whereas 3.47% with tumors > 2 cm did not undergo RHC in the present study [34]. For patients with tumors > 2 cm, 96.53% of them underwent colectomy or greater surgery, and 86.71% of patients with tumors ≤ 2 cm underwent colectomy or greater surgery. Thus, these findings suggested that it is not appropriate to perform colectomy or greater surgery only on the basis of tumor size. Grozinsky-Glasberg et al. [33] suggested that when using the latest ENETS criteria for RHC, the risk of residual disease is high in patients with a primary tumor size of 1-2 cm, and residual disease may be missed in 18% of ANET patients because pathological factors are ignored. Univariate survival analysis showed that there was a significant difference between patients with tumors > 2 cm and ≤ 2 cm in the present study, but there was no survival difference between the two surgeries stratified according to tumor size. Mehrvarz Sarshkeheh et al. [16] suggested that differentiation grade and LN involvement are associated with prognosis irrespective of surgery type. Groth et al. [31] reported that there is no significant difference in the survival rate between hemicolectomy and appendectomy. Similar results were obtained in our study for patients with tumors ≤ 2 cm and > 2 cm. Colectomy or greater resection did not statistically improve the outcome, but there was a better survival rate for patients with tumors ≤ 2 cm and patients who underwent local resection. Importantly, 74.78% of patients with tumors ≤ 2 cm underwent colectomy or greater resection, indicating that some patients do not undergo proper surgical treatment and that colectomy or greater resection should be strictly applied, especially for those patients with tumors ≤ 2 cm. Volante et al. [36] suggested that RHC recommended by the NANET/ENETS guidelines should be followed even though there is no survival difference. Our data analysis showed that when the tumor size was less than 2 cm, there was no survival benefit due to expansion surgery. Therefore, for ANETs less than 2 cm, right hemicolectomy should be carefully selected. According to our analysis results, when the tumor was larger than 2 cm, the two different surgical methods did not show the expected survival difference. However, only 21 patients with tumors larger than 2 cm chose
local resection, which may have produced statistical bias. Thus, our findings suggested that it is inappropriate to perform colectomy or larger surgery based only on the size of the tumor. Therefore, we inferred that the survival benefits of the different surgical methods are not due to the choice of surgical methods but instead are due to the difference in the size of the tumor. Because most patients with tumors larger than 2 cm tend to choose colectomy, the prognosis of such patients is inherently worse than that of patients with tumors smaller than 2 cm. Therefore, the observation that patients who choose colectomy has a worse prognosis than those undergoing local resection is probably not caused by the choice of surgical method but by the size and stage of the tumor itself. Combined with the recommendations of guidelines, most studies and our data analysis suggest that patients with tumors larger than 2 cm are more inclined to choose colon resection and that it is unnecessary to blindly expand the scope of surgical resection for patients with tumors ≤ 2 cm.

ANETs are often thought to have good outcomes, and the 10-year survival rate has been reported to reach up to 95%. A previous study has reviewed 83 ANET patients diagnosed during 1976-1987 and indicated that 53 of 56 (94.6%) were alive[13]. A retrospective study has revealed that the 5-year survival rate of 17 patients with ANETs was as high as 100%[9]. A recent retrospective study with a larger sample reported a low CSS rate. In the present study, the survival data indicated that the 10-, 5-, and 3-year CSS rates were 81.7%, 87.5%, and 91.2%, respectively. Moreover, our analysis also calculated survival rates based on disease stage to obtain additional details for the 3- and 5-year CSS rates of patients with disease stages I-IV. The highest 3-year rate was 99.7% for stage I, and the lowest 5-year rate was 25.1% for stage IV.

LN metastasis is often thought to be associated with poor outcomes. Node-positive patients have a significantly worse survival rate even though patients have undergone hemicolectomy and have 12 ELNs[31]. Similar results have been confirmed in another study, which indicated that survival is markedly worse despite RHC being conducted in mixed adenoneuroendocrine carcinoma patients with LN metastasis[16]. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology recommend that 12 LNs should be evaluated at least in colorectal cancer to allow patients to be pathologically assessed accurately and optimally staged based on adequate resected LNs[37]. However, to date, few studies have focused on the impact of the optimal number of ELNs on survival of patients with ANETs. We divided all patients into two groups according to the number of ELNs, and the most significant survival difference existed between patients with ELNs ≤ 10 and those with ELNs ≥ 11. For a certain lymph status, node-negative patients with ELNs ≥ 7 had the most significant survival difference and ≥ 18 for node-positive patients. The optimal number of ELNs may be transformed into LNs and should be surgically retrieved after further confirmation in the future, especially for patients suspiciously diagnosed as having ANETs preoperatively. Except for tumor size, more factors should be taken into account and more detailed criteria should be adopted to choose a surgery type for ANET patients.

The LN status of most malignancies has long been categorized according to the number of metastatic LNs in the AJCC TNM system[38]. However, the number of LNs to be examined often has an influence on the number of metastatic LNs pathologically confirmed. Moreover, the LNR is considered a better prognostic determinant than the number-based LN staging system for colon cancer[39]. The LNR takes both ELNs and positive LNs into account. There is no unified criterion that has been established for LNR stratification of ANETs. The use of quartiles may be the most prevalent method and has been applied in diverse studies. With X-tile software, we adopted 0.16 and 0.48 as cutoff points to divide patients into three groups. The 3-, 5-, and 10-year CSS rates significantly increased with a lower ratio (≤ 0.16). To some extent, the present study agreed with the study by Vaccaro et al[40], who found that colon cancer patients with an LNR < 0.25 have better survival. Lee et al[39] also suggested that an LNR < 0.11 is associated with a significantly better 5-year disease-free survival. Shinto et al[41] mentioned that patients with a low LNR have a higher 5-year CSS rate; the LNR cutoff is 0.18 for all colon cancer patients and 0.16 and 0.22 for right and left colon cancer patients, respectively. The LNR cutoff of ANETs in the present study was similar to the values proposed by other studies. For node-positive patients, LNR ≤ 0.16 increased the 3-, 5-, and 10-year CSS rates from 67.3%, 58.4%, and 48.9% to 88.5%, 80.8%, and 68.9%, respectively. Our analysis results suggested that higher LNR results in a worse survival prognosis. Thus, LNR ≤ 0.16 may be the critical point for determining a better survival prognosis of patients with ANETs.

CONCLUSION

In summary, the univariate survival analysis conducted in the present study showed that most factors are related to survival. Patients with tumor size > 2 cm are more likely to develop LN invasion and metastasis with a worse prognosis. Regarding the choice of surgical methods, for patients with tumors ≤ 2 cm, there is no need to blindly expand the scope of surgical resection. Higher positive rate of LN metastasis in patients with ANETs result in a worse survival prognosis. The optimal number of ELNs for all patients, node-negative patients, and node-positive patients is 11, 7, and 18, respectively. LNR ≤ 0.16 may be the key point for determining a better survival prognosis of patients with ANETs.
ARTICLE HIGHLIGHTS

Research background
Appendiceal neuroendocrine tumors are often confirmed by pathological examination after appendicectomy. It is unclear how many lymph nodes should be surgically removed for neuroendocrine tumors occurring in the appendix so that the patients could achieve a better survival.

Research motivation
Detailed survival rates of patients with appendiceal neuroendocrine tumors are not clear, especially for those with different disease stages and lymph statuses. The relationship between different numbers of examined lymph nodes and survival rates for appendiceal neuroendocrine tumors has not been described.

Research objectives
With data of 4583 patients with appendiceal neuroendocrine tumors, the study aimed to describe factors that could have an effect on patients survival and survival rates for different disease stages, to verify whether it is reliable to choose surgery type only according to tumor size and the relationship between tumor size and lymph metastasis, and to determine the optimal number of examined lymph nodes and the optimal lymph node positive rate for patients with appendiceal neuroendocrine tumors.

Research methods
This retrospective study included patients with appendiceal neuroendocrine tumors who underwent surgical resection in the SEER database. The clinical characteristics were described. X-tile software was used to determine the optimal cutoff points. Cancer-specific survival curves were plotted using the Kaplan–Meier method and survival differences were estimated by the log-rank test.

Research results
Blindly expanding the scope of surgical resection did not bring survival benefits. There were optimal cutoff points of examined lymph nodes and lymph node positive rate that could bring a better survival.

Research conclusions
The optimal numbers of examined lymph nodes are different according to lymph node status.

Research perspectives
More appendiceal neuroendocrine patients with tumors larger than 2 cm but undergoing local resection can be contrasted to those undergoing colectomy or greater resection in future. The optimal values of examined lymph nodes and lymph node positive rate can be further determined if more factors are taken into account.

FOOTNOTES

Author contributions: Xiao JW conceived the study; Du R collected, performed, and analyzed the data, and wrote the paper; Xiao JW and Du R carried out the data statistical processing and revised the paper; and All authors reviewed the results and approved the final version of the manuscript.

Institutional review board statement: The study was approved by the ethics committee of the First Affiliated Hospital of Chengdu Medical College.

Informed consent statement: The requirement for informed consent was waived by the committee because of the retrospective nature of the study.

Conflict-of-interest statement: All authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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Country/Territory of origin: China
REFERENCES


Observational Study

Clinical and epidemiological features of ulcerative colitis patients in Sardinia, Italy: Results from a multicenter study

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Specialty type: Gastroenterology and hepatology
Provenance and peer review: Unsolicited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report’s scientific quality classification
Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Ogundipe OA, United States; Osawa S, Japan; Osawa S, Japan; Ogundipe OA, United States

Received: August 9, 2021
Peer-review started: August 9, 2021
First decision: August 29, 2021
Revised: September 6, 2021
Accepted: August 22, 2022
Article in press: August 22, 2022
Published online: October 26, 2022

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Abstract

BACKGROUND
There are little data on the epidemiological and clinical features of adult patients with ulcerative colitis (UC) in the different Italian regions, mainly derived from the absence of a national registry. This prevents correct interpretation of the disease burden.

AIM
To assess the main clinical and epidemiological features of adult patients diagnosed with UC in Sardinia, Italy.

METHODS
We performed a multicenter, observational, cross-sectional study that included adult patients with UC enrolled in seven gastroenterology unit centers in Sardinia. Data were obtained from the patients’ medical records and from a questionnaire administered at the inclusion visit.

RESULTS
Four hundred and forty-two patients with UC were included. The median age at diagnosis was 39 years (interquartile range 28-48). After a median disease duration of 10 years, 53 patients experienced proximal extension of proctitis or left-sided colitis. Seventy-five patients developed extraintestinal manifestations. Nineteen patients (4.3%) developed cancer: two with colorectal cancer and seventeen with extracolonic cancers. Mesalazine (5-ASA) remains the mainstay of treatment for UC. Overall, 95 patients (21.5%) were treated with one or more biologic agents, whereas 15 patients (3.4%) underwent surgery, mostly colectomy.

CONCLUSION
Our results provide important insights into the clinical and epidemiological features of patients with UC, and while waiting for a national Italian registry, present eligible data on the UC population in Sardinia.

Key Words: Inflammatory bowel disease-basic; Inflammatory bowel disease-clinical; Ulcerative colitis; Epidemiology; Natural history; Treatment

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INTRODUCTION
Inflammatory bowel disease (IBD), which includes Crohn’s disease (CD) and ulcerative Colitis (UC), are
ch~rnic-relapsing inflammatory diseases of the gastrointestinal tract, mainly affecting the young and middle-aged[1,2].

A considerable variation in the incidence of IBD is observable worldwide, as it increased quickly in Western developed countries during the last 50 years of the 20th century, while newly industrialized nations are documenting the greatest increases in incidence since the years of globalization (2000s)[3].

Currently in Italy, a national disease register for IBD has not yet been developed. This prevents correct interpretation of the disease burden. Based on the disease-specific payment exemptions register, between 150000 and 200000 people are estimated to be affected by IBD, with a prevalence of 100/100000 inhabitants for CD and 121/100000 for UC. Epidemiological data from the European Crohn's and Colitis Organisation's (ECCO) Epidemiological Committee inception cohort showed that the Italian incidence is 10.5/100000 inhabitants per year, indicating lower rates of new diagnosis compared to European ones (>25/100000), but twofold compared to old Italian data[4-6].

The management of these diseases is arduous, as inflammation often persists even in the absence of gastrointestinal symptoms[7], and this may lead to progressive bowel damage and complications requiring long-term treatments and strict medical follow-up, and in some cases hospitalizations and surgery[8,9]. At the same time, impaired bowel function ultimately leads to a considerable burden not only for patients[10] but also for the healthcare systems[11].

In particular, UC affects mostly young adults around 20-40-years-old with a second peak between 60 years and 80 years, with no differences between sexes[12,13]. Both the clinical presentation and course vary among patients and can range from mostly quiescent to chronic, refractory disease with need of surgery, sometimes complicated by cancer or contributing to cause of death[14].

There are little data on the epidemiological and clinical features of adult UC patients in the different Italian regions, mainly derived from administrative sources such as the Hospital Discharge Register[5,15,16].

Based on these premises, the aim of this study was to assess the main clinical and epidemiological features of adult patients diagnosed with UC in Sardinia, including location at diagnosis, extraintestinal manifestations, disease progression over time, and treatment.

### MATERIALS AND METHODS

#### Study design and population

We performed a multicenter, observational, cross-sectional study that included adult patients with UC, enrolled between February 2017 and December 2018 in seven Gastroenterology/Endoscopy Units in Sardinia, an Italian region with a population of approximately 1600000 inhabitants. All patients provided written informed consent. The study was approved by the Ethics Board (Prot. PG/2016/17911) and conducted according to the Declaration of Helsinki.

#### Inclusion and exclusion criteria

We included adult patients (≥18-years-old) with an established diagnosis of UC, based on standard clinical, endoscopic, and histologic criteria. We excluded patients <18-years-old at the time of enrollment, patients unable to understand the study’s questionnaires, or patients previously enrolled in a randomized clinical trial.

#### Diagnostic criteria

Diagnosis was made at least 3 mo before the study inclusion and the minimum follow-up time was 1 mo. Data were obtained from patients’ medical records at each center and from a questionnaire administered at the inclusion visit. The following data were collected: sex, date of birth, lifestyle (smoking habits, alcohol consumption), personal and/or familial history of neoplasia, vaccination status (hepatitis B virus [HBV], human papilloma virus [HPV] and Streptococcus pneumoniae), year of diagnosis and age at diagnosis, disease extent both at diagnosis and at study inclusion (according to Montreal classification)[17], extraintestinal manifestations (EIMs), use of UC-related medications (mesalazine [5-ASA], corticosteroids, immunosuppressors, biologic agents), and surgery. Disease extension and regression were defined as a proximal progression or distal regression from the initial extent at diagnosis, respectively, as determined by endoscopy. We also focused on elderly-onset patients, namely patients diagnosed with UC after the age of 60 years.

#### Statistical analyses

Given an estimated prevalence rate of about 124 cases per 100000 inhabitants for UC in Sardinia[16], we aimed to enroll 400 patients with UC, equivalent to 20% of the UC population in Sardinia. Data were reported on a Microsoft Excel worksheet and analyzed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, United States). Statistics were descriptive: categorical variables are expressed as proportion, while continuous variables are expressed as the median and interquartile range (IQR).
RESULTS

Sex, age at diagnosis, and smoking status
Between February 2017 and December 2018, 442 patients with an established diagnosis of UC were included: 231 (52.3%) were female, with a female-to-male ratio of about 1.1 (Table 1). The median age at diagnosis was 39 years (IQR 28-48). At the time of diagnosis, 4.5% (20/442) of patients were < 16-years-old, 52.7% (233/442) were diagnosed between 17-years-old and 40-years-old, and 42.8% (189/442) at age > 40. About three-quarters of patients were diagnosed between 17-years-old and 49-years-old (23.2% between 17 and 29, 25.5% between 30 and 39, and 23.2% between 40 and 49). In all, 10.9% (48/442) of patients were active smokers and 36.2% (160/442) were former smokers.

Disease extent
Disease extent at the time of diagnosis was proctitis [E1] in 81 (18.3%) patients, left-sided colitis [E2] in 178 (40.3%), and extensive colitis [E3] in 176 (39.8%). Data were not available for 7 patients (1.6%). After a median disease duration of 10 years (IQR 3-15.5), 53 patients (12%) experienced proximal extension of proctitis or left-sided colitis: 13 (24.5%) patients from E1 to E2, 12 (22.7%) from E1 to E3, and 28 (52.3%) from E2 to E3. In 28 patients (6.3%), there was a regression of disease extent after a median disease duration of 10.5 years (IQR 7-16.75): 10 patients (35.7%) from E2 to E1, 8 (28.6%) from E3 to E1, and 10 (35.7%) from E3 to E2.

EIMs, malignancies, and vaccinations
Seventy-five patients (16.3%) developed EIMs, the most frequent being articular (50/72, 69.4%), followed by hepatobiliary (11/72, 15.3%, of which 6 patients with primary sclerosing cholangitis), cutaneous (9/72, 12.5%) and ocular (5/72, 6.9%); in 3 patients (4.2%) there was a combination of articular and ocular manifestations. After UC diagnosis, 19 patients (4.3%) developed cancer: 2 with colorectal cancer (CRC) and 17 with extracolonic cancers (5 breast, 4 skin, 2 prostate, 2 thyroid, 1 pancreas, 1 stomach, 1 gastric MALT lymphoma, 1 multiple myeloma). In the study population, patients’ self-reported vaccination rates were 30.3% (134/442) for HBV, 2% (9/442) for HPV, and 1.6% (7/442) for S. pneumoniae.

Medical and surgical treatment
Details on medical therapy are shown in Table 2. Twenty-eight patients (6.3%) received no UC treatment at the inclusion visit. The most common therapy at inclusion visit was 5-ASA: 368 (86.6%) of patients were taking it at baseline, whereas 46 (10%) withdrew it. No data were available for 17 patients. Nine percent of patients started with corticosteroids, either systemic or with low bioavailability, whereas 51.7% were exposed to one or more courses of steroids during their disease course. Azathioprine was used by 40 (9%) patients; 69 (15.6%) withdrew it during their disease course, mainly for adverse events.

Overall, 95 patients (21.5%) were treated with one or more biologic agents: 72 patients (75.8%) were treated with one biologic agent, 17 (19.7%) with two and 6 (6.3%) with three. At study inclusion, infliximab was the most common anti-tumor necrosis factor alpha (TNFα) biologic used (55/442, 12.4%), followed by adalimumab (12/442, 2.7%) and golimumab (5, 1.1%); while vedolizumab (VDZ) was used in 11 (2.5%) patients. Nine of the eleven patients with VDZ were previously treated with anti-TNFα, while two were naïve to any biologic.

Eleven patients (2.5%) were treated with a combination therapy of immunosuppressant drug plus biologic: ten in association with anti-TNFα agents, one with VDZ. None of the patients was treated with a combination of biologics.

A total of 15 patients (3.4%) had a resection performed. Of these, 13 patients (87%) underwent colectomy, while 2 (13%) underwent hemicolecotomy for CRC. The median time between diagnosis and surgery was 5 years (IQR 2-20). The vast majority of patient who underwent surgery were with extensive colitis at diagnosis (12 patients, 80%) compared with 3 patients (20%) with left-sided colitis.

Elderly-onset UC
Fifty-one patients (11.5%) were diagnosed with UC after the age of 60 years. Among them, 31 (60.8%) were male. Disease extent at diagnosis was E1 in 7 patients (13.7%), E2 in 24 (47.1%), and E3 in 20 (37.2%); data were not present in 1 patient. After a median follow-up time of 4 years (IQR 1-6), there was a proximal extension of disease in 3 patients (5.9%).

Three patients (5.9%) developed EIMs (two articular and one erythema nodosum). Four patients (7.8%) had a history of neoplasia (two with skin cancer, one with prostate cancer, one with breast cancer).

The most common therapy at the time of inclusion visit was 5-ASA, used by 368 (83.2%) of patients. Four patients (7.8%) were taking corticosteroids, while 50.1% received one or more courses of steroids after the diagnosis, either systemic or with low bioavailability. Two patients (3.9%) were under treatment with azathioprine, while three patients withdrew it during their disease course (two for adverse events and one for disease remission). Four patients (7.8%) were under treatment with biologic agents alone.
Table 1 Clinical and demographical characteristics of patients with ulcerative colitis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n = 442, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>231 (52)</td>
</tr>
<tr>
<td>Age at diagnosis, yr (IQR)</td>
<td>39 (28-48)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>48 (10.9)</td>
</tr>
<tr>
<td>Former</td>
<td>160 (36.2)</td>
</tr>
<tr>
<td>Never</td>
<td>234 (52.9)</td>
</tr>
<tr>
<td>Disease extent at diagnosis</td>
<td></td>
</tr>
<tr>
<td>E1, proctitis</td>
<td>81 (18.3)</td>
</tr>
<tr>
<td>E2, left-sided colitis</td>
<td>178 (40.3)</td>
</tr>
<tr>
<td>E3, extensive colitis</td>
<td>176 (39.8)</td>
</tr>
<tr>
<td>Uncertain extent</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>Disease extent</td>
<td></td>
</tr>
<tr>
<td>E1 to E2</td>
<td>13 (25)</td>
</tr>
<tr>
<td>E2 to E3</td>
<td>28 (52.3)</td>
</tr>
<tr>
<td>E1 to E3</td>
<td>12 (22.7)</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td></td>
</tr>
<tr>
<td>Articular</td>
<td>50 (69.4)</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>11 (15.2)</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>9 (12.5)</td>
</tr>
<tr>
<td>Ocular</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>Previous surgery</td>
<td></td>
</tr>
<tr>
<td>Colectomy</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Hemicolectomy</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Malignancies</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Breast</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Skin</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Prostate</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1 (5)</td>
</tr>
<tr>
<td>MALT lymphoma</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Self-reported vaccination status</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>134 (30.3)</td>
</tr>
<tr>
<td>HPV</td>
<td>9 (2)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>7 (1.6)</td>
</tr>
</tbody>
</table>

HBV: Hepatitis B virus; HPV: Human papilloma virus.

agent: three with infliximab and one with VDZ. No one underwent colectomy.
Table 2 Medical treatment in patients with ulcerative colitis

<table>
<thead>
<tr>
<th>Medical therapy</th>
<th>Current users, n (%)</th>
<th>Former users, n (%)</th>
<th>Never used, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalazine, n = 425</td>
<td>368 (86.6)</td>
<td>46 (10.8)</td>
<td>11 (2.6)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>41 (9.1)</td>
<td>228 (51.7)</td>
<td>173 (39.2)</td>
</tr>
<tr>
<td>Thiopurines</td>
<td>40 (9)</td>
<td>69 (15.6)</td>
<td>333 (75.4)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>5 (1.1)</td>
<td>4 (1)</td>
<td>432 (97.9)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>55 (12.4)</td>
<td>22 (5.0)</td>
<td>365 (82.6)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>12 (2.7)</td>
<td>6 (1.4)</td>
<td>424 (95.9)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>5 (1.1)</td>
<td>11 (2.5)</td>
<td>426 (96.4)</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>11 (2.5)</td>
<td>1 (0.2)</td>
<td>430 (97.3)</td>
</tr>
</tbody>
</table>

DISCUSSION

In this study, we summarized the main characteristics and natural history of UC in a large population study of a single Italian region, Sardinia, including demographic data, disease extension, EIMs, malignancies, vaccinations, and medical and surgical treatment.

Disease extent in UC is an important feature because it is an indicator of severity of disease, as well as the type of treatment needed. Patients with initial diagnosis of pancolitis appear to have a worse disease course and need a more aggressive treatment, both medical and surgical, while distal UC is associated with a better prognosis[18]. In our cohort, diagnosis of proctitis was made in 18.3% of patients, left-sided colitis in 40.3%, and extensive colitis in 39.8%. The overall rate of extension was 12% after a median follow-up of 10 years, which was significantly lower than in others that reported highest rates [19,20]. This feature could be explained in different ways. First, a possible explanation is linked to the time of UC diagnosis that in our cohort was 39 years, substantially comparable with European data[4], but earlier than the North American countries, where the highest rate of UC extension is reported[21]. If the diagnosis is significantly delayed, as well as the start of therapy, patients are predisposed to a major risk of disease extension and an aggressive course. Moreover, we can speculate that Sardinia, a region geographically isolated from European continent, has a selected population, less pre-disposing to develop a more aggressive disease due to genetic or environmental factors. Among the latter, diet plays an important role in IBD pathogenesis, by modulating the gut microbiota, and consequently, it could have an impact on IBD course[22]. In particular, if several lines of evidence point to aspects of the typical Western diet that may promote the development of IBD and its course, less is known about the beneficial role of Mediterranean diet (Md), more frequently adopted in Southern Europe, particularly in Sardinia. Md is characterized by a high intake of fruits and vegetables, olive oil and oily fish, grains and nuts[23]. Chicco et al[24] conducted an observational study in a Sardinian population of IBD patients showing a spontaneous improvement of disease activity and inflammatory markers in patients that adopted a Md. Further prospective studies are needed in this setting.

EIMs are common in IBD and adversely impact patient’s quality of life and can even be life-threatening. The real prevalence and burden of EIMs have not been fully evaluated yet stands around 15%-50% since prospective studies are lacking[25]. The analysis of clinical characteristics revealed that 16.3% of our populations experienced EIMs, the most was frequent articular (69.4%), followed by hepatobiliary (15.2%), cutaneous (12.5%), and ocular (6.9%).

5-ASA remains the mainstay of treatment for UC. In our cohort, we observed that almost all patients received 5-ASA, while only 10% were formerly used, mainly because of the concomitant treatment with immunomodulators or biologics. However more recent publications have demonstrated no benefit to concomitant 5-ASA in UC patients escalated to anti-TNFα or VDZ[26]. Despite the increasing therapeutic armamentarium available, clinics still prescribe 5-ASA even when it fails or in step-up therapy. One of the reasons could be the role of 5-ASA in CRC prevention. American guidelines suggest that 5-ASA therapy may be stopped in patients that achieved long remission or are treated with biologics[27]. Instead ECCO guidelines emphasize the role of 5ASA in CRC prevention suggesting a withdrawal only in low-risk patients (limited disease extent, a history of remission for several years, no previous requirement of systemic corticosteroids)[28]. Considering also the burden on healthcare budgets and albeit rare potential adverse effects, there is a need to consider withdrawing 5-ASA in a subset of patients.

Regarding biological therapy we observed that 21% of patients were exposed to one or more biologics, a proportion significantly higher than the European population[29]. This trend might follow a top-down approach with rapid escalation as the result of the “era of mucosal healing” as a treatment goal[30]. However, the majority of participating centers were tertiary biologic-prescribing IBD hospitals with greater propensity to use biologics. The impact of this more aggressive therapeutic approach on the
disease course needs to be further evaluated. Another important finding seen in this study is that the majority of patients did not receive combination therapy with an anti-TNFα or VDZ and an immunomodulatory drug.

Population-based cohorts of patients diagnosed after the introduction of biologics in Europe and North America have reported surgery rates of 3%-6% in UC[13,31]. These numbers are comparable to the surgery rates observed in the present cohort. Recent studies have shown a reduced rate of colectomy in UC assuming that this trend is strongly linked to use of biologic agents that positively influence the disease course[32]. It remains to be proven if current IBD treatment strategy can influence the course in the long term.

CRC has always garnered special attention in IBD. Population-based data from our cohort demonstrate only two cases of CRC. This finding seems to be in line with the results of an Italian study conducted by Taborelli et al[33], which showed that CRC risk among both UC and CD patients was similar to that expected in the general population. These data could be explained by several factors as diet, chemoprevention or colonoscopy surveillance. Differently, we observed a higher rate of extraintestinal tumors. However, it is difficult to establish whether there is an influence of the natural history of intestinal disease or is the result of unrelated factors.

Patients with IBD are vulnerable to infections because of the immunological disorder caused by the disease itself or to the immunosuppression induced by the treatment[34]. Thus, the determination of vaccination status is important to limit under-immunization. Despite the current practice recommendations for routine vaccination in IBD[35,36], our findings demonstrate significant deficiencies in self-reported vaccination uptake with a low rate of adherence to vaccination schedules, in particular for S. Pneumoniae and HPV. Inadequate counseling, deficiencies in physicians’ knowledge about vaccinations and uncertainties about vaccination indications in IBD patients have been implicated as an important contributor to poor uptake of vaccination[37]. This suggests that more attention needs to be given to vaccination counseling. A structured review of vaccination status at time of diagnosis, prior to the initiation of immunosuppressive therapy and an annual review represent an optimal strategy in this setting. By contrast, in our study, the rate of self-reported vaccination for HBV was 30.3%, higher than that reported in others[38,39]. These data are clearly due to the vaccination campaign introduced in Italy in 1991 that makes vaccination mandatory for all people born since 1979 rather than through intervention by gastroenterologists.

Our study had some limitations that need to be taken into consideration. These include the heterogeneity of the participating centers in terms of health care of which they are part. In addition, few centers have contributed to the collection of the majority of data making potentially skewed the data collection. Moreover, the study may be limited by the retrospective data collection. Although we controlled for many potential confounders, unmeasurable variables might alter data extractions.

CONCLUSION

In conclusion, although a national IBD registry is not yet available, this is one of the first studies conducted in Italy that provides important insights on the clinical and epidemiological features of patients with UC as well as the management and its natural history. Our data seem in line with Italian and European data. While waiting for a national registry, our results present eligible features of UC population in Sardinia considering that the number of patients enrolled represents about 20% of the population.

ARTICLE HIGHLIGHTS

Research background
There are little data on the epidemiological and clinical features of patients with adult ulcerative colitis (UC) in Italy.

Research motivation
This population-based observational study evaluated an entire population in a defined geographic area over an extended period of time. This is ideal to inform the natural history of disease and also to avoid selection biases associated with referral center cohort studies.

Research objectives
To describe the characteristics of patients at the time of UC diagnosis and to register the use of immunosuppressive treatments and biological drugs, surgeries, and malignancies after diagnosis of UC.
Research methods
Consecutive patients with UC in ambulatory follow-up, at the time of the visit, were invited, after obtaining informed consent, to fill out a questionnaire concerning the natural history of their chronic disease object of the study.

Research results
Four hundred and forty-two patients were included in the study. A high proportion of patients were treated with one or more biologics. 5-ASA remains the mainstay of UC treatment. Left-sided colitis is the most frequent location.

Research conclusions
This is one of the first large-scale nationwide, observational studies to investigate the epidemiological characteristics of UC in Italy. Sardinia, a region geographically isolated from the European continent. This selected population is less likely to develop aggressive disease due to genetic or environmental factors.

Research perspectives
Correct and objective mapping of the epidemiological and clinical characteristics of patients with UC, but in general with inflammatory bowel disease, cannot be separated from the presence of a national registry that compiles national data. It is desirable that this happens in Italy.

FOOTNOTES

Author contributions: Magrì S and Mocci G performed the study design, data capture, and data validation; Magri S, Demurtas M, and Picchio M performed the statistical analyses; Magri S drafted the manuscript; Magri S, Demurtas M, Onidi MF, Picchio M, Elisei W, Marzo M, Miculan F, Manca R, Dore MF, Quarta Colosso BM, Cugia L, Pisano R, Carta M, Binaghi L, Usai P, Lai M, Chieco F, Fantini MC, Cabras F, Armuzzi A, and Mocci G performed the data capture and revised the manuscript; Mocci G approved the final version of the manuscript.

Institutional review board statement: The research project has been approved by the Ethics Board (Prot. PG/2016/17911).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Chang KL
L-Editor: Filipodia
P-Editor: Chang KL
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Clinical observation of laparoscopic cholecystectomy combined with endoscopic retrograde cholangiopancreatography or common bile duct lithotripsy

Hong Niu, Fei Liu, Yi-Bo Tian

Abstract

BACKGROUND

The incidence of common bile duct (CBD) stones accounts for approximately 10%–15% of all CBD diseases. Approximately 8%–20% of these patients also have gallstones with heterogenous signs and symptoms.

AIM

To investigate the clinical effects of laparoscopic cholecystectomy (LC) combined with endoscopic retrograde cholangiopancreatography (ERCP) and LC with CBD excision and stone extraction in one-stage suture (LBEPS) for the treatment of gallbladder and CBD stones.

METHODS

Ninety-four patients with gallbladder and CBD stones were selected from our hospital from January 2018 to June 2021. They were randomly divided into study and control groups with 47 patients each. The study group underwent LC with ERCP, and the control group underwent LC with LBEPS. Surgery, recovery time of gastrointestinal function, complication rates, liver function indexes, and stress response indexes were measured pre- and postoperatively in both the groups.

RESULTS

The durations of treatment and hospital stay were shorter in the study group than in the control group. There was no significant difference between the one-time...
stone removal rate between the study and control groups. The time to anal evacuation, resumption of oral feeding, time to bowel sound recovery, and time to defecation were shorter in the study group than in the control group. The preoperative serum direct bilirubin (DBIL), total bilirubin (TBIL), and alanine aminotransferase (ALT) levels were insignificantly higher in the study group than that in the control group. A day after surgery, the postoperative serum DBIL, TBIL, and ALT levels were lower than their preoperative levels in both groups, and of the two groups, the levels were lower in the study group. Although the preoperative serum adrenocorticotrophic (ACTH), cortisol (COR), epinephrine (A), and norepinephrine (NE) levels were higher in the study group than that in the control group, these differences were not significant ($P > 0.05$). The serum ACTH, COR, A, and NE levels in both groups decreased one day after surgery compared to the preoperative levels, but the inter-group difference was statistically insignificant. Similarly, $(91.79 \pm 10.44)$ ng/mL, A, and NE levels were lower in the study group than in the control group. The incidence of complications was lower in the study group than in the control group.

CONCLUSION
LC combined with ERCP induces only a mild stress response; this procedure can decrease the risk of complications, improve liver function, and achieve and promote a faster recovery of gastrointestinal functions.

Key Words: Laparoscopic cholecystectomy; Endoscopic retrograde cholangiopancreatography; Choledochootomy with one-stage suture; Gallbladder stones; Common bile duct stones

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Core Tip: Laparoscopic cholecystectomy (LC) combined with endoscopic retrograde cholangiopancreatography and LC combined with choledochotomy and lithotripsy are commonly used for the treatment of gallstones; in this study, we further investigated the efficacy and safety of these procedures.

Citation: Niu H, Liu F, Tian YB. Clinical observation of laparoscopic cholecystectomy combined with endoscopic retrograde cholangiopancreatography or common bile duct lithotripsy. World J Clin Cases 2022; 10(30): 10931-10938
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/10931.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.10931

INTRODUCTION
The incidence of common bile duct (CBD) stones is approximately 10%-15% of the total incidence of all CBD diseases. Approximately 8%-20% of these patients also have gallstones, presenting with complex and diverse clinical manifestations[1,2]. If patients of gallstones with coexisting CBD stones do not receive timely and effective intervention, biliary obstruction may lead to severe infections and complications like toxic shock as well as many other threats to patients’ life and health[3,4].

Traditionally, patients with gallbladder and CBD stones are treated by open surgery. This method can achieve good results but at the expense of being more traumatic, potentially more complicating, and with longer postoperative recovery times of bodily functions[5]. Laparoscopy is a modern and popular minimally invasive surgical technique. Laparoscopic cholecystectomy (LC) combined with endoscopic retrograde cholangiopancreatography (ERCP) and LC combined with choledochotomy and lithotomy (LBEPS) are very commonly used. Both procedures have their own unique characteristics and can achieve the treatment purpose[6-8].

To further explore the efficacy and safety of LC combined with ERCP and LC combined with LBEPS in gallbladder and CBD stones, 94 patients with this condition from our hospital were selected for this study, and the aforementioned contents were discussed in groups.

MATERIALS AND METHODS
General information
Ninety-four patients with gallbladder and CBD stones in our hospital from January 2018 to June 2021 were selected and randomly divided into a study group and a control group, with 47 cases in each.
There were 26 men and 21 women in the study group; the age ranged from 46 to 76 years (average age: 55.97 ± 11.29 years). The number of CBD stones ranged from 1 to 4 (average: 2.41 ± 1.10), and the diameter of the CBD stones ranged from 3.1 to 8.6 mm (average: 5.89 ± 1.64 mm). There were 29 men and 18 women in the control group; the age ranged from 43 to 79 years (average: 60.44 ± 10.71 years); and the diameter of the CBD stones ranged from 3.1 to 8.6 mm (average: 5.89 ± 1.64 mm). The clinical data on sex, age, the diameter of the CBD stones, and the number of CBD stones were balanced and comparable between the two groups ($P > 0.05$). This study was approved by the ethics committee of our hospital.

Selection criteria

The inclusion criteria were: (1) Diagnosis confirmed by abdominal computed tomography or hepatobiliary ultrasound; (2) age less than 80 years; (3) knowledge of the study and provision of signed informed consent; and (4) good compliance and cooperation, with an ability to understand and communicate for smooth conduction of the study.

The exclusion criteria were: (1) Patients with coagulation and bleeding disorders; (2) patients unfit for carbon dioxide pneumoperitoneum and general anesthesia intubation; (3) patients with anomalous bile duct anatomy; (4) patients with severe acute pancreatitis and purulent obstructive cholangitis; and (5) patients with bile duct/gallbladder malignancy.

Study group

LC combined with ERCP was performed in this group. The patient was assisted to lie in a supine position under general anesthesia for 8 h. The patient’s abdomen was assessed via a three-/four-hole approach. The gallbladder triangle was explored and separated, its artery and the cystic duct were clamped, and the gallbladder was removed from the gallbladder bed. After ensuring hemostasis, a Wen drain was left in place and the wound was sutured. The patient was then turned to the left lateral position. A duodenoscope was introduced through the mouth and via the esophagus and the duodenal papilla was identified in the duodenum. Selective intubation of the CBD was performed with a guidewire, a contrast medium was injected, and ERCP was completed. Endoscopic duodenal papillary sphincterotomy was performed at the 11 o’clock position of the duodenal papilla by the retracting knife method. The stones were then extracted and retrieved orally. Papillary balloon dilation was performed in accordance with the number, size, location, and softness of the stones. After the stone extraction, a cholangiogram was performed to check for residual stones, which if found, were managed by repeat duodenoscopic removal. A nasobiliary drainage tube was routinely left for flushing the bile duct and for draining the bile. If no abnormality was observed 6 h postoperatively, the patient was orally allowed to consume clear liquids. The patient was permitted to consume normal food 24 h postoperatively in case serum amylase and lipase levels were found to be in the normal range. The nasobiliary drainage tube was withdrawn one to two days postoperatively only after a normal nasobiliary ductography.

Control group

For the control group, LC combined with LBEPS was performed; LC was completed in the manner similar to that of the study group.

LBEPS was performed as follows: An incision was made, and the CBD was exposed; a 10-mm incision was made in the anterior wall of the CBD, and a fiberoptic cholangioscope was inserted in the subxiphoid process to investigate the upper and lower segments of the CBD; any bile duct stones detected were removed through a lithotripsy basket, while sediment-like stones and small stones that were difficult to remove by the basket were flushed out into the duodenum. The CBD incision was closed by a one-stage suture using 4-0 absorbable sutures (interrupted) after the following conditions were confirmed on examination: only a mild inflammation of the CBD; normally functioning sphincter of Oddi; and no residual stones in the CBD. A drain was placed in the gallbladder bed at the end of the surgery. The trocar subcutaneous tissues were sutured, the skin was glued with tissue glue, and the gastric tube was removed after surgery.

Observed indicators

Time durations of treatment, hospitalization, and primary stone extraction rate were documented to compare the two groups. The recovery times of gastrointestinal functions in both groups were documented, including the time to anal evacuation, resumption of oral feeding, time to recovery of bowel sounds, and the time to defecation. The levels of liver function indexes, including ALT, TBIL, and DBIL, were measured pre- and postoperatively in both groups; 4 mL of blood was drawn from the medial cubital vein, centrifuged, and the levels of the liver function indexes were measured by a Hitachi 7180 automatic biochemical analyzer. The levels of stress indicators, including ACTH, COR, A, and NE, were measured pre- and postoperatively in both groups by enzyme-linked immunosorbent assay of peripheral venous blood. Finally, the incidence of complications in both groups was counted.
Statistical analysis
Data were analyzed by SPSS 22.0, and the measured data (mean ± SD) were expressed by the t-test. The measured data n (%) were expressed by the χ² test, and P < 0.05 indicated statistical significance.

RESULTS

Comparison of surgical conditions between the study and control groups
The treatment time was 97.64 ± 17.51 min and the duration of hospital stay was 7.08 ± 1.82 d in the study group, which was significantly longer in the control group [119.62 ± 24.37 min and 9.33 ± 2.29 d, respectively (P < 0.05)]. There was no significant difference between the one-time stone retrieval rate in the study group (97.87%) and the control group (95.74%) (P > 0.05) (Table 1).

Comparison of the recovery of gastrointestinal function between the two groups
In the study group, the time to anal evacuation was 25.02 ± 3.68 h, time to resume oral feeding was 7.82 ± 3.44 h, time to recovery of bowel sounds was 16.56 ± 3.58 h, and time to defecation was 33.35 ± 6.07 h. These values were significantly longer in the control group [28.29 ± 4.11 h, 9.62 ± 4.09 h, 18.94 ± 4.29 h, 36.96 ± 7.11 h, respectively (P < 0.05)] (Table 2).

Comparison of liver function index levels before and after surgery between the two groups
The preoperative serum levels of DBIL, TBIL, and ALT were 182.10 ± 82.33 umol/L, 258.62 ± 100.54 umol/L, and 38.56 ± 7.18 U/L, respectively, in the study group. These were not significantly different from those of the control group [178.89 ± 79.59 umol/L, 261.45 ± 96.77 umol/L, and 40.04 ± 6.69 U/L, respectively (P > 0.05)]. The serum DBIL, TBIL, and ALT levels were significantly lower in both groups a day after surgery as compared to the levels before treatment (P < 0.05). The serum levels of DBIL, TBIL, and ALT were 93.37 ± 40.02 umol/L, 156.98 ± 83.31 umol/L, and 26.83 ± 6.65 U/L, respectively, in the study group. These values were significantly longer in the control group [111.51 ± 36.33 umol/L, 191.03 ± 72.12 umol/L, and 30.13 ± 7.92 U/L respectively (P < 0.05)] (Table 3).

Comparison of stress index levels before and after surgery between the two groups
Preoperative serum levels of ACTH, COR, A, and NE were 14.78 ± 2.28 ng/mL, 126.67 ± 11.59 ng/mL, 1.39 ± 0.15 nmol/L, and 3.68 ± 0.65 nmol/L, respectively, in the study group. These were not significantly different from those of the control group [15.36 ± 2.35 ng/mL, 130.68 ± 12.01 ng/mL, 1.42 ± 0.12 nmol/L, 3.83 ± 0.72 nmol/L, respectively (P > 0.05)]. The serum ACTH, COR, A, and NE levels in both groups decreased significantly one day after surgery compared to the levels measured before surgery (P < 0.05). The levels of serum ACTH, COR, A, and NE one day after surgery were 6.19 ± 2.05 ng/mL, 91.79 ± 10.44 ng/mL, 0.71 ± 0.24 nmol/L, and 1.41 ± 0.51 nmol/L, respectively, in the study group. These were significantly lower than that in the control group [8.68 ± 3.88 ng/mL, 105.32 ± 11.65 ng/mL, 0.96 ± 0.37 nmol/L, 2.21 ± 0.73 nmol/L, respectively (P < 0.05)] (Table 4).

Comparison of complications between the two groups
The complication rate was significantly lower in the study group (6.38%) than in the control group (21.28%) (P < 0.05) (Table 5).

DISCUSSION

Gallbladder and CBD stones have a high prevalence rate, with a recent increase in incidence due to several factors such as poor lifestyle habits and changes in dietary structure[9,10]. Patients with gallbladder and CBD stones require timely and effective intervention to prevent the disease from worsening and are thus more difficult to treat.

Open surgery, the traditional clinical treatment for gallbladder and CBD stones, though effective requires longer preoperative fasting and hospitalization. The T-tube-associated complications create both psychological and physical burdens for patients[11,12]. LC combined with either ERCP or LBEPS has changed the nature of treatment of gallbladder and bile duct stones because of their minimally invasive nature. LBEPS requires maximum placement of the choledochoscope into the gallbladder and CBD to assess the location, number, and volume of stones under direct vision. In a narrow biliary tract, it is difficult to maneuver the scope distally into the bile duct. This may be unfavorable for stone removal with LC[13,14]. Moreover, it has been reported that LBEPS requires T-tube drainage, which can cause serious invasive injury, including bile duct injury, which is not favorable for prognosis[15]. In contrast, ERCP provides information on the distribution, number, and morphology of stones even in a narrow bile duct. ERCP is simpler to perform, does not require a T-tube, and hence preserves the integrity and normal physiological function of the bile duct, which is more desirable and safe[16].
In this study, LC combined with ERCP and LC combined with LBEPS were used to treat patients with gallbladder and CBD stones in our hospital. The study results showed that the surgery and postoperative recovery of gastrointestinal functions in the study group were better than those of the control group. The complication rates were significantly lower in the study group (6.38%) than those in the control group (21.28% with \( P < 0.05 \)), indicating that LC combined with ERCP was more effective than LC combined with LBEPS in reducing the number of gallstones and CBD stones. LC combined with ERCP was found to be more effective and safer as it reduced the likelihood of intraoperative injury, shortened postoperative gastrointestinal function recovery time, and reduced the risk of complications. The main reasons for this are as follows: (1) With dual-scope combined procedures, gallstones and CBD stones can be treated simultaneously. Cholecystectomy and LBEPS have similar operative duration; however, ERCP take significantly lesser time than choledochoscopy; (2) LC combined with LBEPS requires routine removal of the gallbladder, and parallel dissection of the CBD; and (3) LC combined with LBEPS requires routine removal of the gallbladder, separation, and dissection of the CBD and anterior choledochotomy. In contrast, choledochotomy requires a longer time to perform cholangioscopic stone extraction through the mouth, which can increase bleeding. Therefore, LC combined with ERCP overcomes these problems and ensures treatment safety\[17,18\].

Although LC combined with ERCP and LC combined with LBEPS are both minimally invasive procedures for gallbladder and CBD stones, they are nonetheless invasive, and can cause varying degrees of liver function derangements and trigger stress reactions. These factors negatively impact...
Table 4 Comparison of stress response index levels before and after surgery between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Groups</th>
<th>ACTH (ng/ml)</th>
<th>COR (ng/ml)</th>
<th>A (nmol/L)</th>
<th>NE (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research Group (n = 47)</td>
<td>14.78 ± 2.28</td>
<td>126.67 ± 11.59</td>
<td>1.39 ± 0.15</td>
<td>3.68 ± 0.65</td>
</tr>
<tr>
<td>Control group (n = 47)</td>
<td>15.36 ± 2.35</td>
<td>130.68 ± 12.01</td>
<td>1.42 ± 0.12</td>
<td>3.83 ± 0.72</td>
</tr>
<tr>
<td>t value</td>
<td>1.214</td>
<td>1.647</td>
<td>1.071</td>
<td>1.060</td>
</tr>
<tr>
<td>P value</td>
<td>0.228</td>
<td>0.103</td>
<td>0.287</td>
<td>0.292</td>
</tr>
<tr>
<td>1 d after surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research Group (n = 47)</td>
<td>6.19 ± 2.05a</td>
<td>91.79 ± 10.44a</td>
<td>0.71 ± 0.24a</td>
<td>1.41 ± 0.51a</td>
</tr>
<tr>
<td>Control group (n = 47)</td>
<td>8.68 ± 3.88a</td>
<td>105.32 ± 11.65a</td>
<td>0.96 ± 0.37a</td>
<td>2.21 ± 0.73a</td>
</tr>
<tr>
<td>t value</td>
<td>3.890</td>
<td>5.929</td>
<td>3.886</td>
<td>6.159</td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*P < 0.05 vs this group preoperatively.

ACTH: Serum adrenocorticotrophic; COR: Cortisol; A: Epinephrine; NE: Norepinephrine.

Table 5 Comparison of complications between the two groups, n (%)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Hemorrhage</th>
<th>Biliary tract infection</th>
<th>Bile leak</th>
<th>Pancreatitis</th>
<th>Total incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Group (n = 47)</td>
<td>0 (0.00)</td>
<td>1 (2.13)</td>
<td>0 (0.00)</td>
<td>2 (4.26)</td>
<td>3 (6.38)</td>
</tr>
<tr>
<td>Control group (n = 47)</td>
<td>5 (10.64)</td>
<td>3 (6.38)</td>
<td>1 (2.13)</td>
<td>1 (2.13)</td>
<td>10 (21.28)</td>
</tr>
<tr>
<td>χ² value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.374</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.036</td>
</tr>
</tbody>
</table>

disease recovery and prognosis. In this study, serum DBIL, TBIL, and ALT levels were higher in the study group than in the control group. Conversely, serum ACTH, COR, A, and NE levels were lower in the study group than in the control group (P < 0.05), suggesting that LC combined with ERCP is more advantageous in reducing the stress response and liver function damage. This further supports the clinical efficacy of LC combined with ERCP therapy for the treatment of gallbladder and CBD stones from the perspective of serum markers. In addition, with dual-scope combination, after the resection of the gallbladder, the LC is immediately followed by ERCP. This shortens the duration of carbon dioxide pneumoperitoneum, thereby reducing the stress reaction in vivo. Liver function also improves due to smooth and rapid draining of bile, facilitated by placement of the biliary plastic stent or a nasobiliary tube. For LC combined with ERCP, if intraoperative CBD stones are difficult to remove, plastic biliary stents can be left in place to reduce the occurrence of vagal biliary fistula or obstructive purulent cholangitis. Furthermore, ERCP can be repeated safely in cases of residual removal or difficulty in stone removal and thus can prevent the trauma caused by reoperation [19, 20].

Our study has some limitations. The sample size was not large enough; a larger multicenter study is needed to confirm these results. Moreover, long-term follow-up was not performed in this study.

CONCLUSION

In conclusion, the treatment of gallbladder and CBD stones by LC combined with ERCP is worth promoting because it can reduce trauma, decrease the risk of complications, reduce the impact on liver function, induce only a mild stress reaction, and promote a faster recovery of gastrointestinal function. A larger trial with longer follow-up is needed to confirm whether patients with gallbladder and CBD stones can benefit from LC combined with ERCP therapy in the long term.
ARTICLE HIGHLIGHTS

Research background
The incidence of common bile duct (CBD) stones is approximately 10%-15% of the total incidence of all CBD diseases.

Research motivation
If patients of gallstones with coexisting CBD stones do not receive timely and effective intervention, biliary obstruction may lead to severe infections and complications like toxic shock as well as many other threats to patients’ life and health.

Research objectives
This study aimed to explore the efficacy and safety of laparoscopic cholecystectomy (LC) combined with endoscopic retrograde cholangiopancreatography (ERCP) and LC combined with LC with CBD excision and stone extraction in one-stage suture in gallbladder and CBD stones.

Research methods
Total 94 patients with this condition from our hospital were selected for this study.

Research results
The incidence of complications was lower in the study group than in the control group.

Research conclusions
The treatment of gallbladder and CBD stones by LC combined with ERCP is worth promoting.

Research perspectives
The sample size was not large enough; a larger multicenter study is needed to confirm these results.

FOOTNOTES

Author contributions: Tian YB designed the research study; Niu H performed the research; Liu F contributed new reagents and analytic tools; Niu H analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Jincheng Hospital Institutional Review Board (Approval No. 2021LL1203).

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors report none of conflict of interest.

Data sharing statement: No additional data are available.

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S-Editor: Wang JL
L-Editor: A
P-Editor: Wang JL

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Prospective Study

Patient reported outcome measures in anterior cruciate ligament rupture and reconstruction: The significance of outcome score prediction

Oday Al-Dadah, Lee Shepstone, Simon T Donell

Abstract

BACKGROUND

Numerous anterior cruciate ligament (ACL) clinical outcome measures exist. However, the result of one score does not equate to the findings of another even when evaluating the same patient group.

AIM

To investigate if statistically derived formulae can be used to predict the outcome of one knee scoring system when the result of another is known in patients with ACL rupture before and after reconstruction.

METHODS

Fifty patients with ACL rupture were evaluated using nine clinical outcome measures. These included Tegner Activity Score, Lysholm Knee Score, Cincinnati Knee Score, International Knee Documentation Committee (IKDC) Objective Knee Score, Tapper and Hoover Meniscal Grading Score, IKDC Subjective Knee Score, Knee Outcome Survey - Activities of Daily Living Scale (KOS-ADLS), Short Form-12 Item Health Survey and Knee Injury and Osteoarthritis Outcome Score. Thirty-four patients underwent an ACL reconstruction and were reassessed post-
RESULTS

The mean total of each of the nine outcome scores appreciably differed from each other. Significant correlations and regressions were found between most of the outcome scores and were stronger post-operatively. The strongest correlation was found between Cincinnati and KOS-ADLS \((r = 0.91, P < 0.001)\). The strongest regression formula was also found between Cincinnati and KOS-ADLS \((R^2 = 0.84, P < 0.001)\).

CONCLUSION

The formulae produced from this study can be used to predict the outcome of one knee score when the results of the other are known. These formulae could facilitate the conduct of systematic reviews and meta-analysis in studies relating to ACL injuries by allowing the pooling of substantially more data.

Key Words: Anterior cruciate ligament; Prediction; Regression; Correlation; Patient reported outcome measures; Reconstruction; Rupture

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Core Tip: Numerous anterior cruciate ligament (ACL) knee scoring systems exist in the literature. However, the result of one outcome measure does not equate to the findings of another even when evaluating the same patient group. Comparing the results of studies that have investigated the same field but have used different outcome measures then becomes problematic. These restrictions are especially pronounced when researchers attempt to pool data from the published literature for the purpose of statistical analysis in the context of meta-analysis and systematic reviews. The formulae produced from this study can be used to predict the outcome of one knee score when the results of the other are known. These formulae could facilitate the conduct of systematic reviews and meta-analysis in studies relating to ACL injuries by allowing the pooling of substantially more data.

Citation: Al-Dadah O, Shepstone L, Donell ST. Patient reported outcome measures in anterior cruciate ligament rupture and reconstruction: The significance of outcome score prediction. World J Clin Cases 2022; 10(30): 10939-10955

URL: https://www.wjgnet.com/2307-8960/full/v10/i30/10939.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.10939

INTRODUCTION

Patient reported outcome measures (PROMs) can be used to determine injury severity and evaluate the effectiveness of treatment. PROMs can quantify the end results of interventions and focus on the patients’ experiences, preferences and values. Clinical outcome scores have an important academic and clinical role in all fields of medicine as they are patient centred. PROMs can assess impairment and disability. Impairment is the physiological or anatomical loss or abnormality of structure or function at the organ level (i.e. reduced range of joint movement or increased joint translation). Disability is the functional limitation consequent to impairment which restricts the ability to perform certain activities (i.e. walking, running, participating in sport). Handicap is the physical disadvantage incurred in the context of the individual as a result of impairment and disability[1]. An anterior cruciate ligament (ACL) rupture can give rise to excessive knee joint laxity (impairment) which can result in difficulty with fast cutting actions (disability) and so can be a handicap for a professional athlete but not necessarily for a sedentary office worker. Outcome measures (also known as instruments) often take the form of questionnaires which include a standardised set of questions and response choices which yield data that are amenable to further statistical analysis. Each questionnaire is comprised of a series of items. Each item represents a single question or statement along with its standardised set of responses. The final scores in many instruments are usually calculated by summing the answers to each of the individual question items. The total scores in some outcome measures can be graded and expressed as excellent, good, fair or poor.

PROMs can be broadly categorised into generic, disease-specific, clinician-completed and patient-completed instruments. The use of these instruments in clinical research allows the patients’ perspective to be taken into consideration when investigating a disease process or evaluating the results of an intervention. Although traditionally end-points such as plain radiographs, measured ligament laxity
Table 1 Demographics of subjects

<table>
<thead>
<tr>
<th>ACL patients (n = 50)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yr) (SD)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Male:Female</td>
<td>36:14</td>
</tr>
<tr>
<td>Injured knee (Right:Left)</td>
<td>24:26</td>
</tr>
<tr>
<td>Mean height (m) (SD)</td>
<td>1.72 (0.1)</td>
</tr>
<tr>
<td>Mean weight (kg) (SD)</td>
<td>78.1 (14.4)</td>
</tr>
<tr>
<td>Mean BMI (kg/m^2) (SD)</td>
<td>26.2 (3.8)</td>
</tr>
</tbody>
</table>

ACL: Anterior cruciate ligament; BMI: Body mass index; SD: Standard deviation.

and clinical findings have been used as the primary outcome measures, an increasing emphasis on the
use of health-related quality of life instruments is emerging in the conduct of clinical trials. This is
reflected by the dramatic increase in the number of validated clinical outcome measures reported in the
literature today.

Between 1984 and 1997 over 200 articles were published relating to ACL injuries according to a
review article[2]. There were 54 distinctly different outcome measures identified that were specifically
designed for assessing ACL injuries. This indicates that there is no single agreed ‘gold standard’ PROM
relating to ACL outcome research. O’Donoghue[3] described the first outcome score used to assess the
results of ACL surgery in 1955. This was a clinician-completed rating scale which included an objective
examination and a 100-point questionnaire completed by the interviewer. In order to evaluate patients
with ACL injuries, many more individual clinical outcome measures have been created.

As a result, numerous ACL knee scoring systems exist in the literature. However, the result of one
outcome measure does not equate to the findings of another even when evaluating the same patient
group. In a prospective study, Bollen et al[4] assessed a group of patients with ACL injuries and found
that the subjects scored consistently higher on the Lysholm knee score than on the Cincinnati score.
Other authors[5,6] have found similar discrepancies among comparisons of various other validated
knee outcome scores.

We conducted a prospective longitudinal study analysing PROM data in patients with ACL rupture
before and after reconstructive knee surgery. The primary aim of this study was to assess the statistical
correlation between all the clinical outcome scoring systems. The secondary aim of this study was to
investigate if statistically derived formulae from regression analysis can be used to predict the outcome
of one knee scoring system when the result of another is known.

MATERIALS AND METHODS

Full approval was received for the study from the Research Ethics Committee and the Research
Governance Committee. All subjects signed informed consent forms to participate. This therapeutic
study is a prospective longitudinal cohort study and formed part of the first author’s Doctorate thesis.
Some data points in this study also served as data in the therapeutic arm of another case-control study
submitted for publication.

A total of 50 subjects were recruited to the study. Their demographics are detailed in Table 1. The
mean time from injury to clinic review was 63 wk (SD = 59). An ACL rupture was diagnosed by clinical
history and examination and MRI scan of the injured knee for all patients. The diagnosis was confirmed
at the time of knee arthroscopy. Clinical history and examination confirmed a normal contra-lateral
knee. The flow of patients through the study is illustrated in Figure 1. Four patients with delayed
surgical intervention postponed their operation for personal reasons (i.e. work or university
commitments). Of the 34 patients who underwent ACL reconstruction, 25 had an ipsilateral middle
third bone-patella tendon-bone autograft and nine had an ipsilateral quadrupled hamstring autograft.
At the time of surgery 11 patients were found to have a concomitant medial meniscal tear, eight patients
had a lateral meniscal tear and 11 patients had both a medial and a lateral meniscal tear. The mean time
to follow-up was 14 wk (SD = 4) following surgery.

Inclusion criteria were subjects 16 to 45 years of age. Exclusion criteria included patients with a
concomitant posterior cruciate ligament, medial collateral ligament or lateral collateral ligament tear of
the knee, significant history of ankle or hip pathology, lumbar spine symptoms (including radiculopathy
in either limb), neurological or vestibular disease, diabetes or regular use of opiate analgesics.

A total of nine clinical outcome measures were used in this study. Five were clinician-completed
instruments and four were patient-completed instruments. These instruments were chosen because they
are the most commonly used in the literature with the exception of the Tapper and Hoover Grading Score which was included as it is the only outcome measure specifically developed to assess meniscal injuries. All of the above clinical outcome measures have been validated for use in assessing patients with knee injuries. The clinician-completed knee scores were undertaken at the time of the subjects’ attendance at the research clinic. The patient-completed knee scores were mailed to the subjects approximately 7 d prior to their attendance at the research clinic. Therefore, the participants completed these outcome measures in their own time and provided a completely uninfluenced evaluation and perception of their functional knee impairment. All subjects were assessed with these outcome measures at baseline (pre-operatively) and reassessed post-operatively (for the subjects who were followed-up after surgery).

The patient reported outcome measures investigated in this study included: Tegner Activity Score\(^7\); Lysholm Knee Score\(^7\); Cincinnati Knee Score\(^8-10\); International Knee Documentation Committee (IKDC) Examination Score\(^11,12\); Tapper and Hoover Meniscal Grading Score\(^13\) (T&H); IKDC Subjective Knee Score\(^14,15\); Knee Outcome Survey - Activities of Daily Living Scale\(^16\) (KOS-ADLS); Short Form - 12 Item Health Survey\(^17\) (SF-12); Knee Injury and Osteoarthritis Outcome Score\(^18,19\) (KOOS).

**Statistical analysis**

A post-hoc power calculation for this study was derived from the results of the longitudinal within-group data of the Lysholm score as detailed in Table 2. The sample size of 34 subjects based on a conventional type I error of 5% with a within-group mean difference of 13.6 and a within-group standard deviation of 12.8 yielded a statistical power calculation of 99.1% for this study. All continuous data variables displayed a normal distribution as verified by both plotted histograms and the Shapiro-Wilks test. The results were evaluated using the Pearson product moment correlation test and the linear and multiple linear regression tests to analyse the continuous variables. The results of both the IKDC Examination score and the T&H score were categorical ordinal variables and the appropriate non-parametric statistical test (Spearman rank-order correlation test) was used for their analysis. The level of statistical significance was set at \(P < 0.05\). Statistical analysis was performed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, United States). The power calculation was performed using Minitab statistical software version 19 (Minitab LLC, State College, PA, United States).

**RESULTS**

The mean and mode averages for each of the clinical outcome measures (continuous and categorical variables respectively) are displayed in Table 2.

Table 3 presents the results of the correlation analysis between each of the knee outcome scores (continuous variables) pre-operatively. In general, a significant correlation was found between most of the knee outcome scores with the strongest correlation being between the Lysholm and the Cincinnati scores. The SF-12 mental component summary (MCS) was found to be the weakest correlate variable overall.

Table 4 presents the results of the correlation analysis between each of the knee outcome scores (categorical with continuous variables) pre-operatively. The Tapper and Hoover Meniscal Grading score was found to have a significant correlation with all of the knee outcome scores except for the SF-12 MCS score. The IKDC examination score had a poorer correlation with all the knee outcome scores compared to the Tapper and Hoover Meniscal Grading score. There was also no correlation found between the
Table 2 Results of knee outcome scores

<table>
<thead>
<tr>
<th></th>
<th>Pre-operative (n = 50)</th>
<th>Post-operative (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD</td>
</tr>
<tr>
<td>Tegner</td>
<td>3.3 (1.2)</td>
<td>4.1 (0.9)</td>
</tr>
<tr>
<td>Lysholm</td>
<td>71.7 (12.8)</td>
<td>85.3 (10.5)</td>
</tr>
<tr>
<td>Cincinnati</td>
<td>62.6 (14.7)</td>
<td>75.9 (9.2)</td>
</tr>
<tr>
<td>IKDC Sub.</td>
<td>51.5 (17.0)</td>
<td>58.1 (15.6)</td>
</tr>
<tr>
<td>KOS-ADLS</td>
<td>71.9 (20.5)</td>
<td>76.5 (14.3)</td>
</tr>
<tr>
<td>SF-12 PCS</td>
<td>41.8 (9.1)</td>
<td>43.2 (10.0)</td>
</tr>
<tr>
<td>SF-12 MCS</td>
<td>51.3 (9.2)</td>
<td>52.6 (7.9)</td>
</tr>
<tr>
<td>KOOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>72.5 (15.1)</td>
<td>71.3 (14.4)</td>
</tr>
<tr>
<td>Pain</td>
<td>76.9 (14.4)</td>
<td>77.9 (15.8)</td>
</tr>
<tr>
<td>ADL</td>
<td>84.5 (15.1)</td>
<td>87.3 (11.3)</td>
</tr>
<tr>
<td>Sp. &amp; Rec.</td>
<td>49.2 (24.9)</td>
<td>43.2 (26.1)</td>
</tr>
<tr>
<td>QOL</td>
<td>25.8 (18.7)</td>
<td>39.0 (18.0)</td>
</tr>
<tr>
<td>IKDC Exam.</td>
<td>Abnormal</td>
<td>Nearly normal</td>
</tr>
<tr>
<td>T&amp;H</td>
<td>Fair</td>
<td>Good</td>
</tr>
</tbody>
</table>

IKDC: International Knee Documentation Committee; Sub: Subjective knee score; Exam: Examination score; KOS-ADLS: Knee Outcome Survey - Activities of Daily Living Scale; SF-12: Short Form - 12 Item Health Survey; PCS: Physical component summary; MCS: Mental component scores; KOOS: Knee Injury and Osteoarthritis Outcome Score; ADL: Activities of daily living; QOL: Quality of life; T&H: Tapper and Hoover Meniscal Grading Score; SD: Standard deviation.

Table 5 presents the results of the correlation analysis between each of the knee outcome scores (continuous variables) post-operatively. Overall a significant correlation was found between most of the knee outcome scores with the strongest correlation being between the Cincinnati and the KOS-ADLS scores. It is also evident that in general, the post-operative correlations are stronger in comparison to the pre-operative results.

Table 6 presents the results of the correlation analysis between each of the knee outcome scores (categorical with continuous variables) post-operatively. The Tapper and Hoover Meniscal Grading score was found to have a significant correlation with all of the knee outcome scores and had a stronger correlation with each knee score compared to the IKDC examination score. There was also no correlation found between the IKDC examination score and the Tapper and Hoover Meniscal Grading score.

Figure 2 displays the results of the linear regression analysis between the knee outcome measures (continuous variables) pre-operatively which produce one overall outcome result. The stated formulae can be used to predict the outcome of a knee score when the result of the other is known. The Lysholm vs Cincinnati knee score comparison yielded the strongest regression coefficient ($R^2 = 0.68$). The Tegner score was found to be the weakest regression variable overall ($R^2 < 0.3$).

Table 7 shows the results of the multiple linear regression analysis between the knee outcome measures (continuous variables) pre-operatively which produce two or more outcome results (i.e. SF-12 and KOOS scores). The stated formulae can be used to predict the outcome of a knee score when the results of the other variables are known. The KOS-ADLS vs KOOS knee score comparison yielded the strongest regression coefficient ($R^2 = 0.74$). The Tegner score was found to be the weakest comparator overall ($R^2 < 0.3$).

Figure 3 displays the results of the linear regression analysis between the knee outcome measures (continuous variables) post-operatively which produce one overall outcome result. The outcome of one knee score can be predicted by the formulae when the result of the other is known. The Cincinnati vs KOS-ADLS knee score comparison yielded the strongest regression coefficient ($R^2 = 0.84$). The Tegner score was found to be the weakest comparator overall ($R^2 < 0.3$). It is also evident that in general, the post-operative regression analyses are stronger in comparison to the pre-operative results.
Table 3 Correlations between pre-operative knee outcome scores (n = 50)

<table>
<thead>
<tr>
<th>Correlation coefficient</th>
<th>Tegner</th>
<th>Lysholm</th>
<th>Cincinnati</th>
<th>IKDC Sub.</th>
<th>KOS ADLS</th>
<th>SF-12, PCS</th>
<th>SF-12, MCS</th>
<th>KOOS Symp.</th>
<th>KOOS pain</th>
<th>KOOS ADL</th>
<th>KOOS Sp. &amp; Rec.</th>
<th>KOOS QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegner</td>
<td>-</td>
<td>0.32</td>
<td>0.49</td>
<td>0.47</td>
<td>0.39</td>
<td>0.5</td>
<td>0.12</td>
<td>0.36</td>
<td>0.3</td>
<td>0.26</td>
<td>0.37</td>
<td>0.3</td>
</tr>
<tr>
<td>Lysholm</td>
<td>0.32</td>
<td>-</td>
<td>0.83</td>
<td>0.62</td>
<td>0.74</td>
<td>0.49</td>
<td>0.38</td>
<td>0.68</td>
<td>0.64</td>
<td>0.52</td>
<td>0.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Cincinnati</td>
<td>0.023a</td>
<td>0.034a</td>
<td>-</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>0.007a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
</tr>
<tr>
<td>IKDC Sub.</td>
<td>0.47</td>
<td>0.62</td>
<td>0.66</td>
<td>-</td>
<td>0.73</td>
<td>0.65</td>
<td>0.36</td>
<td>0.68</td>
<td>0.69</td>
<td>0.65</td>
<td>0.75</td>
<td>0.63</td>
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<tr>
<td>KOS-ADLS</td>
<td>0.006a</td>
<td>0.74</td>
<td>0.8</td>
<td>0.73</td>
<td>-</td>
<td>0.69</td>
<td>0.52</td>
<td>0.72</td>
<td>0.73</td>
<td>0.82</td>
<td>0.65</td>
<td>0.59</td>
</tr>
<tr>
<td>SF-12, PCS</td>
<td>0.04a</td>
<td>0.49</td>
<td>0.56</td>
<td>0.65</td>
<td>0.69</td>
<td>-</td>
<td>0.27</td>
<td>0.63</td>
<td>0.65</td>
<td>0.65</td>
<td>0.6</td>
<td>0.55</td>
</tr>
<tr>
<td>SF-12, MCS</td>
<td>0.12</td>
<td>0.38</td>
<td>0.37</td>
<td>0.36</td>
<td>0.52</td>
<td>0.27</td>
<td>-</td>
<td>0.32</td>
<td>0.41</td>
<td>0.47</td>
<td>0.17</td>
<td>0.28</td>
</tr>
<tr>
<td>KOOS ADL</td>
<td>0.416</td>
<td>0.007a</td>
<td>0.009a</td>
<td>0.011a</td>
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<td>-</td>
<td>0.024a</td>
<td>0.004a</td>
<td>0.001a</td>
<td>0.247</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>Symp.</td>
<td>0.36</td>
<td>0.68</td>
<td>0.54</td>
<td>0.68</td>
<td>0.72</td>
<td>0.63</td>
<td>0.32</td>
<td>-</td>
<td>0.79</td>
<td>0.68</td>
<td>0.68</td>
<td>0.47</td>
</tr>
<tr>
<td>Pain</td>
<td>0.013a</td>
<td>0.014a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>0.024a</td>
<td>-</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>0.001a</td>
</tr>
<tr>
<td>ADL</td>
<td>0.3</td>
<td>0.64</td>
<td>0.63</td>
<td>0.69</td>
<td>0.73</td>
<td>0.65</td>
<td>0.41</td>
<td>0.79</td>
<td>-</td>
<td>0.8</td>
<td>0.61</td>
<td>0.53</td>
</tr>
<tr>
<td>Sp. &amp; Rec.</td>
<td>0.040a</td>
<td>0.014a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>0.004a</td>
<td>-</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
</tr>
<tr>
<td>QOL</td>
<td>0.26</td>
<td>0.52</td>
<td>0.58</td>
<td>0.65</td>
<td>0.82</td>
<td>0.65</td>
<td>0.47</td>
<td>0.68</td>
<td>0.8</td>
<td>0.64</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>QOL</td>
<td>0.074</td>
<td>0.014a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>0.247</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
<td>&lt; 0.001a</td>
</tr>
</tbody>
</table>

*Correlation coefficient indicates the strength and direction of the relationship between the variables.*

*P value indicates the statistical significance of the correlation.*
Table 4 Correlations between pre-operative knee outcome scores (n = 50)

<table>
<thead>
<tr>
<th>Correlation coefficient, P value</th>
<th>Tegner</th>
<th>Lysholm</th>
<th>Cincinnati</th>
<th>IKDC Sub.</th>
<th>KOS ADLS</th>
<th>SF-12, PCS</th>
<th>SF-12, MCS</th>
<th>KOOS Symp.</th>
<th>KOOS pain</th>
<th>KOOS ADL</th>
<th>KOOS Sp. &amp; Rec.</th>
<th>KOOS QOL</th>
<th>IKDC Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>IKDC Exam.</td>
<td>-0.11</td>
<td>-0.22</td>
<td>-0.31</td>
<td>-0.27</td>
<td>-0.33</td>
<td>-0.17</td>
<td>-0.17</td>
<td>-0.34</td>
<td>-0.23</td>
<td>-0.31</td>
<td>-0.34</td>
<td>-0.23</td>
<td>___</td>
</tr>
<tr>
<td>T&amp;H</td>
<td>-0.43</td>
<td>-0.67</td>
<td>-0.66</td>
<td>-0.64</td>
<td>-0.61</td>
<td>-0.6</td>
<td>-0.14</td>
<td>-0.63</td>
<td>-0.6</td>
<td>-0.51</td>
<td>-0.54</td>
<td>-0.46</td>
<td>0.17</td>
</tr>
<tr>
<td>0.002*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>0.001*</td>
<td>0.243</td>
</tr>
</tbody>
</table>

*Statistically significant at < 0.05 level.

Results of Spearman rank-order correlation analysis. IKDC: International Knee Documentation Committee; Sub: Subjective knee score; Exam: Examination score; KOS-ADLS: Knee Outcome Survey - Activities of Daily Living Scale; SF-12: Short Form - 12 Item Health Survey; PCS: Physical component summary; MCS: Mental component scores; KOOS: Knee Injury and Osteoarthritis Outcome Score; ADL: Activities of daily living; QOL: Quality of life; SD: Standard deviation.

Table 8 shows the results of the multiple linear regression analysis between the knee outcome measures (continuous variables) post-operatively which produce two or more outcome results (i.e. SF-12 and KOOS scores). The outcome of one knee score can be predicted by the formulae when the results of the other variables are known. The KOS-ADLS vs KOOS knee score comparison yielded the strongest regression coefficient ($R^2 = 0.87$). The Tegner score was again found to be the weakest comparator overall. It is apparent that the post-operative regression analyses are stronger in comparison to the pre-operative results.

**DISCUSSION**

Significant correlations were found between most of the clinical outcome scores before and after surgery. The strength of the correlations was higher post-operatively. Further statistical analysis produced formulae which allowed the outcome of one knee score to be calculated based on the results of the other outcome measures used in this study in patients with ACL ruptures.
Table 5 Correlations between post-operative knee outcome scores (n = 34)

<table>
<thead>
<tr>
<th></th>
<th>Tegner</th>
<th>Lysholm</th>
<th>Cincinnati</th>
<th>IKDC Sub.</th>
<th>KOS ADLS</th>
<th>SF-12, PCS</th>
<th>SF-12, MCS</th>
<th>KOOS Symp.</th>
<th>KOOS pain</th>
<th>KOOS ADL</th>
<th>KOOS Sp. &amp; Rec.</th>
<th>KOOS QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegner</td>
<td>0.36</td>
<td>0.47</td>
<td>0.51</td>
<td>0.37</td>
<td>0.49</td>
<td>0.35</td>
<td>0.35</td>
<td>0.28</td>
<td>0.38</td>
<td>0.16</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Lysholm</td>
<td>-</td>
<td>0.037</td>
<td>0.006</td>
<td>0.005</td>
<td>0.032</td>
<td>0.004</td>
<td>0.046</td>
<td>0.044</td>
<td>0.121</td>
<td>0.028</td>
<td>0.384</td>
<td>0.002</td>
</tr>
<tr>
<td>Cincinnati</td>
<td>0.36</td>
<td>-</td>
<td>0.09</td>
<td>0.71</td>
<td>0.77</td>
<td>0.32</td>
<td>0.61</td>
<td>0.74</td>
<td>0.72</td>
<td>0.34</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>IKDC Sub.</td>
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<td>-</td>
<td>0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.07</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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<td>&lt; 0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>KOOS-ADLS</td>
<td>0.47</td>
<td>0.006</td>
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<td>0.025</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
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<td>&lt; 0.001</td>
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<td>&lt; 0.001</td>
</tr>
<tr>
<td>SF-12, PCS</td>
<td>0.49</td>
<td>0.77</td>
<td>0.91</td>
<td>0.84</td>
<td>0.77</td>
<td>0.47</td>
<td>0.74</td>
<td>0.74</td>
<td>0.81</td>
<td>0.59</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>SF-12, MCS</td>
<td>0.35</td>
<td>0.32</td>
<td>0.39</td>
<td>0.47</td>
<td>0.45</td>
<td>0.25</td>
<td>0.56</td>
<td>0.45</td>
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<tr>
<td>KOOS</td>
<td>0.48</td>
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<td>0.025</td>
<td>0.006</td>
<td>0.008</td>
<td>0.16</td>
<td>-</td>
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<td>0.008</td>
<td>0.004</td>
<td>0.288</td>
<td>0.010</td>
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<tr>
<td>Symp.</td>
<td>0.35</td>
<td>0.61</td>
<td>0.73</td>
<td>0.74</td>
<td>0.82</td>
<td>0.57</td>
<td>0.56</td>
<td>-</td>
<td>0.75</td>
<td>0.69</td>
<td>0.61</td>
<td>0.58</td>
</tr>
<tr>
<td>Pain</td>
<td>0.44</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ADL</td>
<td>0.28</td>
<td>0.74</td>
<td>0.82</td>
<td>0.74</td>
<td>0.87</td>
<td>0.72</td>
<td>0.45</td>
<td>0.75</td>
<td>-</td>
<td>0.86</td>
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<td>0.53</td>
</tr>
<tr>
<td>Sp. &amp; Rec.</td>
<td>0.38</td>
<td>0.72</td>
<td>0.85</td>
<td>0.81</td>
<td>0.86</td>
<td>0.83</td>
<td>0.48</td>
<td>0.69</td>
<td>0.86</td>
<td>-</td>
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<td>0.54</td>
</tr>
<tr>
<td>QOL</td>
<td>0.28</td>
<td>0.034</td>
<td>0.004</td>
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<td>&lt; 0.001</td>
<td>0.005</td>
<td>0.288</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>-</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Al-Dadah O et al. ACL score prediction

Results of Pearson product moment correlation analysis. IKDC: International Knee Documentation Committee; Sub: Subjective knee score; KOS-ADLS: Knee Outcome Survey - Activities of Daily Living Scale; SF-12: Short Form - 12 Item Health Survey; PCS: Physical component summary; MCS: Mental component scores; KOOS: Knee Injury and Osteoarthritis Outcome Score; ADL: Activities of daily living; QOL: Quality of life; SD: Standard deviation.

Table 6 Correlations between post-operative knee outcome scores (n = 34)

<table>
<thead>
<tr>
<th>Correlation coefficient, P value</th>
<th>Tegner</th>
<th>Lysholm</th>
<th>Cincinnati</th>
<th>IKDC Sub.</th>
<th>KOS ADLS</th>
<th>SF-12, PCS</th>
<th>SF-12, MCS</th>
<th>KOOS Symp.</th>
<th>KOOS pain</th>
<th>KOOS ADL</th>
<th>KOOS Sp. &amp; Rec.</th>
<th>KOOS QOL</th>
<th>IKDC Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>IKDC Exam.</td>
<td>-0.34</td>
<td>-0.3</td>
<td>-0.39</td>
<td>-0.42</td>
<td>-0.35</td>
<td>-0.39</td>
<td>0.02</td>
<td>-0.17</td>
<td>-0.35</td>
<td>-0.35</td>
<td>-0.36</td>
<td>-0.38</td>
<td>-</td>
</tr>
<tr>
<td>0.056</td>
<td>0.095</td>
<td>0.024&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.016&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.044&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.024&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.93</td>
<td>0.324</td>
<td>0.044&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.043&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.035&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.025&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>T&amp;H</td>
<td>-0.51</td>
<td>-0.62</td>
<td>-0.55</td>
<td>-0.61</td>
<td>-0.63</td>
<td>-0.6</td>
<td>-0.55</td>
<td>-0.62</td>
<td>-0.59</td>
<td>-0.45</td>
<td>-0.61</td>
<td>0.2</td>
<td>0.26</td>
</tr>
<tr>
<td>0.002&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.009&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

Statistically significant at < 0.05 level.

Results of Spearman rank-order correlation analysis. IKDC: International Knee Documentation Committee; Sub: Subjective knee score; Exam: Examination score; KOS-ADLS: Knee Outcome Survey - Activities of Daily Living Scale; SF-12: Short Form - 12 Item Health Survey; PCS: Physical component summary; MCS: Mental component scores; KOOS: Knee Injury and Osteoarthritis Outcome Score; ADL: Activities of daily living; QOL: Quality of life; T&H: Tapper and Hoover Meniscal Grading Score; SD: Standard deviation.

A longitudinal approach was undertaken to test the hypotheses in this study. This allowed the correlation results pre-operatively to be compared directly to that of the post-operative findings of the same individuals. The strength of the correlations was found to be greater following ACL reconstruction. This may be due to a more uniform comparison from time of surgery to clinic assessment post-operatively as compared to the greater diversity with regards to time of injury to clinic review pre-operatively of the ACL patients. Most of the patients with an ACL rupture had chronic injuries however some subjects had relatively acute ruptures which may have had a bearing on the results of the outcome measures prior to surgery. This could explain the slightly lower correlation between the pre-operative knee scores as compared to the post-operative results. The strongest correlation was found between the Lysholm and the Cincinnati knee scores ($r = 0.83$) pre-operatively. The weakest overall comparator before surgery was the SF-12, in particular the MCS sub-score. This may be explained by the fact that the SF-12 is a generic outcome measure while all the other eight instruments are disease-specific to knee pathology. Post-operatively the strongest correlation was found between the Cincinnati and the KOS-ADLS scores ($r = 0.91$). The IKDC objective examination score is a more elaborate and detailed outcome measure than the Tapper and Hoover Meniscal grading system which was originally designed to assess meniscal tears. However, the latter outcome measure was found to have a stronger correlation with all the other knee scores than the IKDC objective score before
and after surgery.

Linear and multiple linear regression analyses were used to generate predictive formulae which allowed the outcome of one knee score to be calculated based on the result of another instrument. These formulae could facilitate the conduct of systematic reviews and meta-analysis in studies relating to ACL injuries by allowing the pooling of data of the results of different knee scoring systems. Similar to the correlation analyses, the results of the regression analyses were stronger post-operatively as compared to the pre-operative findings. The main weakness of this component of the study was the regression analysis results pertaining to the Tegner activity score which was consistently found to be the weakest variable pre-operatively ($R^2 < 0.3$) and post-operatively. A small regression coefficient (i.e. value near to 0) implies that the explanatory variable $X$ (i.e. Tegner activity score) can only account for and explain a small proportion of the total variation of the response variable $Y$ (i.e. Lysholm score, $R^2 = 0.11$) when the results are fitted into the regression equation ($Y = a + bX$ were $a =$ intercept and $b =$ slope).

There are many clinical outcome measures available which can be used in association with ACL injuries. Bollen et al\cite{4} compared the results obtained from the Lysholm and Cincinnati knee scores in patients with ACL deficient knees and found that the latter scale consistently produced lower scores for each patient as compared to that of the Lysholm knee score. This was also noted in the present study both in the pre-operative and post-operative results. A small regression coefficient (i.e. value near to 0) implies that the explanatory variable $X$ (i.e. Tegner activity score) can only account for and explain a small proportion of the total variation of the response variable $Y$ (i.e. Lysholm score, $R^2 = 0.11$) when the results are fitted into the regression equation ($Y = a + bX$ were $a =$ intercept and $b =$ slope).

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### Table 8 Multiple linear regression analysis of post-operative knee outcome scores (n = 34)

<table>
<thead>
<tr>
<th>Equation (R², P value, σₑ)</th>
<th>KOOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegner = 1.2 + (0.01 × Symp.) + (0.02 × Pain) + (0.04 × ADL) - (0.01 × Sp. &amp; Rec.) + (0.02 × QOL)</td>
<td>(R² = 0.33, P = 0.042, σₑ = 0.8)</td>
</tr>
<tr>
<td>Lysholm = 31.6 + (0.12 × Symp.) + (0.29 × Pain) + (0.28 × ADL) - (0.08 × Sp. &amp; Rec.) + (0.02 × QOL)</td>
<td>(R² = 0.60, P &lt; 0.001, σₑ = 7.2)</td>
</tr>
<tr>
<td>Cincinnati = 20.9 + (0.12 × Symp.) + (0.14 × Pain) + (0.39 × ADL) - (0.04 × Sp. &amp; Rec.) + (0.09 × QOL)</td>
<td>(R² = 0.80, P &lt; 0.001, σₑ = 4.5)</td>
</tr>
<tr>
<td>IKDC Subjective = (0.23 × Symp.) - (0.07 × Pain) + (0.69 × ADL) + (0.05 × Sp. &amp; Rec.) + (0.27 × QOL) - 26.5</td>
<td>(R² = 0.79, P &lt; 0.001, σₑ = 7.9)</td>
</tr>
<tr>
<td>KOS-ADLS = (0.29 × Symp.) + (0.25 × Pain) + (0.42 × ADL) + (0.000009 × Sp. &amp; Rec.) + (0.11 × QOL) - 5.4</td>
<td>(R² = 0.87, P &lt; 0.001, σₑ = 5.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equation (R², P value, σₑ)</th>
<th>SF-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegner = 0.8 + (0.04 × PCS) + (0.03 × MCS)</td>
<td>(R² = 0.30, P = 0.005, σₑ = 0.8)</td>
</tr>
<tr>
<td>Lysholm = 44.4 + (0.70 × PCS) + (0.20 × MCS)</td>
<td>(R² = 0.52, P &lt; 0.001, σₑ = 7.5)</td>
</tr>
<tr>
<td>Cincinnati = 34.1 + (0.67 × PCS) + (0.24 × MCS)</td>
<td>(R² = 0.65, P &lt; 0.001, σₑ = 5.6)</td>
</tr>
<tr>
<td>IKDC Subjective = (1.07 × PCS) + (0.58 × MCS) - 18.8</td>
<td>(R² = 0.68, P &lt; 0.001, σₑ = 9.2)</td>
</tr>
<tr>
<td>KOS-ADLS = 7.9 + (0.97 × PCS) + (0.51 × MCS)</td>
<td>(R² = 0.65, P &lt; 0.001, σₑ = 8.8)</td>
</tr>
</tbody>
</table>

R²: Regression coefficient; σₑ: Root mean squared error. IKDC: International Knee Documentation Committee; Sub: Subjective knee score; KOS-ADLS: Knee Outcome Survey - Activities of Daily Living Scale; SF-12: Short Form - 12 Item Health Survey; PCS: Physical component summary; MCS: Mental component scores; KOOS: Knee Injury and Osteoarthritis Outcome Score; ADL: Activities of daily living; QOL: Quality of life.

Both the Lysholm and the Cincinnati knee scores produce results that are continuous variables. They can be converted into overall categorical ratings (i.e., excellent, good, fair or poor). However, in the present study the results were kept in their original raw continuous data format in order to facilitate the linear regression analysis. Sgaglione et al.[21] evaluated knee scoring instruments in patients who underwent ACL reconstruction. These included the Lysholm, Tegner and Cincinnati scores. They also found the scores obtained from the latter outcome measure were lower than the results obtained from the Lysholm scores for each individual patient. Furthermore, they found the results of the knee scores were inflated when the raw scores were converted to categorical ratings. They found that in general, the use of clinical outcome measures can lead to higher scores in patients with low activity levels as compared to subjects who are more active and place higher demands on their knee and so consequently experience greater symptoms. However, this can be accounted for by the inclusion of the Tegner activity score which takes into consideration the activity level of the subject.

In general, there are a number of factors which can influence the end result for each PROM score as reported by the individual patient themselves. These include the patient’s age, gender, level of athletic commitment, type of sport as the intricacies of many sports are different, chronicity of condition, type of surgery, patients that had opted out of surgery, ease of return-to-sport and level of return-to-sport all may affect the questionnaire scores.

As yet there is no single outcome measure that is universally considered as the solitary gold standard and therefore many studies use a combination of instruments when evaluating the results of their intervention. As different knee scoring systems yield different results, it is consequently difficult to analyse and compare the relative success of different interventions. This limitation is magnified when attempting to conduct a meta-analysis on a particular topic relating to ACL injury or surgery as the use of different outcome measures in each study limit the capacity to which the outcome data can be pooled.
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A

Lysholm = 25.4 + (0.72 \times \text{cincinnati})

R^2 = 0.68, P < 0.001, \sigma = 7.2

B

Lysholm = 48.0 + (0.46 \times \text{IKDC subjective})

R^2 = 0.38, P < 0.001, \sigma = 10.0

C

Lysholm = 36.1 + (0.50 \times \text{KOS-ADLS})

R^2 = 0.54, P < 0.001, \sigma = 8.6

D

Cincinnati = 35.6 + (0.56 \times \text{IKDC subjective})

R^2 = 0.43, P < 0.001, \sigma = 11.0

E

Cincinnati = 20.3 + (0.62 \times \text{KOS-ADLS})

R^2 = 0.64, P < 0.001, \sigma = 8.7

F

IKDC subjective = 4.5 + (0.66 \times \text{KOS-ADLS})

R^2 = 0.54, P < 0.001, \sigma = 11.6
CONCLUSION

Significant correlations were found between most of the clinical outcome measures used in this study with the strength of the correlations being greater post-operatively. Statistically derived formulae produced from this study can be used to predict the outcome of one knee score when the results of the other are known. These formulae could facilitate the conduct of systematic reviews and meta-analysis in studies relating to ACL injuries by allowing the pooling of substantially more data of the most commonly used knee outcome scores.
Al-Dadah O et al. ACL score prediction

- **A**: $\text{Lysholm} = 8.1 + (1.02 \times \text{cincinnati})$
  $R^2 = 0.80, P < 0.001, \sigma E = 4.8$

- **B**: $\text{Lysholm} = 57.3 + (0.48 \times \text{IKDC subjective})$
  $R^2 = 0.51, P < 0.001, \sigma E = 7.5$

- **C**: $\text{Lysholm} = 41.7 + (0.57 \times \text{KOS-ADLS})$
  $R^2 = 0.60, P < 0.001, \sigma E = 6.8$

- **D**: $\text{Cincinnati} = 45.9 + (0.52 \times \text{IKDC subjective})$
  $R^2 = 0.75, P < 0.001, \sigma E = 4.7$

- **E**: $\text{Cincinnati} = 30.5 + (0.59 \times \text{KOS-ADLS})$
  $R^2 = 0.84, P < 0.001, \sigma E = 3.8$

- **F**: $\text{IKDC subjective} = (0.92 \times \text{KOS-ADLS}) - 11.8$
  $R^2 = 0.70, P < 0.001, \sigma E = 8.6$
ARTICLE HIGHLIGHTS

Research background
Many different types of clinical outcome scores exist regarding the anterior cruciate ligament (ACL).

Research motivation
To evaluate how the commonly used patient reported outcome scores (PROMs) differ from each other in the context of ACL injuries.

Research objectives
To develop mathematical formulae which will allow the results of one score to be calculated from the results of the other.

Research methods
PROM data was collected from patients before and after ACL reconstruction surgery and statistically analyzed using correlation and regression tests.

Research results
Statistically significant results for both the correlation and regression analyses were found between most of the outcome scores and were generally stronger following surgery.
Research conclusions
The mathematical formulae produced from this study can be used to predict the outcome of one knee score when the results of the other are known.

Research perspectives
These mathematical formulae can facilitate the conduct of systematic reviews and meta-analysis in studies relating to ACL surgery by allowing the pooling of substantially more data.

FOOTNOTES

Author contributions: Al-Dadah O made substantial contributions to conception and design of the study and acquisition of data; He also performed the analysis and interpretation of data; Has been involved in drafting the manuscript and revising it critically for important intellectual content; Has given final approval of the version to be published; Shepstone L made substantial contributions to conception and design of the study; He also made substantial contributions to the analysis and interpretation of data; Has been involved in drafting the manuscript and revising it critically for important intellectual content; Has given final approval of the version to be published; Donell ST made substantial contributions to conception and design of the study; He also made substantial contributions to the interpretation of data; Has been involved in drafting the manuscript and revising it critically for important intellectual content; Has given final approval of the version to be published.

Institutional review board statement: Full approval was received for the study from the Research Ethics Committee and the Research Governance Committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee [East Norfolk and Waveney Research Governance Committee, United Kingdom (ID 116/07/07)] and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Clinical trial registration statement: This study was not registered on any trial registry.

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare that they have no conflict of interest.

Data sharing statement: The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study and in keeping with the United Kingdom General Data Protection Regulation and also the host study organization’s patient confidentiality guidelines.

CONSORT 2010 statement: The authors have read the CONSORT Statement—checklist of items, and the manuscript was prepared and revised according to the CONSORT Statement—checklist of items.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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Body mass index and outcomes of patients with cardiogenic shock: A systematic review and meta-analysis

Wen-Xia Tao, Guo-Ying Qian, Hong-Dan Li, Feng Su, Zhou Wang

BACKGROUND
Cardiogenic shock continues to be a highly morbid complication that affects around 7%-10% of patients with acute myocardial infarction or heart failure. Similarly, obesity has become a worldwide epidemic.

AIM
To analyze the impact of higher body mass index (BMI) on outcomes of patients with cardiogenic shock.

METHODS
A systematic and comprehensive search was undertaken on the electronic databases of PubMed, Embase, ScienceDirect, CENTRAL, and Google Scholar for all types of studies comparing mortality outcomes of patients with cardiogenic shock based on BMI. All studies defined overweight or obese patients based on the World Health Organization BMI criteria. The data were then extracted and assessed on the basis of the Reference Citation Analysis (https://www.referencecitationanalysis.com/).

RESULTS
Five studies were included. On pooled analysis of multivariable-adjusted ratios, we noted a statistically significantly reduced risk of mortality in overweight/obese vs normal patients (three studies; odds ratio [OR] = 0.92, 95% confidence interval [CI]: 0.85-0.98, \(P = 85\%\)). On meta-analysis, we noted that crude mortality rates did not significantly differ between overweight/obese and normal patients after cardiogenic shock (OR = 0.95, 95%CI: 0.79-1.15, \(P = 99\%\)). The results were not stable on sensitivity analysis and were associated with substantial heterogeneity.

CONCLUSION
Current evidence on the association between overweight/obesity and mortality...
after cardiogenic shock is scarce and conflicting. The obesity paradox might exist in patients with cardiogenic shock but could be confounded by the use of mechanical circulatory support. There is a need for further studies to clarify this relationship.

**Key Words:** Obese; Overweight; Myocardial infarction; Shock; Mortality

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**Core Tip:** Cardiogenic shock continues to be a highly morbid complication that affects around 7%-10% of patients and similarly, obesity is now prevalent around the globe. We reviewed data from five studies to assess the impact of obesity on outcomes of cardiogenic shock. Pooled analysis of adjusted data indicated that overweight/obese was associated with a reduced risk of mortality vs normal patients but the same relationship was not noted in the analysis of crude mortality rates. Thus, current evidence on the association between overweight/obesity and mortality after cardiogenic shock is scarce and conflicting and there is a need for further studies.

**Citation:** Tao WX, Qian GY, Li HD, Su F, Wang Z. Body mass index and outcomes of patients with cardiogenic shock: A systematic review and meta-analysis. *World J Clin Cases* 2022; 10(30): 10956-10966

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i30/10956.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i30.10956

**INTRODUCTION**

Obesity is a recognized global health problem that has significantly burdened the entire healthcare system[1]. The epidemic of obesity has touched countries across the globe and more than 2 billion people are affected by it[2]. According to estimates, the prevalence of obesity has tripled since 1975 and more than 39% of adults older than 18 years were overweight in 2016[3]. The World Health Organization (WHO) defines obesity based on measurements of the body mass index (BMI) wherein an individual with a BMI ≥ 30 kg/m² is defined as obese while BMI ≥ 25 kg/m² is overweight[3]. The heightened prevalence of overweight and obesity can be attributed to the increasingly sedentary lifestyle which has affected most workplaces. Lack of physical activity and an unhealthy diet has significantly increased obesity in the past decade[4,5]. An important implication of high body fat is an increased risk of metabolic disorders like diabetes mellitus, coronary artery disease (CAD), cerebrovascular disorders, hypertension, and heart failure[6]. Despite the heightened risk of several cardiovascular diseases with obesity, recent research has uncovered the prevalence of the “obesity paradox” which suggests that patients with higher BMI have a better prognosis and lower mortality rates as compared to normal BMI patients[7]. Niedziela et al[8] in a meta-analysis of patients with acute coronary syndrome have shown that overweight, obese, and severely obese patients had significantly lower mortality rates as compared to those with normal BMI. Similar outcomes have been noted by researchers for heart failure and septic shock[9,10]. Cardiogenic shock continues to be a highly morbid complication that affects around 7%-10% of patients with acute myocardial infarction (AMI) or heart failure[11,12]. It is a complex and hemodynamically diverse state of end-organ hypoperfusion which leads to high morbidity and mortality[11]. While several studies have analyzed the impact of obesity on outcomes of patients with acute coronary syndrome, it is still unclear how high BMI affects outcomes of patients with cardiogenic shock. The question that needs to be answered is: Does an obesity paradox exists in the prognosis of patients with cardiogenic shock or do obese patients have higher mortality as compared to normal BMI patients? To the best of our knowledge, this research question has been systematically analyzed by only one review to date. Meng et al[13] in a recently published meta-analysis pooled data from three studies to assess the association between high BMI and mortality after cardiogenic shock. An important limitation of their review was that two of the three studies were from the same database with a considerable overlap of data. To overcome this limitation, we hereby conducted an updated systematic review and meta-analysis to analyze the impact of high BMI on outcomes of cardiogenic shock.

**MATERIALS AND METHODS**

The methodology of our review was based on reporting guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[14]. The protocol of the review was
prospectively registered on PROSPERO (No. CRD42021274841).

**Literature search**

A systematic and comprehensive search was undertaken on the electronic databases of PubMed, Embase, ScienceDirect, and CENTRAL. Google Scholar was used to search the gray literature, but only for the first 200 results of each search query. To minimize single reviewer bias, two authors separately explored the databases. The search limits were set from the time of inception of databases up to 25th August 2021. Search terms included were: "obese", "obesity", "overweight", "body mass index", and "cardiogenic shock". Further details of the search strategy which was common for all databases are presented in Supplementary Table 1. Reference Citation Analysis (https://www.referencecitation-analysis.com/) was used to supplement the search. After the initial search, the results were deduplicated and the remaining articles were assessed by their titles and abstracts. We identified studies relevant to the review and extracted their full texts. The two reviewers independently evaluated these studies for final inclusion in the review. Any discrepancies in study selection were resolved by consensus. In the end, manual scoping of the reference list of included studies was carried out for any missed references.

**Eligibility criteria**

The inclusion criteria were: (1) All types of studies comparing mortality rates of patients with cardiogenic shock based on BMI; (2) Studies that clearly defined overweight or obese patients based on the WHO BMI criteria (i.e., overweight > 25 kg/m² and obese > 30 kg/m²) and compared outcomes with normal BMI patients; and (3) Language of publication should have been English. We excluded the following studies: (1) Studies including less than 50 patients; (2) Studies not reporting mortality outcomes; (3) Non-comparative studies; and (4) Studies reporting duplicate data. If the same database was used by two studies, we judged the period of overlap. In case of partial overlap, the study was included and the strength of the results was analyzed by a sensitivity analysis.

**Data extraction and quality assessment**

Two authors independently extracted the following data: Author details, publication year, study type, study location, BMI definition, primary diagnosis, sample size, demographic details, comorbidities (diabetes mellitus, hypertension, chronic kidney disease, dyslipidemia, and cardiovascular disease), revascularization details, use of mechanical circulatory support (MCS), and study outcomes. The primary outcome of the study was early mortality defined as in-hospital or 30-d mortality. The methodological quality of studies was assessed using the Newcastle-Ottawa scale[15]. It was conducted by two authors independent of each other. Any disagreements were solved by a discussion. Studies were assessed for selection of study population, comparability, and outcomes, with each domain being awarded a maximum of four, two, and three points, respectively. The maximum score which can be awarded was nine. Studies with a score of 9 points, 7-8 points, and 6 points and below were considered to have a low, moderate, and high risk of bias, respectively.

**Statistical analysis**

The meta-analysis was performed using “Review Manager” (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014). We extracted multivariable-adjusted odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs) on mortality rates and pooled them using the generic inverse variance function of RevMan. The final effect size was calculated as OR with 95% confidence interval (CI). Crude mortality rates were also extracted from the included studies and pooled OR was generated. All meta-analyses were conducted using the random-effects model. Heterogeneity was assessed using the I² statistic. I² values of 25%-50% represented low, values of 50%-75% medium, and more than 75% represented substantial heterogeneity. Funnel plots were not used to assess publication bias as less than ten studies were available for each meta-analysis. A sensitivity analysis was carried out to assess the contribution of each study to the pooled estimate by removing one study at a time and recalculating the pooled effect estimates for the remaining studies.

**RESULTS**

The search strategy and the number of records at each stage are presented in Figure 1. Based on the screening criteria, a total of five studies were included in this systematic review and meta-analysis[16-20]. Details of included studies are presented in Table 1. Three studies[16,17,20] were conducted in the United States, one in Denmark[18], and one in Pakistan[19]. All, except for one[19], were retrospective cohort studies. The primary diagnosis was AMI in all studies but the study of Sreenivasan et al[16] also included patients with heart failure. Two studies[17,20] used the same “National Inpatient database” from the United States with a partial overlap of data. Patlolla et al[17] and Chatterjee et al[20] used the database from 2008 to 2017 and 2004 to 2013, respectively. Thus, an overlap of six years was noted in these studies, albeit with a minor difference. Patlolla et al[17] reported combined data of overweight and
Table 1 Details of included studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Location</th>
<th>Type</th>
<th>Primary diagnosis</th>
<th>Groups</th>
<th>Definition as per BMI (kg/m²)</th>
<th>Sample size</th>
<th>Age (yr)</th>
<th>Male gender (%)</th>
<th>Smokers (%)</th>
<th>DM (%)</th>
<th>HTN (%)</th>
<th>CKD (%)</th>
<th>DL (%)</th>
<th>PCI (%)</th>
<th>CABG (%)</th>
<th>MCS (%)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sreenivasan et al [16], 2021</td>
<td>United States</td>
<td>R</td>
<td>AMI or HF</td>
<td>Severe obesity</td>
<td>&gt; 40</td>
<td>8782</td>
<td>59.9</td>
<td>52.3</td>
<td>NR</td>
<td>64.4</td>
<td>72.2</td>
<td>41.3</td>
<td>NR</td>
<td>53.2</td>
<td>25.8</td>
<td>100</td>
<td>30-d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate obesity</td>
<td>35-39.9</td>
<td>6862</td>
<td>60.9</td>
<td>68.9</td>
<td>NR</td>
<td>66</td>
<td>77.6</td>
<td>38.4</td>
<td>47.1</td>
<td>31</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild obesity</td>
<td>30-34.9</td>
<td>10880</td>
<td>62.9</td>
<td>71.2</td>
<td>NR</td>
<td>59.1</td>
<td>75.4</td>
<td>33.1</td>
<td>54.4</td>
<td>32.2</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
<td>20-29.9</td>
<td>7111</td>
<td>65.9</td>
<td>71.6</td>
<td>NR</td>
<td>45.4</td>
<td>65.5</td>
<td>39.8</td>
<td>47</td>
<td>27.5</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Underweight</td>
<td>&lt; 19.9</td>
<td>1920</td>
<td>65.6</td>
<td>67.9</td>
<td>NR</td>
<td>30.9</td>
<td>54</td>
<td>30.9</td>
<td>37.3</td>
<td>14.7</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patlolla et al [17], 2021</td>
<td>United States</td>
<td>R</td>
<td>AMI</td>
<td>Overweight/Obes.</td>
<td>&gt; 24.9</td>
<td>46675</td>
<td>63.8</td>
<td>60.3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>53.6</td>
<td>24.9</td>
<td>49</td>
<td>In-hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
<td>19.9-24.9</td>
<td>290333</td>
<td>69</td>
<td>64.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>53.6</td>
<td>16.3</td>
<td>45.7</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Underweight</td>
<td>&lt; 19.9</td>
<td>2356</td>
<td>73.7</td>
<td>49.4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>39.8</td>
<td>12.2</td>
<td>27.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hermansen et al [18], 2021</td>
<td>Denmark</td>
<td>R</td>
<td>AMI</td>
<td>Moderate/Severe</td>
<td>≥ 35</td>
<td>42</td>
<td>63</td>
<td>69</td>
<td>68</td>
<td>43</td>
<td>75</td>
<td>NR</td>
<td>55</td>
<td>100</td>
<td>0</td>
<td>17</td>
<td>30-d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Obesity</td>
<td>30-34.9</td>
<td>131</td>
<td>64</td>
<td>80</td>
<td>82</td>
<td>21</td>
<td>54</td>
<td>NR</td>
<td>34</td>
<td>100</td>
<td>0</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild obesity</td>
<td>25-29.9</td>
<td>391</td>
<td>65.2</td>
<td>82</td>
<td>79</td>
<td>21</td>
<td>55</td>
<td>NR</td>
<td>33</td>
<td>100</td>
<td>0</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overweight</td>
<td>&lt; 25</td>
<td>453</td>
<td>66.1</td>
<td>75</td>
<td>74</td>
<td>13</td>
<td>42</td>
<td>NR</td>
<td>29</td>
<td>100</td>
<td>0</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Hashmi et al [19], 2018</td>
<td>Pakistan</td>
<td>P</td>
<td>AMI</td>
<td>Obese</td>
<td>≥ 30</td>
<td>137</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>In-hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
<td>&lt; 30</td>
<td>214</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>In-hospital</td>
<td></td>
</tr>
<tr>
<td>Chatterjee et al [20], 2017</td>
<td>United States</td>
<td>R</td>
<td>AMI</td>
<td>Obese</td>
<td>≥ 30</td>
<td>25835</td>
<td>63.1</td>
<td>63</td>
<td>34.3</td>
<td>45.2</td>
<td>68.8</td>
<td>23.5</td>
<td>54.8</td>
<td>50.9</td>
<td>19.6</td>
<td>NR</td>
<td>In-hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
<td>&lt; 30</td>
<td>265059</td>
<td>69.4</td>
<td>62.3</td>
<td>24</td>
<td>24.4</td>
<td>50.6</td>
<td>18.9</td>
<td>33.8</td>
<td>47.9</td>
<td>13.6</td>
<td>In-hospital</td>
<td></td>
</tr>
</tbody>
</table>

AMI: Acute myocardial infarction; HF: Heart failure; BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; CKD: Chronic kidney disease; DL: Dyslipidemia; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; MCS: Mechanical circulatory support; NR: Not reported; R: Retrospective; P: Prospective.

Obese patients whereas Chatterjee et al [20] classified their sample as obese and non-obese only. All the studies used the WHO classification of overweight and obesity. Two studies [16,17] additionally classified obesity as mild, moderate, and severe. However, for the meta-analysis, all groups were combined into a single group of obese patients. The mean age of the patients was above 55 years in the majority of studies. The percentage of patients undergoing revascularization varied across the included studies. In the study of Hermansen et al [18], all patients underwent percutaneous coronary intervention and none underwent coronary artery bypass grafting (CABG). In general, fewer patients underwent CABG as compared to percutaneous interventions in the remaining studies across obese and non-obese groups. Two studies did not report data on the percentage of patients receiving MCS [19,20]. In the study of Sreenivasan et al [16], all patients received MCS while in the remaining two studies, the percentage...
varied from 15% to 49% across the study sub-groups. Two studies reported mortality outcomes within 30 d while the remaining reported in-hospital outcomes[16,18].

**Meta-analysis**

Amongst the included studies, three[16,17,20] reported multivariable-adjusted ratios on the relationship between overweight/obesity and early mortality. On pooled analysis, we noted a statistically significantly reduced risk of early mortality after cardiogenic shock in overweight/obese vs normal patients (OR = 0.92, 95%CI: 0.85-0.98) (Figure 2). There was significantly high heterogeneity in the meta-analysis (I² = 85%). Given the high heterogeneity, we conducted a sensitivity analysis by excluding one study at a time and recalculating the effect size. Results are presented in Table 2. In the exclusion of the study of Patlolla et al[17] and Chatterjee et al[20], the results indicated no difference in the risk of mortality in overweight/obese vs normal patients. Second, we also extracted crude early mortality rates and pooled them in a meta-analysis. Including data from all five studies[16-20], we noted that crude mortality rates did not significantly differ between overweight/obese and normal patients after cardiogenic shock (OR = 0.95, 95%CI: 0.79-1.15) (Figure 3). There was significantly high heterogeneity in the meta-analysis (I² = 99%). On sensitivity analysis (Table 2), we noted that the exclusion of the study of Sreenivasan et al[16] changed the significance of the results with a reduced risk of mortality in overweight/obese patients as compared to normal patients. A similar tendency was noted in the exclusion of the study of Hashmi et al[19].

We were unable to conduct any subgroup analysis to explore the source of high heterogeneity in the included studies due to the limited number of the included studies. However, a few studies conducted subgroup analysis in their respective cohorts and their results are descriptively presented in Table 3. Sreenivasan et al[16] further compared outcomes of obese and non-obese patients based on the primary diagnosis (acute AMI or heart failure) and age (< 60 years and ≥ 60 years). On the other hand, Chatterjee et al[20] conducted a subgroup analysis based on the type of AMI (ST-elevated and non-ST elevated) and the use of revascularization.

**Risk of bias**

The risk of bias analysis of included studies is presented in Table 4. Four studies[16,17,19,20] received a score of 7 while one study[18] received a score of 5.
Table 2 Sensitivity analysis for mortality rates

<table>
<thead>
<tr>
<th>Excluded study</th>
<th>Odds ratio</th>
<th>Adjusted mortality rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sreenivasan et al[16], 2021</td>
<td>0.89 95%CI: 0.87, 0.91</td>
<td>$I^2 = 0%$</td>
</tr>
<tr>
<td>Patilola et al[17], 2021</td>
<td>1.15 95%CI: 0.67, 2.00</td>
<td>$I^2 = 93%$</td>
</tr>
<tr>
<td>Chatterjee et al[20], 2017</td>
<td>1.15 95%CI: 0.67, 2.00</td>
<td>$I^2 = 93%$</td>
</tr>
</tbody>
</table>

Crude mortality rates

<table>
<thead>
<tr>
<th>Excluded study</th>
<th>Odds ratio</th>
<th>Adjusted mortality rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sreenivasan et al[16], 2021</td>
<td>0.79 95%CI: 0.70, 0.89</td>
<td>$I^2 = 95%$</td>
</tr>
<tr>
<td>Patilola et al[17], 2021</td>
<td>1.12 95%CI: 0.76, 1.67</td>
<td>$I^2 = 99%$</td>
</tr>
<tr>
<td>Hermansen et al[18], 2021</td>
<td>0.98 95%CI: 0.80, 1.20</td>
<td>$I^2 = 99%$</td>
</tr>
<tr>
<td>Hashmi et al[19], 2018</td>
<td>0.83 95%CI: 0.69, 1.00</td>
<td>$I^2 = 99%$</td>
</tr>
<tr>
<td>Chatterjee et al[20], 2017</td>
<td>1.13 95%CI: 0.80, 1.60</td>
<td>$I^2 = 99%$</td>
</tr>
</tbody>
</table>

Table 3 Subgroup analysis of mortality reported by included studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Subgroups</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sreenivasan et al[16], 2021</td>
<td>Acute MI only</td>
<td>Significantly higher mortality in severely obese patients as compared to normal patients</td>
</tr>
<tr>
<td></td>
<td>Acute HF only</td>
<td>Significantly higher mortality in severely obese patients as compared to normal patients</td>
</tr>
<tr>
<td></td>
<td>Age &lt; 60 years</td>
<td>Significantly higher mortality in severely obese patients as compared to normal patients</td>
</tr>
<tr>
<td></td>
<td>Age ≥ 60 years</td>
<td>Significantly higher mortality in severely obese patients as compared to normal patients</td>
</tr>
<tr>
<td>Chatterjee et al[20], 2017</td>
<td>ST-elevated MI</td>
<td>No statistically significant difference in mortality between obese and normal patients</td>
</tr>
<tr>
<td></td>
<td>Non-ST elevated MI</td>
<td>Significantly lower mortality in obese as compared to normal patients</td>
</tr>
<tr>
<td></td>
<td>Revascularization group</td>
<td>Significantly lower mortality in obese as compared to normal patients</td>
</tr>
<tr>
<td></td>
<td>Non-revascularization group</td>
<td>No statistically significant difference in mortality between obese and normal patients</td>
</tr>
</tbody>
</table>

MI: Myocardial infarction; HF: Heart failure.

![Figure 2](https://i.imgur.com/3Q5Q5Q5.png)

Figure 2  Meta-analysis of adjusted mortality rates between overweight/obese and normal patients with cardiogenic shock.

DISCUSSION

Obesity has been a well-recognized risk factor for a wide spectrum of cerebrovascular and cardiovascular diseases. Higher body fat increases the bulk of atherosclerotic plaques, which leads to plaque instability. It also generates a low-grade generalized inflammatory state which increases proinflammatory cytokines like C-reactive protein and interleukins[21]. Indeed, recent research suggests that anti-inflammatory therapies may reduce the risk of adverse cardiovascular events in patients with CAD, lending support to the inflammation hypothesis[22]. These proinflammatory cytokines have also been implicated in the pathophysiology of heart failure due to their cardio-depressant properties[23]. Despite being associated with the etiology of both CAD and heart failure, the mechanism by which high
Table 4: Risk of bias analysis based on Newcastle-Ottawa scale

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Follow-up long enough for outcomes</th>
<th>Adequate follow up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Representativeness of the exposed cohort</td>
<td>Selection of the non exposed cohort</td>
<td>Ascertainment of exposure</td>
<td>Demonstration that outcome of interest</td>
<td>Basis of the design or analysis</td>
<td>Assessment of outcome</td>
</tr>
<tr>
<td>Sreenivasan et al [16], 2021</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Patlolla et al [17], 2021</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hermansen et al [18], 2021</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hashmi et al [19], 2018</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chatterjee et al [20], 2017</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4: Risk of bias analysis based on Newcastle-Ottawa scale

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Overweight/Obese Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Odds ratio M-H, Random, 95%CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chatterjee 2017</td>
<td>7286</td>
<td>25835</td>
<td>96747</td>
<td>265059</td>
<td>0.68 (0.66, 0.70)</td>
<td>2017</td>
</tr>
<tr>
<td>Hashmi 2018</td>
<td>84</td>
<td>137</td>
<td>73</td>
<td>214</td>
<td>3.06 (1.96, 4.78)</td>
<td>2018</td>
</tr>
<tr>
<td>Hermansen 2021</td>
<td>221</td>
<td>564</td>
<td>198</td>
<td>453</td>
<td>0.83 (0.65, 1.07)</td>
<td>2021</td>
</tr>
<tr>
<td>Patlolla 2012</td>
<td>12882</td>
<td>46675</td>
<td>99003</td>
<td>290333</td>
<td>0.74 (0.73, 0.75)</td>
<td>2021</td>
</tr>
<tr>
<td>Sreenivasan 2020</td>
<td>7754</td>
<td>26424</td>
<td>1877</td>
<td>7111</td>
<td>1.16 (1.05, 1.23)</td>
<td>2021</td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>99635</td>
<td>563170</td>
<td>100%</td>
<td></td>
<td>0.95 (0.79, 1.15)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>28227</td>
<td>197898</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.04, Chi² = 291.16, df = 4 (P < 0.00001); I² = 99%
Test for overall effect: Z = 652 (P = 0.61)

Figure 3: Meta-analysis of crude mortality rates between overweight/obese and normal patients with cardiogenic shock.

BMI is associated with better outcomes in these patients, i.e., the obesity paradox, is still incompletely understood. Lavie et al [24] have pointed out that BMI per se does not describe the body composition and they found that patients with higher lean mass along with higher body fat had lower mortality due to CAD as compared to those with lower lean mass and lower body fat. Another aspect to consider is the cardiorespiratory fitness of the individual as poor fitness levels are associated with a poorer prognosis in CAD, independent of adiposity [25]. While the obesity paradox is firmly established in several cardiovascular diseases, its association with outcomes of patients with cardiogenic shock is still unclear. In the previous meta-analysis of three studies, Meng et al [13] noted no difference in all-cause mortality between obese and non-obese patients with cardiogenic shock (OR = 0.88, 95% CI: 0.71-1.08, I² = 96%). In a sub-group analysis, they found that cardiogenic shock mortality was lower in developed countries (United States), but higher in developing countries (Pakistan). In addition to the lower number of studies in this meta-analysis, several other errors make this previous review unreliable. Foremost is that the two included studies in their review used the same United States database from 2005-2014 and 2004-2013, which is a considerable overlap. Second, in their multivariable analysis, the authors included the trial of Hashmi et al [19] which only reported unadjusted ORs.

In our updated meta-analysis of five studies, we noted that overweight/obese patients did not have an increased risk of early mortality after cardiogenic shock as compared to normal BMI patients when only crude mortality rates were pooled. However, it is important to note that the significant heterogeneity in the meta-analyses reduces the confidence of our results. Assessing the included studies individually, we noted extremely divergent results amongst the studies. The studies of Sreenivasan et al [16] and Hashmi et al [19] demonstrated that obese patients had significantly higher mortality as compared to normal patients after cardiogenic shock. On the other hand, Patlolla et al [17] and Chatterjee et al [20] who used the same United States database with a partial overlap noted that an obesity paradox existed with cardiogenic shock as they found significantly lower mortality in higher BMI patients. The
lone study of Hermansen et al[18] was neutral and they found no impact of obesity on outcomes of cardiogenic shock in a contemporary cohort of Danish patients. Furthermore, it needs to be pointed out that several confounders can also influence outcomes of cardiogenic shock in addition to obesity. Hence, to establish the independent role of overweight/obesity on mortality rates, a multivariable-adjusted analysis is needed. A limitation of our review is that only three studies reported such data and their results were similar to the crude mortality data, with Patlolla et al[17] and Chatterjee et al[20] reporting better outcomes in overweight/obese patients and Sreenivasan et al[16] reporting worse outcomes in such individuals. On meta-analysis of these three studies, we noted a reduced risk of mortality in overweight/obese patients but again with high heterogeneity.

One cause of the divergent results amongst the studies could be related to the use of MCS. In the study of Sreenivasan et al[16], 100% of patients received MCS while the number was much lower in the remaining studies. In a separate cohort (for which details were unavailable), Sreenivasan et al[16] noted that amongst individuals not receiving MCS, patients with mild obesity had significantly lower mortality compared with the non-obese patients (OR = 0.8, 95%CI: 0.6–0.9), but this difference was non-significant for moderately and severely obese patients. These results conform to the obesity paradox found by Patlolla et al[17] and Chatterjee et al[20]. Higher mortality in patients receiving MCS could be due to the increased morbidity and complications like major bleeding, thrombosis, and vascular complications associated with the invasive procedure and MCS devices[16]. The study of Sreenivasan et al[16] also had a significant proportion of patients with severe obesity. It is plausible that higher grades of obesity are associated with severe comorbidities like diabetes, end-organ damage, and worse hemodynamic function which requires more robust MCS support like Impella or/Tandem Heart and extracorporeal membrane oxygenation as compared to intra-aortic balloon pump required for patients with mild obesity[16]. This may also have contributed to the opposing results of Sreenivasan et al[16]. Furthermore, the contradictory results of Hashmi et al[19] and the neutral results of Hermansen et al[18] need to be interpreted with caution considering the small sample size of obese patients in their cohorts.

Several diverse mechanisms have also been put forward that may explain better or even worse outcomes in obese patients with cardiogenic shock. Higher lean and fat mass in obese patients may contribute to the higher metabolic reserve in such individuals and guard them against the inflammatory cascade of cardiogenic shock[26]. Lower levels of tumor necrosis factor-alpha and monocyte chemottractant protein-1 in obese patients may attenuate the inflammatory damage associated with cardiogenic shock[27]. Adipose cells secrete adiponectin which has anti-inflammatory properties. Obese patients may also have a better neurohormonal profile and reduced B-type natriuretic peptide (BNP). BNP is associated with adverse outcomes in cardiogenic shock[28]. Larger coronary arteries in obese patients may also lower the extent of CAD and improve outcomes[29].

Contrastingly, obesity augments the metabolic demand of the body which requires greater blood volume and increased cardiac output. High volumes increase venous return and subsequently myocardial wall tension and cause ventricular dilation. While initial ventricular hypertrophy overcomes this process, with further increase in volume, the ventricles no longer adapt and systolic dysfunction occurs. Hypertension, arrhythmias, and CAD associated with obesity can cause several functional and structural alterations which could lead to worse outcomes in obese patients[16]. Our meta-analysis has some limitations. First, only a small number of predominantly retrospective studies were available for meta-analysis. Selection bias is an important limitation of these studies which can skew the results. Furthermore, databases are also prone to errors in record keeping. Second, the sample size of the included studies varied widely with two studies including a small cohort of obese patients. As mentioned earlier, there was a partial overlap of data in another two studies. Third, overweight patients were also merged into the obese group of one study which may have influenced the results. Since separate analyses for different grades of obesity were not available from all included studies, subgroup analysis for the same could not be carried out. Fourth, the treatment modality varied across the studies and obese and non-obese groups. While we used adjusted mortality data for the pooled analysis, it was not reported by all studies. A meta-regression based on treatment modality could not be conducted due to a scarcity of data. Fifth, BMI is not the sole indicator of obesity and may not correctly represent the relationship between obesity and outcomes. Several other factors like cardiorespiratory fitness, lean mass, and fat mass could also influence the relationship between the two entities. Lastly, data in our meta-analysis were from a limited number of countries and hence not generalizable to the world population.

CONCLUSION

Current evidence on the association between overweight/obesity and mortality after cardiogenic shock is scarce and conflicting. The obesity paradox might exist in patients with cardiogenic shock but could be confounded by the use of MCS. There is a need for further studies to clarify this relationship.
ARTICLE HIGHLIGHTS

Research background
Cardiogenic shock continues to be a highly morbid complication that affects around 7%-10% of patients with acute myocardial infarction or heart failure. Similarly, obesity has become a worldwide epidemic.

Research motivation
Despite intense research on the outcomes of cardiogenic shock, it is still unclear how obesity affects the outcomes of patients with cardiogenic shock.

Research objectives
We aimed to compare mortality outcomes of patients with cardiogenic shock based on body mass index (BMI).

Research methods
A systematic search of the literature was conducted on the databases of PubMed, Embase, ScienceDirect, CENTRAL, and Google Scholar for all types of studies comparing mortality outcomes of patients with cardiogenic shock based on BMI.

Research results
Five studies were eligible for inclusion. On pooled analysis of multivariable-adjusted ratios, we noted a statistically significantly reduced risk of mortality in overweight/obese vs normal patients with cardiogenic shock (three studies; OR = 0.92, 95%CI: 0.85-0.98, \(I^2 = 85\%\)). In meta-analysis, we also noted that crude mortality rates did not significantly differ between overweight/obese and normal patients after cardiogenic shock (OR = 0.95, 95%CI: 0.79-1.15, \(I^2 = 99\%\)). The results were not stable on sensitivity analysis and were associated with substantial heterogeneity.

Research conclusions
Based on the current review, we found that the association between overweight/obesity and mortality after cardiogenic shock is scarce and conflicting. The obesity paradox might exist in patients with cardiogenic shock but could be confounded by the use of mechanical circulatory support.

Research perspectives
Given the scarce number of studies available, there is a need for further research on the impact of obesity on outcomes of cardiogenic shock. Future studies should be prospective with a large sample size and also assess the impact of mechanical circulatory support on the outcomes.

FOOTNOTES

Author contributions: Tao WX conceived and designed the study; Qian GY, Li HD, and Su F were involved in literature search and data collection; Tao WX, Qian GY, and Li HD analyzed the data; Tao WX and Wang Z wrote the paper; Wang Z reviewed and edited the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors provided the PRISMA 2009 Checklist.

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S-Editor: Xing YX
L-Editor: Wang TQ
P-Editor: Xing YX
REFERENCES


Impact of being underweight on peri-operative and post-operative outcomes of total knee or hip arthroplasty: A meta-analysis

Yun-Ping Ma, Qiu Shen

BACKGROUND
Many systematic reviews have focused on assessing the effect of body mass index (BMI) on the outcomes and complications associated with total hip arthroplasty (THA) and total knee arthroplasty (TKA), but primarily dealt with obesity compared to normal weight (NW). None of these reviews attempted to assess the effect of low BMI or underweight (UW) compared to NW in patients undergoing THA or TKA.

AIM
This review aims to compare specific operative outcomes such as operation duration, length of hospital stay, and post-operative complications including mortality, infections, deep vein thrombosis, etc. along with re-hospitalization and reoperation rates between UW and NW patients undergoing THA, TKA or both.

METHODS
An electronic search was performed in PubMed, Scopus, Excerpta Medica database (EMBASE), Web of Science (WoS), and Cochrane Central Register of Controlled Trials (CENTRAL) along with a manual search. The quality of the studies was assessed using the Newcastle-Ottawa scale for cohort studies. The data were subjected to both qualitative and quantitative analysis.

RESULTS
Thirteen retrospective and five prospective cohort studies were included. The quality of included studies was assessed to be good to fair. The length of hospital stay after TKA or THA was found to be significantly higher for UW patients when compared to NW patients, with a mean difference: 0.39 95%CI: [0.06, 0.72], P = 0.02 (in days). Studies presenting both THA and TKA together as total joint arthroplasty showed an increased incidence of mortality in patients treated with THA or TKA alone, Odds ratio: 4.18 95%CI: [2.88, 6.07]. A higher incidence of post-operative complications was also observed in UW patients undergoing THA.

Abstract

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CONCLUSION

UW patients undergoing THA or TKA had a higher incidence of post-operative complications and were associated with a higher readmission rate. Moreover, UW patients were associated with an increased incidence of mortality in the studies that reported THA and TKA together.

Key Words: Underweight; Total knee arthroplasty; Total hip arthroplasty; Systematic review; Meta-analysis

INTRODUCTION

Body mass index (BMI) plays a pivotal role in predicting the outcomes and associated complications after total hip arthroplasty (THA) and total knee arthroplasty (TKA)[1]. BMI in the population is mainly divided into 5 categories: Underweight (score of < 18.5); normal weight (18.5-24.9); overweight (25-29.9); obese (30-34.9) and morbidly obese (> 40). This score is defined by weight in kilograms per square meter of height[2].

Extreme values of BMI are regarded as a risk factor for various systemic diseases such as diabetes, cardiovascular diseases, pulmonary diseases, dementia, and notable osteoarthritis in the elderly[3]. Obesity has already been proved to be associated with poor clinical outcomes, and lower success rates in patients undergoing total joint arthroplasty (TJA)[4,5]. Obese patients present with a higher incidence of infection, and complications compared to normal weight (NW) individuals[6]. However, the results were conflicting. Despite this negative relation between obesity and the success of THA or TKA, some studies established that no difference was observed between obese and non-obese patients in terms of clinical outcomes, survival rate, and complications[7-9].

Underweight (UW) patients suffer from poor nutrition, anemia, vitamin deficiencies, and most importantly osteoporosis due to calcium and vitamin D deficiency. Osteoporosis is a major risk factor for patients with osteoarthritis requiring THA or TKA. The understanding of prognosis post-THA or TKA in UW patients is less studied and not clearly understood. The literature which focused on evaluating the effect of BMI also showed the outcomes of UW patients undergoing arthroplasty. It was interesting to note that UW patients may also lead to poor post-operative outcomes, including increased rates of post-operative infection, transfusion, cardiovascular events, and renal complications[10,11]. UW patients have also been shown to potentially delay mobilization, increase length of stay and hospital expenditures[12,13]. However, the evidence is scarce, and very few studies directly attempted to assess the effect of UW compared to NW individuals.

Many systematic reviews have focused on assessing the effect of BMI on the outcomes and complications associated with TJA[14-17], but primarily dealt with obesity compared to NW. None of the reviews attempted to assess the effect of low BMI or UW in patients undergoing THA or TKA. The risk of UW patients undergoing TJA is debatable and no substantial evidence has been put forth. This is the first review to compare operative and post-operative complications between UW and NW patients undergoing THA or TKA. The objective of this review is to compare the specific operative outcomes such as operation duration, length of hospital stay, and post-operative complications including mortality, infections, deep vein thrombosis (DVT), etc. along with rehospitalization and reoperation rates between UW and NW patients undergoing THA, TKA or both.
Table 1 Search strategy

<table>
<thead>
<tr>
<th>Database</th>
<th>Search strategy</th>
<th>Results</th>
</tr>
</thead>
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<tr>
<td>PubMed</td>
<td>(((&quot;Under-weight&quot;) OR (Low body mass index)) OR (malnourished)) AND (((&quot;total knee arthroplasty&quot;[All Fields]) OR (&quot;total joint arthroplasty&quot;[All Fields]) OR (&quot;total knee replacement&quot;[All Fields])) OR (&quot;total hip arthroplasty&quot;[All Fields]))) AND (((mortality OR (complications)) OR (readmissions)) OR (rehospitalization)) OR (length of hospital stay))</td>
<td>243</td>
</tr>
<tr>
<td>CENTRAL</td>
<td>#1 Underweight</td>
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</tr>
<tr>
<td></td>
<td>#2 Low body mass index</td>
<td></td>
</tr>
<tr>
<td></td>
<td>#3 Malnourished</td>
<td></td>
</tr>
<tr>
<td></td>
<td>#4 #1 OR #2 OR #3</td>
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</tr>
<tr>
<td></td>
<td>#5 MeSH descriptor: [Arthroplasty, Replacement, Knee] explode all trees</td>
<td></td>
</tr>
<tr>
<td></td>
<td>#6 MeSH descriptor: [Arthroplasty, Replacement, Hip] explode all trees</td>
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</tr>
<tr>
<td></td>
<td>#7 MeSH descriptor: [Arthroplasty, Replacement] explode all trees</td>
<td></td>
</tr>
<tr>
<td></td>
<td>#8 #5 OR #6 OR #7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>#9 #4 AND #8</td>
<td></td>
</tr>
<tr>
<td>EMBASE</td>
<td>(((&quot;Under-weight&quot;) OR (Low body mass index)) OR (malnourished)) AND (((&quot;total knee arthroplasty&quot;[All Fields]) OR (&quot;total joint arthroplasty&quot;[All Fields]) OR (&quot;total knee replacement&quot;[All Fields])) OR (&quot;total hip arthroplasty&quot;[All Fields]))) AND (((mortality OR (complications)) OR (readmissions)) OR (rehospitalization)) OR (length of hospital stay))</td>
<td>67</td>
</tr>
<tr>
<td>WoS</td>
<td>TS=&quot;(under-weight&quot;) OR 'low body mass index' OR malnourished OR 'Total knee arthroplasty' OR 'Total joint arthroplasty' OR 'Total hip arthroplasty' AND TS=(mortality OR complications OR rehospitalization OR readmissions OR &quot;length of hospital stay&quot;)</td>
<td>110</td>
</tr>
<tr>
<td>SCOPUS</td>
<td>ALL (&quot;under-weight&quot;) OR 'low body mass index' OR malnourished AND ALL (&quot;Total knee arthroplasty&quot; OR &quot;Total joint arthroplasty&quot; OR &quot;Total hip arthroplasty&quot;) AND ALL (mortality OR complications OR rehospitalization OR re-admissions OR &quot;length of hospital stay&quot;)</td>
<td>261</td>
</tr>
</tbody>
</table>

MeSH: Medical subheadings; TS: Topic; WoS: Web of science.

MATERIALS AND METHODS

This systematic review and meta-analysis were performed according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines[18]. The protocol for conducting this review was predefined and employed to conduct the systematic review efficiently in a smooth manner. Ethics approval was not required for this review.

Research question

What is the impact of UW compared to NW on operative outcomes, rehospitalization and reoperation rates, and post-operative complications in patients undergoing THA or TKA?

The following PICO strategy was employed to formulate the research question and search strategy to identify eligible articles: Patients (P): Patients undergoing THA or TKA; Exposure (E): UW patients with BMI < 18.5 kg/m²; Comparison (C): NW patients with BMI between 18.5-24.9 kg/m²; Outcome (O): Operation duration (in min), length of hospital stay (in days), and post-operative complications such as mortality, infections, DVT, pulmonary embolism, genito-urinary complications, dislocation/subluxation, fracture along with rehospitalization and reoperation rates expressed as a proportion (event/total); Study design (S): All observational studies comparing outcomes of UW vs NW patients undergoing THA or TKA or TJA.

Search strategy

A comprehensive search strategy was developed to identify the relevant articles to answer the question. An electronic search was performed in PubMed, Scopus, Excerpta Medica database (EMBASE), Web of Science (WoS), and Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was framed using the following relevant keywords: underweight; "low body mass index"; malnourished; "Total knee arthroplasty"; "Total joint arthroplasty"; "Total hip arthroplasty"; mortality; complications; rehospitalization; readmissions; "length of hospital stay". The details of the search strategy are provided in Table 1. No limits or restrictions were applied to the electronic search. The last electronic search was carried out in June 2021. An additional manual search was also carried out in peer-reviewed relevant journals such as the Journal of Orthopedics; Journal of Arthroplasty; Journal of Orthopedic Surgery and Research; and Journal of Knee Surgery, Sports Traumatology, and Arthroscopy. The reference list of previously conducted relevant systematic reviews and other relevant studies were screened for possible inclusion of eligible articles. The identified reports along with electronic search results were imported...
into a citation manager (ENDNOTE) in order to discard duplicates obtained from multiple databases.

**Study selection**
The reports were screened by two independent reviewers based on the below-mentioned inclusion and exclusion criteria:

**Inclusion criteria:** All studies comparing outcomes of UW vs NW patients undergoing THA or TKA or TJA. Studies reporting outcomes such as operation duration, length of hospital stay, and post-operative complications including mortality, infections, DVT, pulmonary embolism, genito-urinary complications, dislocation/subluxation, fracture along with rehospitalization and reoperation rates. Studies attaining a minimum score of 7 assessed using the Newcastle-Ottawa scale (NOS) of quality assessment were included.

**Exclusion criteria:** Studies published in other than the English language. Studies not reporting relevant outcomes. Studies recruiting patients with other systemic diseases, and immune-compromised patients. Studies with a score less than 7 assessed using the NOS of quality assessment were excluded.

**Data extraction**
Data extraction was performed by two independent reviewers (YM, and QS) using an Excel spreadsheet. The demographic characteristics and details of outcomes such as operation duration, length of hospital stay, and post-operative complications including mortality, infections, DVT, pulmonary embolism, genito-urinary complications, dislocation/subluxation, fracture along with rehospitalization and reoperation rates were extracted. The authors were contacted by email for clarification on missing data or unclear information.

**Data synthesis**
The extracted data were subjected to both qualitative and quantitative analysis. The outcomes which could not be combined for quantitative analysis were summarized. The continuous data of the extracted outcomes were expressed as mean and standard deviation. The dichotomous outcomes were expressed as an absolute number of events, ratio, and proportion. The outcome effect was calculated between UW and NW patients as the mean difference for continuous outcomes and odds ratio for dichotomous outcomes. The quantitative data were subjected to meta-analysis using RevMan v 5.4 software. The meta-analysis was carried out only if two or more studies with similar outcomes were available. A P value < 0.05 for assessing the outcome effect was considered significant. A random effect model was chosen if the included studies presented a varied population. The heterogeneity among the studies was assessed using I² statistics. The heterogeneity was considered low if the I² value was found to be < 40%, moderate for a value of 40%-70%, and high for a value more than 70%. The studies presented the data on THA or TKA alone and reported both THA and TKA data together. Hence, a sub-group analysis was carried out based on the type of joint arthroplasty reported. For outcomes such as mortality, a subgroup analysis was carried out based on the time frame.

**Quality of included studies**
The methodological quality of included studies was assessed by two independent reviewers using the NOS. The NOS consists of eight items grouped into three categories, namely: selection, comparability, and outcome. A scoring system, ranging from zero to nine stars, was used to classify the quality of the study being reviewed. Each included study received the following categorical scores representing its quality: good (three or four scores in the selection domain AND one or two scores in the comparability domain AND two or three scores in the outcome domain), fair (two scores in selection domain AND one or two scores in comparability domain AND two or three scores in outcome domain) or poor (zero or one score in selection domain OR zero score in comparability domain OR zero or one score in outcome domain).

**RESULTS**
A total of eighteen studies[10,11,19-34] were included in this review. Twenty-two eligible studies[4,35-37] were screened from a pool of 671 records identified from both electronic and manual searches, purely based on title and abstract. The inclusion and exclusion criteria were strictly applied to carry out the full-text assessment of eligible studies. Finally, eighteen studies were deemed inclusive after satisfying the pre-defined criteria. The complete study selection process is described in **Figure 1**, and the detailed search strategy employed in all databases is provided in **Table 1**.

**Demographic characteristics**
Thirteen retrospective cohort studies[10,11,19-23,25,26,28,29,31,33] and five prospective cohort studies [24,27,30,32,34] were included. The studies included a total of 1136506 subjects undergoing TKA or THA
with a mean age of 65.32 years. The subjects comprised 469387 males and 667119 females. Out of these recruited subjects undergoing TKA or THA, 213028 subjects were NW individuals with a BMI between 18.5 and 24.9, and only 10785 subjects were UW individuals with a BMI < 18.5. Sixteen studies[10,19,21-34] assessed the outcomes for THA and nine studies[11,19,20,23,26,28,30,31,33] for TKA. Only seven studies[19,23,26,28,30,31,33] presented data with both THA and TKA. The demographic characteristics of the included studies are provided in Table 2. The quality of studies assessed using NOS was found to be good to fair quality. Details of the Newcastle-Ottawa scoring criteria according to domains were well presented and are shown in Table 3.

**Meta-analysis**

**Operation duration (in min):** The operation duration between UW (n = 2102) and NW (n = 55701) patients undergoing THA or TKA, was found to be not significantly different with MD: 1.66 95%CI: [-1.89, 5.21], P = 0.36. A subgroup analysis was carried out based on the type of procedure to analyze the heterogeneity (I² = 75%). No difference in the result was observed in patients undergoing THA MD: 0.73 95%CI: [-3.31, 4.77], P = 0.72 and TKA MD: 2.54 95%CI: [-3.59, 8.66], P = 0.42 (Figure 2).

**Length of hospital stay (in days):** The length of hospital stay after arthroplasty was found to be significantly higher for UW patients (n = 4555), when compared to NW patients (n = 58890). MD: 0.39 95%CI: [0.06, 0.72], P = 0.02, I² = 81%.

The subgroup analysis showed no significant differences between UW and NW patients undergoing THA or TKA. However, in patients undergoing both THA and TKA, the length of hospital stay was found to be significantly higher for UW patients (n = 2207) MD: 0.76 95%CI: [0.43, 1.09], P < 0.0001. Low heterogeneity was also observed with an I² value of 31% (Figure 3).

**30-90-day readmission rate:** No significant difference in readmission rate was observed between UW and NW patients undergoing THA or TKA with OR: 1.42 95%CI: [0.71, 2.87], P = 0.32; F = 36%. No subgroup differences were observed. UW patients (n = 408) undergoing THA presented with an increased OR: 1.75 95%CI: [0.58, 5.27], P = 0.32, F = 49% (not significant) of 30-90 d readmission compared to NW patients (Figure 4).

**Re-operation rate:** No significant difference in reoperation rate was observed between UW and NW patients undergoing THA with OR: 1.22 95%CI: [0.43, 3.42], P = 0.71; F = 0%. No subgroup differences were observed (Figure 5).
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Type of study</th>
<th>Total participants</th>
<th>Age (mean)</th>
<th>Follow up time</th>
<th>Gender (F/M)</th>
<th>Treatment</th>
<th>Groups</th>
<th>Number of participants per group</th>
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<tbody>
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<td>Hartford et al[20], 2020</td>
<td>Retrospective</td>
<td>1774</td>
<td>67.08</td>
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<td>4802</td>
<td>65.9</td>
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<td>2698/2104</td>
<td>THA and TKA</td>
<td>Underweight2</td>
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<td>Kwon et al[19], 2020</td>
<td>Retrospective</td>
<td>118</td>
<td>70.75</td>
<td>2 yr</td>
<td>118/0</td>
<td>TKA</td>
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</tr>
<tr>
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<td>224912/153863</td>
<td>THA and TKA</td>
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<td>Hung et al[24], 2019</td>
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<td>830/735</td>
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<td>Sayed-Noor et al [23], 2019</td>
<td>Prospective</td>
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<td>2 yr (90 d mortality)</td>
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<td>104742/68024</td>
<td>THA and TKA</td>
<td>THA + Underweight</td>
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<td>Retrospective</td>
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<td>61.33</td>
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<td>9986/8187</td>
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<td>Zusumanovich et al [9], 2018</td>
<td>Retrospective</td>
<td>840</td>
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<td>Prospective</td>
<td>415598</td>
<td>67.75</td>
<td>3 mo</td>
<td>246780/168818</td>
<td>THA</td>
<td>Underweight</td>
<td>3588</td>
</tr>
<tr>
<td>Manrique et al[10], 2017</td>
<td>Retrospective</td>
<td>108</td>
<td>69.7</td>
<td>3.8 yr</td>
<td>93/24</td>
<td>TKA</td>
<td>Underweight</td>
<td>27</td>
</tr>
<tr>
<td>Anoushiravani et al [30], 2016</td>
<td>Retrospective</td>
<td>4864</td>
<td>70.54</td>
<td>NA</td>
<td>4064/800</td>
<td>THA and TKA</td>
<td>THA + Underweight1</td>
<td>1762</td>
</tr>
<tr>
<td>Husted et al[29], 2016</td>
<td>Prospective</td>
<td>13730</td>
<td>NR</td>
<td>3 mo</td>
<td>NR</td>
<td>THA and TKA</td>
<td>TKA + Underweight</td>
<td>1787</td>
</tr>
<tr>
<td>Shaparin et al[28], 2016</td>
<td>Retrospective</td>
<td>880</td>
<td>61.33</td>
<td>1 mo</td>
<td>541/339</td>
<td>THA</td>
<td>Underweight</td>
<td>17</td>
</tr>
</tbody>
</table>
Underweight and total joint arthroplasty

Ma YP et al. Underweight and total joint arthroplasty

Zhao et al[31], 2014 Prospective 236 36.5 NA 34/202 THA Underweight 91
Normal 145

Thornqvist et al [32], 2014 Retrospective 34744 70.6 1 mo 20438/14306 THA and TKA Underweight 353
Normal 9859

Zhang et al[33], 2012 Prospective 714 62.17 5-20 yr 315/399 THA Underweight 62
Normal 413

Underweight < 19.5 kg/m².
Underweight < 20 kg/m².
Underweight < 18.5 kg/m², Normal = 18.5 – 24.9 kg/m². THA: Total hip arthroplasty; TKA: Total knee arthroplasty; NA: Not available; NR: Not reported.

**Post-operative mortality:** UW patients (n = 6880) had higher odds of post-operative mortality than NW patients (126040) with OR: 2.20 95%CI: [1.43, 3.37], P = 0.0003. However, a high heterogeneity with an I² value of 91% was observed. Following subgroup analysis, it was found that studies reporting THA and TKA together showed an increased incidence of mortality in UW patients (n = 438) OR: 4.18 95%CI: [2.88, 6.07], P < 0.0001 with I² = 0%. Although not significant, the incidence of post-operative mortality was less likely to be observed in UW patients, compared to NW patients (Figure 6).

A subgroup analysis carried out based on timeframe showed higher 31-365 d mortality in UW patients with OR: 2.35 95%CI: [1.31, 3.54], P < 0.0001, I² = 29%, than NW patients (Supplementary Figure 1).

**Post-operative infection:** No significant difference in the incidence of post-operative infection was observed between UW (n = 2955) and NW patients (n = 8261) undergoing THA or TKA with OR: 1.88 95%CI: [0.34, 10.41], P = 0.47, I² = 56% (Figure 10).

**Total complications:** No significant difference in hazard ratios computing total complications was observed between UW and NW patients. The incidence of total or overall complications observed between the two groups of patients undergoing arthroplasty was similar with HR: 1.27 95%CI: [0.50, 3.22], P = 0.61, I² = 27% (Figure 8).

**Post-operative complications in patients undergoing THA:** UW patients (n = 31619) showed higher odds for the incidence of post-operative complications with OR: 1.44 95%CI: [1.10, 1.88], P = 0.008, I² = 58%, in patients undergoing THA. Subsequently, a significantly higher incidence of DVT and cardiac infarction among the post-operative complications were observed in UW patients undergoing THA (Figure 9).

**Post-operative complications in patients undergoing TKA:** No significant difference in post-operative infection, DVT and pulmonary embolism was observed in UW (n = 2134) compared to NW (n = 3424) patients undergoing TKA with OR: 1.88 95%CI: [0.34, 10.41], P = 0.47, I² = 56% (Figure 10).

**Figure 2 Operation duration.** CI: Confidence intervals; F: Heterogeneity; IV: Inverse variance; NW: Normal weight; SD: Standard deviation; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; UW: Underweight.

DOI: 10.12998/wjcc.v10.i30.10967 Copyright ©The Author(s) 2022.
**DISCUSSION**

This systematic review and meta-analysis included thirteen retrospective and five prospective cohort studies to compare UW and NW patients undergoing THA or TKA or TJA in terms of specific outcomes such as operation duration, length of hospital stay, and post-operative complications including mortality, infections, DVT, pulmonary embolism, genito-urinary complications, dislocation/subluxation, fracture along with rehospitalization and reoperation rates. The quality of the studies included was good to fair. UW patients undergoing THA or TKA had a higher incidence of post-operative complications and readmission rates. Moreover, studies reporting THA and TKA were associated with an increased incidence of mortality. Also, a higher incidence of DVT and cardiac infarction was evident among the post-operative complications in UW patients undergoing THA. No difference in post-operative complications was found in UW patients undergoing TKA.
Knee and hip osteoarthritis (OA) involves degeneration of articular cartilage, and bone hyperplasia of joint disease, is a common chronic disabling disease, causing physiological and psychological pain in patients[38]. OA is a common disease among the elderly, and elderly patients suffering from OA opt for arthroplasty for improved quality of life and morbidity-free life[39,40]. Modern-day arthroplasty includes the replacement of joints with a compatible metal prosthesis to restore function. TKA involves replacing the articular surfaces (femoral condyles and tibial plateau) of the knee joint with smooth metal and highly cross-linked polyethylene plastic[41,42]. TKA involves the replacement of the acetabulum or...
hip socket, and the head of the femur is removed and replaced with a metal replica[43]. TJA involves both THA and TKA carried out simultaneously to manage OA complications. The prognosis after undergoing both procedures is good and is considered to improve quality of life by reducing pain and increasing function[44].

BMI is considered one of the key predictive tools for assessing outcomes after TKA or THA. An extreme BMI level is believed to worsen the prognosis and is associated with increased complications after TKA or THA. Many systematic reviews have assessed the effect of BMI on these procedures. According to a recent systematic review[45], BMI higher than normal can affect the intra-operative risk of TKA and post-operative recovery, and increase the risk of complications. Another review[46] concluded that increased BMI was associated with an increased risk of peri-prosthetic joint infection (PJJ) after primary THA or TKA. Following THA, patients were more likely to suffer from PJJ than TKA.

Figure 5 Re-operation rate. CI: Confidence intervals; I²: Heterogeneity; M-H: Mantel-Haenszel; NW: Normal weight; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; UW: Underweight.

Figure 6 Mortality. CI: Confidence intervals; I²: Heterogeneity; M-H: Mantel-Haenszel; NW: Normal weight; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; UW: Underweight.
patients. All the systematic reviews and meta-analyses conducted have focused on the effect of obesity or patients with high BMI on various outcomes after undergoing THA or TKA. However, some studies have shown that even low BMI or UW patients have shown both peri-operative morbidity and poor post-operative recovery with complications. A study\textsuperscript{[47]} that evaluated the readmission rate and post-operative infection in UW patients undergoing THA, demonstrated that patients with BMI < 18.5 kg/m\textsuperscript{2} were more likely to be associated with post-discharge infections and thereby increased readmission rates.

Most of the included studies classified underweight patients with a BMI < 18.5 kg/m\textsuperscript{2}; however, a few studies such as those by Katakam et al\textsuperscript{[18]} 2021 and Anoushiravani et al\textsuperscript{[30]} 2016, used an up-bound cut-off of < 20 kg/m\textsuperscript{2} and < 19.5 kg/m\textsuperscript{2} to justify the fact that the present World Health Organization classification of BMI was set based on the findings in a young population and the included patients were elderly with a mean age of over 60 years.

The peri-operative outcomes assessed after undergoing arthroplasty include the operation duration and length of hospital stay. Our meta-analysis showed no significant difference in operation duration between UW and NW patients; however, the length of hospital stay after THA or TKA was found to be significantly higher for UW patients compared to NW patients with MD of 0.39 d 95%CI: [0.06, 0.72], \(P = 0.02\). Poor nutritional status among UW patients leads to musculoskeletal degeneration characterized by
Figure 9 Post-operative complications in patients undergoing total hip arthroplasty. CI: Confidence intervals; DVT: Deep vein thrombosis; $I^2$. 

DOI: 10.12998/wjcc.v10.i30.10967 Copyright ©TheAuthor(s)2022.
less muscle mass, less soft tissue, and a greater probability of osteoporosis. A study in 2016[30] showed a higher proportion of UW patients with a length of hospital stay of more than 4 d compared to normal and obese patients. However, the mean difference of 0.39 d (= 9.4 h) for the length of hospital stay between UW and NW patients undergoing THA or TKA, though statistically significant, was not clinically significant. This negligible difference may be due to delay in discharge related to a system-level reason or inadequate staff availability.

Our systematic review did not find any significant differences in readmission and re-operation rates for both UW and NW patients undergoing THA or TKA or TJA. Although not significant, the 30-90 readmission rate was more likely to be observed in UW patients, compared to NW patients. This result cannot be regarded as sufficient certainty as the readmission rate is positively affected by various independent risk factors such as age, male sex, black race, presence of pre-operative co-morbidities, and increased operation time following TKA[48].

Our meta-analysis showed a significant association with post-operative mortality in UW patients OR: 2.20 95%CI: [1.43, 3.37]. UW patients can be malnourished, and often present with poor nutritional reserve. This may lead to a less pronounced immunological response. This may be a reasonable explanation for the higher incidence of post-operative mortality. The compromised immune response in these patients could trigger numerous debilitating diseases, leading to death. Additionally, patients undergoing both THA and TKA together showed an increased incidence of mortality with UW patients OR: 4.18 95%CI: [2.88, 6.07]. This could be explained by the fact that TJA (THA and TKA) is a more complicated surgery, with a higher incidence of complications than THA or TKA alone. A registry study[33] found U-shaped risk associations between BMI and perioperative cardiovascular events and mortality, which were highest in the UW group undergoing THA and TKA, suggesting that this was a subpopulation at risk.

Several authors have evaluated complications in UW patients; however, some of the reported data is controversial. Many authors suggest that UW patients have a higher complication rate than their NW or even obese counterparts. Our meta-analysis of included studies regarding post-operative complications showed a significantly higher incidence of DVT and cardiac infarction among the post-operative complications observed in UW patients undergoing THA alone. Three studies[11,24,31] showed that UW patients undergoing THA or TKA had increased risks for infection, cardiac complications, and venous thrombo-emboli. The reason for this is not entirely clear; however, in their studies, it appears
that the UW group tended to have lower preoperative hematocrit and albumin which are markers of malnutrition and predispose patients to medical complications. Nowadays, autologous platelet concentrates[49-51] have been proved to be beneficial in the management of bone-related disorders[52-55]. They have also been used as an adjunct to arthroplasty[56,57]. Many studies have opted for this as an alternative to arthroplasty[58,59]. This can be used as an alternative to arthroplasty in less severe cases to improve the quality of life in UW patients.

Our systematic review and meta-analysis are the first to assess the impact of UW on peri-operative and post-operative outcomes of THA or TKA. However, our review also has certain limitations. Confounding factors such as age, presence of comorbidities including anemia, diabetes, hypertension, patients using anticoagulants, and preoperative use of any walking aids, were not taken into consideration to assess the peri-operative outcomes and readmission or reoperation rates. Moreover, no subgroup analysis could be performed based on follow-up time, especially on 30-d and 90-d readmission rates. The exclusion of articles other than the English language could also be a possible limitation as good evidence could have been missed.

CONCLUSION

UW patients undergoing THA or TKA had a higher incidence of post-operative complications and readmission rates. Moreover, UW patients undergoing TJA were associated with an increased incidence of mortality in the 31-365-d time frame. Also, a higher incidence of DVT and cardiac infarction was evident among all the post-operative complications in UW patients undergoing THA. No difference in post-operative complications was found in UW patients undergoing TKA. Hence, careful clinical judgment is needed by clinicians before UW patients undergo THA or TKA.

ARTICLE HIGHLIGHTS

Research background
The effect of body mass index (BMI) on the outcomes and complications associated with total hip arthroplasty (THA) and total knee arthroplasty (TKA) is less studied and is believed to be a determining factor.

Research motivation
Systematic reviews on this issue have primarily focused on obesity compared to normal weight (NW). None of these reviews attempted to assess the effect of low BMI or underweight (UW) compared to NW in patients undergoing THA or TKA.

Research objectives
The objective of this review was to compare specific operative outcomes such as operation duration, length of hospital stay, and post-operative complications including mortality, infections, deep vein thrombosis, etc. along with rehospitalization and reoperation rates between UW and NW patients undergoing THA or TKA or both.

Research methods
An electronic search was performed in PubMed, Scopus, Excerpta Medica database (EMBASE), Web of Science (WoS), and Cochrane Central Register of Controlled Trials (CENTRAL) along with a manual search. The quality of the studies was assessed using the Newcastle-Ottawa scale for cohort studies. The data were subjected to both qualitative and quantitative analysis.

Research results
Thirteen retrospective and five prospective cohort studies were included. The quality of included studies was assessed to be good to fair. The length of hospital stay after TKA or THA was found to be significantly higher for UW patients when compared to NW patients. Mean difference: 0.39 95%CI: [0.06, 0.72], P = 0.02 (in days). Studies presenting both THA and TKA together as total joint arthroplasty showed an increased incidence of mortality in patients who underwent THA or TKA alone with an odds ratio: 4.18 95%CI: [2.88, 6.07]. A higher incidence of post-operative complications was also observed in UW patients undergoing THA.

Research conclusions
UW patients undergoing THA or TKA had a higher incidence of post-operative complications and were associated with a higher readmission rate. Moreover, UW patients were associated with an increased incidence of mortality in the studies that reported THA and TKA together.
Research perspectives
Careful clinical judgment is needed by clinicians before UW patients undergo THA or TKA to attain better outcomes.

FOOTNOTES
Author contributions: Ma YP conceived and designed the study; Ma YP and Shen Q were involved in the literature search and data collection; Ma YP analyzed the data; Ma YP and Shen Q wrote the paper; Ma YP edited the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: All the authors declare no competing interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA checklist and the manuscript was prepared and revised according to the PRISMA checklist.

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S-Editor: Liu JH
L-Editor: Webster JR
P-Editor: Liu JH

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META-ANALYSIS

Branched-chain amino acids supplementation has beneficial effects on the progression of liver cirrhosis: A meta-analysis

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Specialty type: Gastroenterology and hepatology
Provenance and peer review: Unsolicited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0
P-Reviewer: Chen GX, United States; Ielasi L, Italy
Received: July 18, 2022
First decision: August 6, 2022
Revised: August 19, 2022
Accepted: September 19, 2022
Article in press: September 19, 2022
Published online: October 26, 2022

Abstract

BACKGROUND
Liver cirrhosis (LC) is currently the 11th most common cause of death and 15th cause of morbidity globally. The treatment of LC is mainly aimed at etiological intervention, lifestyle intervention, prevention and treatment of complications and nutritional treatment. Nutritional treatment of LC mainly includes increasing dietary intake, food intake time and branched-chain amino acids (BCAAs). Despite the recommendation of BCAAs in some guidelines, adverse effects have been reported in studies so the efficacy and safety of BCAAs remain controversial. Currently, BCAAs have been widely used in chronic liver disease, while the summary of the effect of BCAAs on long-term prognosis is rare.

AIM
To determine the effects of BCAAs in patients with LC.

METHODS
The PubMed, Cochrane Library, Embase and Web of Science databases were searched. The retrieval deadline was 1 October 2021 and there were no language restrictions set in the retrieval. The study was performed in strict accordance with the inclusion and exclusion criteria. Nine studies were finally included. The primary outcome was complications of LC. The secondary outcomes were nutritional status and liver function. This meta-analysis used the Review Manager, version 5 statistical package (Cochrane Collaboration, Oxford, England) for
analysis.

RESULTS
The analysis included nine studies that consisted of 1080 patients (554 in the BCAA groups and 526 in the control groups). The nine studies were randomized control trials (RCTs). The quality of the studies was assessed using the risk of bias method recommended by the Cochrane Collaboration. BCAAs reduced the rate of complications in LC patients [Risk ratio: 0.70, 95% confidence interval (CI): 0.56-0.88, \( P = 0.002 \)] and improved patients’ albumin levels [standard mean difference (SMD): 0.26, 95%CI: 0.12-0.40, \( P = 0.0002 \)]. Meanwhile, BCAAs significantly ameliorated the levels of alanine transaminase (SMD: -2.03, 95%CI: -2.52 to -1.53, \( P < 0.00001 \)) and aspartate aminotransferase (SMD: -1.8, 95%CI: -2.14 to -1.46, \( P < 0.00001 \)). Meanwhile, glucose in the LC was significantly increased in BCAA-treated patients (MD: 13.04, 95%CI: 6.81-19.89, \( P = 0.0002 \)).

CONCLUSION
BCAAs reduce the incidence of complications in patients with LC and ameliorate nutritional status.

Key Words: Liver cirrhosis; Branched-chain amino acids; Complications; Nutrition; Liver function; Glucose

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Core Tip: Liver cirrhosis (LC) is currently the 11th most common cause of death and the 15th cause of morbidity globally. Nutritional treatment of LC mainly includes increasing dietary intake, food intake time and branched chain amino acids (BCAAs). The efficacy and safety of BCAAs remain controversial. We performed a meta-analysis and nine studies were finally included. The primary outcome was complications of LC. The secondary outcomes were nutritional status and liver function. The conclusion is that branched-chain amino acids reduce the incidence of complications in patients with liver cirrhosis and ameliorate nutritional status.

Citation: Du JY, Shu L, Zhou YT, Zhang L. Branched-chain amino acids supplementation has beneficial effects on the progression of liver cirrhosis: A meta-analysis. World J Clin Cases 2022; 10(30): 10984-10996
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/10984.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.10984

INTRODUCTION
As the 11th leading cause of death and 15th leading cause of morbidity worldwide, liver cirrhosis (LC) is the end stage of liver diseases[1]. It is the top 20 causes of disability-adjusted life years and years of life lost and accounts for 1.6% and 2.1% of the worldwide burden. Asrani et al[2] summarized that LC causes two million deaths, one million deaths from cirrhosis complications and one million deaths from viral hepatitis and hepatocellular carcinoma annually.

For the high mortality and poor prognosis, much research has reported the following indicators of poor prognosis of LC[3-6]. Although liver biopsy and hepatic venous pressure gradient are currently recommended invasive indicators to predict the prognosis of LC[3,4], noninvasive prediction tools are commonly used in clinical work. Child Pugh and the model for end-stage liver disease (MELD), including creatinine, International Normalized Ratio and bilirubin are two of the most recommended forecasting tools in recent years[7]. Child Pugh scores included encephalopathy, ascites, urine volume, bilirubin, albumin and prothrombin time[5]. MELD scores included creatinine, International normalized ratio and bilirubin[6]. In our study, nutritional status (serum albumin), the occurrence of complications, and liver functions [aspartate aminotransferase (AST), alanine transaminase (ALT), bilirubin] were chosen as indicators to evaluate and predict the prognosis of LC. The disease progresses to decapsulation, and complications follow, such as the development of ascites, portal hypertensive gastrointestinal bleeding, encephalopathy and jaundice[8]. Similarly, as mentioned above, malnutrition also means a poor prognosis. Protein calorie malnutrition is not only the most common symptom in patients with LC[9] but also an independent risk factor for death[10,11], leading to more severe complications[12,13]. A clinical trial reported that 51% of patients with LC showed some clinical evidence of protein calorie malnutrition[14].

At present, the treatment of LC is mainly for the cause of intervention, lifestyle intervention, and the prevention and treatment of complications[15]. Toshikuni et al[16] mentioned that nutritional therapy for LC mainly included increasing dietary intake, the timing of food intake and branched-chain amino
acids (BCAAs). In recent years, BCAAs have been found to have a unique effect on LC[17-24]. BCAAs are a set of essential amino acids including leucine, isoleucine and valine. It was considered that the end stage of liver disease is characterized by a low concentration of BCAAs and a high concentration of aromatic amino acids (phenylalanine, tyrosine and tryptophan)[21]. Suzuki et al[25] found that in patients with compensated cirrhosis, amino acid imbalance also occurs. Hyperinsulinemia and hyperammonemina are thought to lead to changes in the amino acid ratio in patients with LC[26,27]. The decrease in BCAA levels is considered to be a crucial pathogenic factor in LC[28]. Consequently, studies have reported that oral BCAAs can ameliorate patients’ nutritional status[17,19-21,25,24], reduce the incidence of complications[17,19] and ameliorate liver function[20,22,23]. Although BCAAs have been recommended in some guidelines[29,30], adverse reactions have been reported in recent studies and the effectiveness and safety of BCAAs are still controversial[31,32]. Kobayashi et al[31] considered that BCAAs have no inhibitory effect on the progression from compensatory cirrhosis to decompensated cirrhosis. In addition, the effect of BCAAs on the overall condition of cirrhosis is less well studied. Therefore, we conducted a meta-analysis of these studies to evaluate the effect of its application in LC.

MATERIALS AND METHODS

Objective
This analysis’s ultimate goal was to demonstrate the patients’ treatment effect with LC using BCAAs.

Selection of studies
Studies that conformed to the following criteria were included in our meta-analysis: (1) Randomized controlled studies; (2) the patient was diagnosed with cirrhosis; and (3) the intervention factor was BCAAs.

Studies were excluded if they met at least one of the following exclusion criteria: (1) The patient used BCAAs or other nutritional agents; (2) the patient had a high suspicion of liver neoplasms or had developed liver neoplasms; and (3) the patient had other major non-hepatic diseases.

In addition, filtering studies, abstracts, letters, reviews without original data, expert opinions, editorials, case reports and studies lacking control groups were excluded.

Search strategy
We selected articles from PubMed, Cochrane Library, Embase and Web of Science. The retrieval deadline was 1 October 2021, and there were no language restrictions set in the retrieval. Search terms were utilized in the title, abstract, mesh fields, and the following keywords and their combinations were applied: (((liver cirrhosis[MeSH Terms])) OR (((hepatic[All Fields]) OR (liver)) AND ((cirrhosis[All Fields])) OR (fibrosis)) AND ((Amino Acids, Branched-Chain [MeSH Terms])) OR (((((Acids, Branched-Chain Amino[All Fields])) OR (Branched-Chain Amino Acids)) OR (Amino Acids, Branched Chain)) OR (Branched-Chain Amino Acid)) OR (Acid, Branched-Chain Amino) OR (Amino Acid, Branched-Chain)) OR (Branched Chain Amino Acid)).

The outcomes of the meta-analyses were the occurrence of complications, nutritional status and liver function. These data included albumin, alanine transaminase, aspartate aminotransferase, bilirubin, glucose and the occurrence of ascites, hepatic encephalopathy or esophagogastric varices.

Data extraction
Reviewers independently reviewed the quality and qualification of these studies according to the inclusion and exclusion criteria and the second reviewer (corresponding author) was allowed to intervene.

Statistical analysis
This meta-analysis used the Review Manager, version 5 statistical package (Cochrane Collaboration, Oxford, England) for analysis. A risk ratio (RR) value with a 95% confidence interval (CI) was used for binary variables. Mean difference (MD) or Std MD (SMD) values with a 95%CI are used for continuous variables. The overall effects were measured using a z score with a significance set at $P < 0.05$. If $P \geq 0.05$, there was no significant difference in the results. In contrast, the results are significantly different. Statistical heterogeneity was evaluated using chi-square and I-square ($I^2$) tests with significance set at $P \leq 0.1$. Values of $P \leq 0.1$ and $I^2 > 50\%$ were considered to be significantly heterogeneous. For the articles with $I^2 > 0$, we used the random effect model and sensitivity analysis or subgroup analysis, and for the articles with $I^2 = 0$, we used the fixed-effect model.
RESULTS

Study selection and characteristics of included studies
The analysis included nine studies that consisted of 1080 patients (554 in the BCAA groups and 526 in the control groups)[17,19-24,31,32]. The nine studies were randomized control trials (RCTs) (Figure 1). The characteristics of the studies included in the meta-analysis are shown in Table 1. The patient baseline characteristics of the studies included in the meta-analysis are shown in Table 2.

Risk of bias assessment
The quality of the studies was assessed using the risk of bias method recommended by the Cochrane Collaboration. Some trials had a high risk of bias (Figure 2)[22]. The main reason is that blind methods are not adopted and the inevitable loss of visits is inevitable.

Outcome
Complications rate: Statistical heterogeneity was low across the studies for the complication rate (Tau² = 0.00; χ² = 2.00, df = 4 (P = 0.74); I² = 0%) by fitting a fixed-effects model. The complication rate of LC was significantly reduced in BCAA-treated patients (RR: 0.70, 95%CI: 0.56-0.88, P = 0.002, Figure 3).

Nutritional status: Statistical heterogeneity was high across the studies for nutritional status [Tau² = 0.29; χ² = 36.72, df = 6 (P < 0.00001); I² = 84%] by fitting a random-effects model. The albumin level of LC was significantly ameliorated in BCAA-treated patients (SMD: 0.63, 95%CI: 0.17-1.09, P = 0.007, Figure 4A). Nevertheless, they have slight heterogeneity.

Subgroup analysis was therefore performed according to the number of included patients and studies with a total number of patients less than 50 were excluded. Statistical heterogeneity was low across the studies for nutritional status [Tau² = 0.00; χ² = 2.78, df = 3 (P = 0.43); I² = 0%] by fitting a fixed-effects model. The SMD of the fixed effect model analysis was 0.26 (95%CI: 0.12-0.40, P = 0.0002, Figure 4B).

Additional subgroup analysis included studies with treatment durations greater than 3 mo. Statistical heterogeneity was low across the studies for nutritional status [Tau² = 0.00; χ² = 2.06, df = 3 (P = 0.56); I² = 0%] by fitting a fixed-effects model. The SMD of the fixed effect model analysis was 0.27 (95%CI: 0.13-0.42, P = 0.0002, Figure 4C).

The last subgroup analysis included studies in which the majority of patients had Child grade A or B and treatment duration was greater than 3 mo. Statistical heterogeneity was low across the studies for nutritional status [Tau² = 0.00; χ² = 1.67, df = 2 (P = 0.43); I² = 0%] by fitting a fixed-effects model. The SMD of the fixed effect model analysis was 0.27 (95%CI: 0.11-0.41, P = 0.0005, Figure 4D).

These results further confirmed that BCAs significantly ameliorate nutritional status in these patients.

Liver function
Aspartate aminotransferase (AST): Statistical heterogeneity was low across the studies for AST [Tau² = 0.00; χ² = 3.03, df = 3 (P = 0.39); I² = 1%] by fitting a random-effects model. AST of LC was significantly ameliorated in BCAA treatment patients (SMD: -1.8, 95%CI: -2.14 to -1.46, P < 0.00001, Figure 5).

Alanine transaminase (ALT): Statistical heterogeneity was high across the studies for ALT (Tau² = 1.33; χ² = 24.94, df = 2 (P < 0.00001); I² = 92%) by fitting a random-effects model. The ALT level in the LC was significantly ameliorated in BCAA-treated patients (SMD: -1.43, 95%CI: -2.80 to -0.06, P = 0.04, Figure 6A). Nevertheless, they have slight heterogeneity.

In the sensitivity analysis, the study by Kawamura et al[19] was excluded because the disease cause of most patients in this study was found to be a virus. However, the antiviral drugs available in 2009 temporarily failed to achieve good control of viremia, resulting in persistently high serum AST/ALT levels. Statistical heterogeneity was low across the studies for ALT [χ² = 0.43, df = 1 (P = 0.51); I² = 0%] by fitting a fixed-effects model. The ALT of LC was significantly ameliorated in BCAA-treated patients (SMD: -2.03, 95%CI: -2.52 to -1.53, P < 0.00001, Figure 6B).

Bilirubin: Statistical heterogeneity was high across the studies for bilirubin [Tau² = 0.40; χ² = 15.44, df = 3 (P = 0.001); I² = 81%] by fitting a random-effects model. The results showed that the effect of BCAs on bilirubin in patients with LC was not statistically significant (SMD: -0.37, 95%CI: -1.06-0.32, P = 0.29, Figure 7).

Glucose
Statistical heterogeneity was high across the studies for glucose [Tau² = 57.47; χ² = 8.54, df = 2 (P = 0.01); I² = 77%] by fitting a random-effects model. The results showed that the effect of BCAs on glucose in patients with LC was not statistically significant (MD: 8.10, 95%CI: -1.76-17.95, P = 0.11, Figure 8A). Nevertheless, they have slight heterogeneity.

In the sensitivity analysis, the study by Marchesini et al[23] was excluded because the Child grade of patients included in the other two studies was graded A or B. Statistical heterogeneity was low across the studies for glucose [χ² = 0.26, df = 1 (P = 0.61); I² = 0%] by fitting a fixed-effects model. The Glucose
of the LC was significantly increased in BCAA-treated patients (MD: 13.04, 95% CI: 6.81-19.89, \( P = 0.0002 \), Figure 8B).

**DISCUSSION**

In our meta-analysis, we demonstrated that BCAAs reduce the occurrence of complications in patients with LC. Moreover, nutritional status was improved by BCAA treatment. There was no significant publication bias in the main outcome indicators (Figure 9).

The occurrence of LC complications indicates the decompensated stage of LC, and the prognosis is inferior. It is essential to delay the progression of LC. Most of the complications of LC were hepatic encephalopathy, ascites, and esophageal varices in our analysis. Our study showed that BCAAs can significantly reduce the occurrence of complications. In our opinion, the mechanism by which BCAAs ameliorate hepatic encephalopathy mainly includes the following aspects. First, BCAAs can promote the metabolism of ammonia in muscle and reduce the level of blood ammonia in patients with hepatic encephalopathy[33]. Second, BCAAs can ameliorate albumin levels in patients with hepatic encephalopathy[34,35] thus increasing skeletal muscle weight. The increased muscle mass may increase extrahepatic ammonia detoxification[36]. Third, BCAAs may further enhance the detoxification of ammonia in skeletal muscle through the amidation process of glutamine synthesis[37]. Last, the addition of BCAAs reduces the brain efflux of aromatic amino acids across the blood brain barrier and the imbalance of dopamine, norepinephrine and serotonin synthesis[38]. There is a lack of detailed research on the mechanism by which BCAAs prevent other complications. Although many studies have shown that BCAAs are helpful for delaying LC[17,19], Michel et al[32] and Kobayashi et al[31] showed that BCAAs have no pronounced effect on the progression of LC. However, the subgroup analysis showed that BCAAs could inhibit the occurrence of hepatocellular carcinoma (HCC) in patients with compensated cirrhosis whose serum albumin level was less than 4 g/dL[31].

We also showed that BCAAs increased the nutritional status in patients with LC. The albumin level is an important indicator to evaluate the nutritional status of patients with LC. However, there is no further discussion on the correlation between albumin level and BCAA treatment. Some studies have shown that BCAAs can significantly improve the level of albumin[17,19,20]. In addition, many studies used mid-arm muscle circumference (MAMC) and skinfold thickness to determine patients’ nutritional

### Table 1 Characteristics of studies included in the meta-analysis, \( n = 1080 \)

<table>
<thead>
<tr>
<th>Trail</th>
<th>Country</th>
<th>Group</th>
<th>( n )</th>
<th>Treatment time</th>
<th>Child grade</th>
<th>Mean age</th>
<th>M/F</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etsushi Kawamura, 2009</td>
<td>Japan</td>
<td>BCAA</td>
<td>27</td>
<td>12 mo</td>
<td>A</td>
<td>62.70 ± 10.08</td>
<td>13/14</td>
<td>RCT</td>
</tr>
<tr>
<td>Muto Y, 2005</td>
<td>Japan</td>
<td>BCAA</td>
<td>314</td>
<td>&gt; 5 mo</td>
<td>A/B/C</td>
<td>62 ± 8</td>
<td>147/167</td>
<td>RCT</td>
</tr>
<tr>
<td>Yutaka Nakaya, 2007</td>
<td>Japan</td>
<td>BCAA</td>
<td>19</td>
<td>3 mo</td>
<td>A/B</td>
<td>67 ± 9</td>
<td>13/6</td>
<td>RCT</td>
</tr>
<tr>
<td>Les, 2011</td>
<td>Spain</td>
<td>BCAA</td>
<td>58</td>
<td>56 wk</td>
<td>A/B</td>
<td>64.1 ± 10.4</td>
<td>45/13</td>
<td>RCT</td>
</tr>
<tr>
<td>Tangkijvanich P, 2000</td>
<td>Thailand</td>
<td>BCAA</td>
<td>15</td>
<td>4 wk</td>
<td>-</td>
<td>53.07 ± 10.58</td>
<td>10/5</td>
<td>RCT</td>
</tr>
<tr>
<td>Marchesini G, 1990</td>
<td>Italy</td>
<td>BCAA</td>
<td>29</td>
<td>12 mo</td>
<td>-</td>
<td>60</td>
<td>24/6</td>
<td>RCT</td>
</tr>
<tr>
<td>Michel H, 1985</td>
<td>France</td>
<td>BCAA</td>
<td>36</td>
<td>5 d</td>
<td>A/B/C</td>
<td>60.5 ± 11.5</td>
<td>25/11</td>
<td>RCT</td>
</tr>
<tr>
<td>Ruiz-Margain, A, 2017</td>
<td>Mexico</td>
<td>BCAA</td>
<td>37</td>
<td>6 mo</td>
<td>A/B</td>
<td>54.9 ± 10.3</td>
<td>6/31</td>
<td>RCT</td>
</tr>
<tr>
<td>Masahiro Kobayashi, 2008</td>
<td>Japan</td>
<td>BCAA</td>
<td>19</td>
<td>168 wk</td>
<td>A/B</td>
<td>62.9 ± 5.7</td>
<td>19/0</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>20</td>
<td></td>
<td></td>
<td>59.5 ± 7.2</td>
<td>20/0</td>
<td></td>
</tr>
</tbody>
</table>

BCAA: Branched-chain amino acid; N: Number; M: Male; F: Female; RCT: Randomized controlled trial.
Table 2 Patient baseline characteristics of studies included in the meta-analysis, n = 1080

<table>
<thead>
<tr>
<th>Trail</th>
<th>Group</th>
<th>Albumin in g/dL</th>
<th>Etiology as viral hepatitis/alcoholic/others</th>
<th>Ascites as absent/presence</th>
<th>Hepatic encephalopathy as absent/presence</th>
<th>Esophagogastric varices as absence/presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etsushi, 2009</td>
<td>BCAA</td>
<td>3.70 ± 0.38</td>
<td>25/2/0</td>
<td>27/0</td>
<td>27/0</td>
<td>27/0</td>
</tr>
<tr>
<td>Muto, Y, 2005</td>
<td>BCAA</td>
<td>3.3 ± 0.3</td>
<td>266/20/28</td>
<td>240/74</td>
<td>287/27</td>
<td>144/170</td>
</tr>
<tr>
<td>Yutaka Nakaya, 2007</td>
<td>BCAA</td>
<td>3.0 ± 0.4</td>
<td>-</td>
<td>16/3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Les, 2011</td>
<td>BCAA</td>
<td>2.9 ± 0.6</td>
<td>24/17/17</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tangkijvanich P, 2000</td>
<td>BCAA</td>
<td>3.81 ± 0.86</td>
<td>6/6/2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Marchesini, G, 1990</td>
<td>BCAA</td>
<td>3.41 ± 0.45</td>
<td>9/20/1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Michel, H, 1985</td>
<td>BCAA</td>
<td>2.61 ± 0.10</td>
<td>4/28/4</td>
<td>10/26</td>
<td>0/36</td>
<td>-</td>
</tr>
<tr>
<td>Ruiz-Margain, A, 2017</td>
<td>BCAA</td>
<td>3.2 ± 0.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Masahiro Kobayashi, 2008</td>
<td>BCAA</td>
<td>3.86 ± 0.26</td>
<td>19/0</td>
<td>19/0</td>
<td>9/10</td>
<td>-</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>3.90 ± 0.33</td>
<td>20/0</td>
<td>20/0</td>
<td>10/10</td>
<td>-</td>
</tr>
</tbody>
</table>

BCAA: Branched-chain amino acid.

level with LC[24]. These indexes are essential for evaluating the nutritional level of patients with LC. However, there is no meta-analysis on these indexes in this paper due to the lack of several homogeneous studies. Meanwhile, sarcopenia is a complication of LC and an independent risk factor for the disease[39,40]. Qiu et al[41] confirmed that hyperammonemia-induced autophagy is a potential cause of skeletal muscle loss in cirrhosis. The incidence of sarcopenia is increasing year by year. Kitajima et al[42] confirmed that BCAAs could prevent muscle loss. A large number of experiments are needed to explore the effect of BCAAs on patients with LC and sarcopenia.

Meanwhile, the decreases in AST and ALT were investigated after BCAA treatment. ALT and AST are enzymes of hepatic gluconeogenesis. When hepatocytes are damaged, they are released from the cells. The increase in AST and ALT levels can be used as a reference index of liver function damage, but other diseases may increase AST and ALT levels which need to be excluded[43]. The included studies did not adequately report data on INR, creatinine, resolution of ascites or remission of encephalopathy. Therefore, as a meta-analysis, the relationship between BCAAs and liver function could not be determined at this time. Additionally, with regard to bilirubin, the meta-analysis related to bilirubin was not statistically significant due to the heterogeneity of the included studies and inadequate sample size, and it is hoped that more studies with sufficient data size will be discussed further in the future.

The meta-analysis of the two studies included in this paper demonstrated that BCAAs might increase the glucose level of patients. BCAAs have a specific effect on blood glucose, which has been confirmed in many studies. A review has shown that BCAAs may increase insulin resistance. Elevated BCAAs stimulate mTORC1, a nutrient sensing complex, and IRS-1 serine phosphorylation results in insulin resistance and other metabolic disorders[44]. Simultaneously, it has been widely confirmed that BCAAs upregulate glucose transporters and activate insulin secretion[45-47]. Some studies have shown that BCAAs may induce insulin resistance by inhibiting insulin signaling[48,49]. Recently, a clinical trial showed that BCAAs can induce insulin resistance through mTOR activation[50]. In contrast, it is still reported that BCAAs can decrease insulin resistance[51,52]. Despite the controversy, we recommend, based on our results, that we still need to adhere to monitoring the changes in blood glucose and be alert to endocrine disorders when taking BCAAs. In addition, it has been reported that supplementation with BCAAs may lead to an increase in ammonia produced by glutamine decomposition in the intestine and kidney due to the stimulating effect of BCAAs on glutamine synthesis, which may harm the
development of hepatic encephalopathy. Therefore, BCAAs and α-ketoglutarate or phenyl butyric acid should be used simultaneously to treat hepatic encephalopathy[53].

Our study has some limitations. First, the article only included RCT research, excluding non-RCT research. Second, the article aims to uneven the population areas and lacks targeted research for a specific area. There may be deviations in treatment. Third, because of the lack of high-quality literature in this area, we only selected the articles that met the requirements after excluding the quality problems and needed large-scale experiments to confirm our ideas further.

Finally, our results provide a reference for the nutritional treatment of patients with LC which is helpful for clinical and nursing applications. We hope that there will be better nutritional support treatment plans for LC patients in the future.
CONCLUSION

Branched-chain amino acids could reduce the incidence of complications in patients with liver cirrhosis and ameliorate nutritional status.
Figure 5 Forest plots of the meta-analysis of the aspartate aminotransferase level. BCAA: Branched-chain amino acids; N: Number; CI: Confidence interval; SMD: Standard mean difference; $I^2$: I-square.

Figure 6 Forest plots. A: Forest plots of the meta-analysis of the alanine transaminase (ALT) level; B: Forest plots of subgroup analysis of the ALT level (Kawamura et al.'s study was excluded). BCAA: Branched-chain amino acids; N: Number; CI: Confidence interval; SMD: Standard mean difference; $I^2$: I-square.

Figure 7 Forest plots of the meta-analysis of the bilirubin level. BCAA: Branched-chain amino acids; N: Number; CI: Confidence interval; SMD: Standard mean difference; $I^2$: I-square.
Du JY et al. Branched-chain amino acids use in LC

ARTICLE HIGHLIGHTS

Research background
Liver cirrhosis (LC) mainly includes increasing dietary intake, food intake time and branched-chain amino acids (BCAAs). Despite the recommendation of BCAAs in some guidelines, adverse effects have been reported in studies so the efficacy and safety of BCAAs remain controversial.

Research motivation
We performed a meta-analysis to determine the effects of BCAAs in patients with LC.

Research objectives
To determine the effects of BCAAs in patients with LC.

Research methods
Nine studies were finally included. The primary outcome was complications of LC. The secondary outcomes were nutritional status and liver function. This meta-analysis used the Review Manager, version 5 statistical package (Cochrane Collaboration, Oxford, England) for analysis.

Research results
BCAAs reduced the rate of complications in LC patients (Risk ratio: 0.70, 95% confidence interval (CI):
0.56-0.88, $P = 0.002$) and improved patients’ albumin levels [std mean difference SMD: 0.26, 95%CI: 0.12-0.40, $P = 0.0002$]. Meanwhile, BCAs significantly ameliorated the levels of alanine transaminase (SMD: -2.03, 95%CI: -2.52 to -1.53, $P < 0.00001$) and aspartate aminotransferase (SMD: -1.8, 95%CI: -2.14 to -1.46, $P < 0.00001$). Meanwhile, glucose in the LC was significantly increased in BCAA-treated patients (MD: 13.04, 95%CI: 6.81-19.89, $P = 0.0002$).

Research conclusions
Branched-chain amino acids could reduce the incidence of complications in patients with liver cirrhosis and ameliorate nutritional status.

Research perspectives
Our results provide a reference for the nutritional treatment of patients with LC which is helpful for clinical and nursing applications. We hope that there will be better nutritional support treatment plans for LC patients in the future.

FOOTNOTES
Author contributions: Du JY contributed to conception and design; Zhang L contributed to administrative support; Du JY, Liu S, and Zhou YT contributed to data collection, assembly, analysis and interpretation; all authors contributed to manuscript writing and final approval of the manuscript.

Supported by the Key Research and Development Projects of Sichuan Science and Technology Department, No. 22ZDYF1691, No. 2018FZ0062, and No. 2020YFS0410.

Conflict-of-interest statement: There are no conflicts of interest to report.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Chen YL
L-Editor: Filipodia
P-Editor: Zhang XD

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Wells’ syndrome possibly caused by hematologic malignancy, influenza vaccination or ibrutinib: A case report

Mihela Šajn, Boštjan Luzar, Samo Zver

Abstract

BACKGROUND
Wells’ syndrome (eosinophilic cellulitis) is an uncommon eosinophilic dermatosis of uncertain pathogenesis, characterized by clinical polymorphism and suggestive but nonspecific histopathologic traits. Its course is recurrent, and response to therapy is unpredictable. In a case in which the patient has a number of potential triggers for the manifestation of Wells’ syndrome skin rash, the treating physician must decide or must make an assumption in order to establish the most likely clinical scenario. This is important for the patient’s future treatment plans.

CASE SUMMARY
We describe the clinical case of a 46-year-old female with chronic lymphocytic leukemia who had already received treatment for several months with ibrutinib. She was diagnosed with Wells’ syndrome 10 d after an influenza vaccination containing thimerosal. Based on the literature, the patient was treated with a course of oral steroids. Resolution of clinical symptoms and rash were observed in response to the treatment. Ibrutinib was not discontinued.

CONCLUSION
The etiology of Wells’ syndrome remains unknown. Clinically, it resembles bacterial cellulitis. Lack of response to antibiotic treatment should lead the physician to consider a diagnosis of Wells’ syndrome. Treating the underlying condition is important and may lead to resolution of the syndrome. However, the most common and effective treatment to limit the course of the disease are systemic steroids.

Key Words: Wells’ syndrome; Chronic lymphocytic leukemia; Allogenic hematopoietic stem cell transplantation; Ibrutinib; Thimerosal-containing influenza vaccine; Clinical
Core Tip: Our patient presented with pruritic rash all over her body. Based on the pathohistological features, a diagnosis of Wells’ syndrome (eosinophilic cellulitis) was established. We considered hematological malignancy, ibrutinib and influenza vaccine as possible triggers. The only new event and therefore most probable trigger for Wells’ syndrome was an influenza vaccination with a vaccine containing thimerosal. Clinically, this is a relatively rare case.

INTRODUCTION
Classic eosinophilic dermatoses include eosinophilic cellulitis (Wells’ syndrome), granuloma faciale, eosinophilic fasciitis (Shulman syndrome) and eosinophilic folliculitis (Ofuji disease). Even though these disorders share the common characteristic of tissue eosinophilia, they have a variety of clinical presentations[1]. Fewer than 200 cases of Wells’ syndrome have been reported in the literature[2]. It is characterized by protean cutaneous manifestations with prominent eosinophilia[3]. The diagnosis is corroborated by histopathological findings from a skin biopsy specimen.

The cause of Wells’ syndrome is not known. In literature specific triggers were implicated, including drugs such as penicillin or infliximab, thimerosal-containing vaccines, and hematological malignancies, such as chronic lymphocytic leukemia (CLL), non-Hodgkin’s lymphoma, chronic myeloid leukemia and polycythemia rubra vera[1,2,4]. The most common and effective treatment is oral steroids. Topical corticosteroids are less effective and should be considered in cases of limited disease or persistent residual lesions[2].

In this case report, a female patient with CLL receiving ibrutinib and recently receiving an influenza vaccination at the time of diagnosis of Wells’ syndrome is presented.

CASE PRESENTATION
Chief complaints
A 46-year-old Caucasian woman presented at the Haematology Outpatient Department with pruritic rash all over her body. Prior to this visit, she had been examined by an infectious diseases specialist at her local hospital, who suspected a scabies-related rash.

History of present illness
The patient complained of pruritic, erythematous, blister-like lesions that had arose over the past 14 d. Because of scratching, the blisters were soon replaced with crusts (Figure 1). She reported having noticed no signs of infection, no fevers or chills, and no B-symptoms, and denied having been bitten by an insect or close contact with domestic animals. She was not receiving any medical drugs, with the exception of ibrutinib (started 18 mo earlier) but remembered having received a thimerosal-containing influenza vaccination (VaxigripTetraÒ, Sanofi Pasteur, Lyon, France) 10 d prior to the first skin lesions appearing. She reported never having experienced a similar rash.

History of past illness
The patient had been diagnosed with CLL and treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) in 2017. To address a persistent CLL clone with bone marrow infiltration of 5%, she had received the above-mentioned ibrutinib. More than 3 years after the allo-HSCT, she had presented for an extra outpatient visit to address the itchy rash.

Personal and family history
There is no personal and family history.
**Physical examination**
On admission, the patient was afebrile. Papulonodular, crusted skin eruptions (2-3 mm in diameter) were prominent on her neck, back, arms and legs. An enlarged painful lymph node (3 cm in diameter) was palpable under the left armpit. The influenza vaccination had been given on that same side.

**Laboratory examinations**
The patient’s white blood cell and absolute eosinophil counts in the peripheral blood were within normal ranges ($7.94 \times 10^9/L$ and $0.27 \times 10^9/L$, respectively). Serological and PCR-based testing ruled out reactivation of herpes simplex virus 1 and 2, varicella zoster virus, cytomegalovirus, and Epstein-Barr virus.

**Imaging examinations**
No image inspections are involved.

**Pathohistological examination**
Since the clinical and laboratory examinations did not establish a diagnosis, we opted for skin biopsy. The skin biopsy from the right thigh revealed irregular acanthosis of the epidermis, associated with diffuse superficial and deep perivascular and interstitial inflammatory cell infiltrates composed predominantly of eosinophilic granulocytes admixed with lymphocytes and histiocytes. The inflammatory cell infiltration extended into the septa and lobuli of the subcutaneous fatty tissue (Figure 2).

**FINAL DIAGNOSIS**
Wells’ syndrome (eosinophilic cellulitis).

**TREATMENT**
Based on the overall and up-to-date literature, the patient was treated with a course of oral steroid (methylprednisolone 48 mg at 1 mg/kg), administered daily for 1 wk and followed by a rapid tapering until discontinuation within 4 wk.

**OUTCOME AND FOLLOW-UP**
With the steroid treatment, resolution of the clinical symptoms and rash was observed. The ibrutinib was not discontinued at any point. Repeat bone marrow aspiration flow cytometry and histology findings were consistent with 5% residual infiltration of a CLL clone.
Figure 2 Histological evidence of Wells’ syndrome in skin from the right thigh. A: Psoriasiform hyperplasia and moderately intense superficial and deep perivascular and interstitial inflammatory cell infiltrate are evident, extending into the subcutis (magnification: 40 ×); B: Eosinophilic granulocytes as the main component of the inflammatory cell infiltrate. Here, they are seen in perivascular areas but also within the interstitium between collagen bundles (magnification: 100 ×); C: Inflammatory cell infiltrate mainly composed of eosinophilic granulocytes extending into the subcutaneous fatty tissue (magnification: 200 ×).

DISCUSSION

Wells’ syndrome, a recurrent granulomatous dermatitis with eosinophilia was first described by Wells in 1971. It also goes by the name eosinophilic cellulitis and eosinophilic dermatitis. Clinically, the syndrome resembles bacterial cellulitis because patients usually present with a warm erythematous skin lesion. Cellulitis not responding to antibiotic treatment should lead the physician to suspect Well’s syndrome[2,3]. The classic, plaque-type variant has been shown to be the most common clinical presentation form among children but not among adults. In the latter group, erythematous annular lesions resembling annular granuloma are most frequently recognized, as was the case in our patient[3]; moreover, the pathohistological features were consistent with Wells’ syndrome (Figure 2).

The cause of Well’s syndrome is not known. In literature possible triggers were implicated in the syndrome development: insect bites, viral or bacterial infections, drugs, thimerosal-containing vaccines, hematological malignancies and carcinoma. Most of the reported cases suggest a certain trigger, such as an underlying disorder, and rarely does the syndrome appear to be idiopathic in origin. Although the pathogenesis is not well defined, a type IV hypersensitivity reaction to various stimuli may be involved [2,4].

CLL is the most common leukemia in adults in Western countries, with the average age of diagnosis being 72 years. The disease is characterized by an accumulation of monoclonal, mature, CD5+ B cells in the peripheral blood, bone marrow and secondary lymphoid organs[5]. CLL is accompanied by an increased incidence of other malignancies, and patients are prone to cutaneous infections, particularly viral ones, and have exaggerated, vivid reactions to insect bites[6]. Although overall leukemic skin infiltration occurs in 3%-50% of patients within the entire spectrum of leukemias or lymphomas, it is a rare event among patients with CLL[7].

Eosinophilic dermatosis of hematologic malignancy (EDHM) and/or insect bite-like reactions are a rare event, particularly in association with CLL[8]. There has been debate about whether this phenomenon is due to a delayed hypersensitivity reaction to insect bites, particularly mosquitoes. However, most patients with lymphoproliferative disease presenting with this reaction cannot recall any bite. The condition has therefore been described with many terms, such as (exaggerated) insect bite-like reaction, eosinophilic dermatosis of myeloproliferative disease, and exaggerated arthropod-bite reaction[9].

EDHM has a pleomorphic presentation. The condition is presented by erythematous, urticarial eruptions of papules, nodules, vesicles, or the formation of plaques[10]. Histology reveals the presence of a superficial and deep, dense perivascular lymphocytic and eosinophilic infiltrate[11]. The
pathogenesis of EDHM is not known[10]. It has been suggested that the leukemic cells may cause an excess of interleukin (IL)-4 and (IL)-5 and consequently a proliferation of neoplastic B cells. The fact is that IL-5 is the major eosinophil-recruiting cytokine and neoplastic B cells are thought to be the major driver of the eruption[10,11]. Some authors have considered EDHM and eosinophilic cellulitis in patients with hematologic disorders to be the same entity[12]. Indeed, there is an overlap in clinical and pathological features between EDHM and eosinophilic cellulitis, as follows: (1) Polymorphisms in the clinical features have been described in these two conditions; and (2) Both disorders are pathologically characterized by an eosinophilic infiltration, mainly in the dermis[10].

Our case is unique because a patient who had undergone treatment with allo-HSCT was involved. This had been performed in the context of CLL treatment with adverse prognostic factors (del17, TP53 mutation; IgHV mutation status was not performed) in the young female[13]. However, the treatment was ultimately not curative, and residual disease was still present after immunosuppression withdrawal after the allo-HSCT. The patient was afraid of graft vs host disease[14] and refused a donor lymphocyte infusion, which had been proposed to enhance immune-mediated antitumor activity[15].

Because residual disease is widely associated with a significant risk of CLL progression, ibrutinib, a potent and irreversible small-molecule inhibitor of both Bruton’s tyrosine kinase and IL-2 inducible kinase as well as several other tyrosine kinases, was instituted. Ibrutinib should provide effective CLL treatment of residual disease after allo-HSCT[13,16]. Since a reduced dose of ibrutinib proved effective[17], the initial dosage of 420 mg daily was reduced to 120 mg daily after 1 mo due to severe neutropenia. Our main goal with ibrutinib treatment is to prevent CLL progression. Apart from being a Bruton’s tyrosine kinase inhibitor, ibrutinib has been shown to effectively inhibit epidermal growth factor receptor (EGFR) in a dose-dependent manner. Inhibition of EGFR is known to stimulate apoptosis and inflammation and to inhibit cell cycle progression. Cutaneous eruptions are a well-known adverse effect to EGFR inhibitor by other tyrosine kinase inhibitors, and similarly ibrutinib-induced rash may be related to EGFR inhibition[14,18-20].

EGFR inhibitor-induced toxic effects of the skin are well described and are claimed to be a class effect of this substance group. Patients present with macular, papular or pustular lesions in an acneiform distribution, mainly localized in cosmetically-sensitive areas (e.g., regions rich in sebaceous glands, such as the face and upper trunk) but can also extend to the extremities. Severe acute skin reactions show massive neutrophilic infiltration of the epidermis and profound apoptosis[19]. Cutaneous manifestations, including purpuric eruptions, have been reported in 8%-27% of patients receiving ibrutinib, sometimes resulting in treatment delays or even drug discontinuation[21]. The time of rash onset is highly variable, with onset as late as 300-400 d after the ibrutinib initiation in some patients[21,22].

In our case, if ibrutinib was the trigger, then the rash had appeared more than 600 d after the treatment was begun. In a single-center review of patients with ibrutinib-associated rash performed by Iberri et al[21], 4 patients with grade 3 rash underwent biopsy, demonstrating perivascular infiltration of lymphocytes, neutrophils and eosinophils involving the papillary dermis. However, Bullock et al[23] reported a clinical case of eosinophilic skin rash in a patient with CLL who had recently started ibrutinib. The patient presented to the emergency department with a 4-d history of a severely pruritic, eruptive full-body rash. The clinical differential was among EDHM vs drug eruption, given that she had recently started ibrutinib. After treatment with prednisone, topical corticosteroids and antihistamines, the skin lesions resolved. The patient continued to have complete resolution of her cutaneous eruption despite continuing ibrutinib therapy.

In the case of our patient, the only new event was an influenza vaccination 10 d before the clinical presentation of Wells’ syndrome. A case of Wells’ syndrome in an adult 13 d after influenza vaccination was described by Mascikauchan et al[24]. There are also some cases of children being diagnosed with Wells’ syndrome post-influenza vaccination and 1 case of an adult being diagnosed after receiving a tetanus vaccination[25-27]. Indeed, all the vaccinations described in the literature include thimerosal, a common preservative[24-27]. In the case of the patient with Wells’ syndrome post-tetanus vaccination, a skin test with thimerosal was found to be positive, demonstrating the possibility that part of the pathophysiology of Wells’ syndrome is related to hypersensitivity reactions[27].

CONCLUSION

To conclude, in our case of a patient with Wells’ syndrome, we first hypothesized that the cause was EDHM. Prior to the allo-HSCT when the bone marrow infiltration was higher than 5%, she did not experience skin changes associated with EDHM. Next, we considered ibrutinib to be a possible trigger. She had been receiving the drug for more than 2 years and had not develop any skin changes during that period. The only new event, and therefore the most probable trigger of Wells’ syndrome, was an influenza vaccination with a vaccine containing thimerosal. We have no specific or reliable evidence to state that this was the definite triggering event. It is also possible that there was an intertwining of all three reasons: hematological malignancy, ibrutinib and influenza vaccine. However, the skin rash resolution after treatment with methylprednisolone despite ibrutinib continuation and persistent CLL burden in our case, provides evidence that the influenza vaccination was the most likely factor in the
appearance of Wells’ syndrome.

FOOTNOTES

Author contributions: Šajn M and Zver S designed the manuscript; Šajn M and Luzar B collected the patient’s clinical data; Šajn M, Luzar B and Zver S contributed to the analysis and interpretation of the data, and participated in drafting of the manuscript; Zver S critically revised the manuscript; all authors read and approved the final version of the manuscript.

Informed consent statement: Written informed consent was obtained from the patient before treatment.

Conflict-of-interest statement: All authors report no relevant conflict of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wu YXJ
L-Editor: A
P-Editor: Wu YXJ

REFERENCES


Giant cutaneous squamous cell carcinoma of the popliteal fossa skin: A case report

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Abstract

BACKGROUND
Cutaneous squamous cell carcinoma (cSCC) is a common malignant hyperplasia of the skin epithelium. However, cSCC progressing to giant squamous cell carcinoma of the popliteal fossa skin has not been reported. We used full-thickness skin graft from the lower left quadrant of the abdomen to reconstruct the popliteal fossa skin defect in our patient.

CASE SUMMARY
A 64-year-old woman presented with a 3-year history of a progressively enlarged integumentary tumor located on her left popliteal fossa, which was surgically treated. The resultant defect (15 cm × 25 cm) was repaired using full-thickness skin graft from the lower left quadrant of the abdomen.

CONCLUSION
Full-thickness skin graft is a good choice to repair popliteal fossa defect.

Key Words: Giant cutaneous squamous cell carcinoma; Popliteal fossa skin; Case report

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Core Tip: We report an exceedingly rare case of giant cutaneous squamous cell carcinoma (maximum diameter > 5 cm), which presented as skin invasion of the popliteal fossa that was excised with optimal clinical result.

Citation: Wang K, Li Z, Chao SW, Wu XW. Giant cutaneous squamous cell carcinoma of the popliteal fossa skin: A case report. World J Clin Cases 2022; 10(30): 11004-11009
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11004.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11004

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is a non-melanoma skin and keratinocyte cancer, accounting for 20% of all skin cancers, and it is the second most common cancer worldwide[1]. Unfortunately, cSCC is not included in the national cancer registry in the United States, which makes it difficult for us to know the exact morbidity and mortality in China. European data show that the age-standardized incidence of cSCC is 9 to 96 cases per 100000 male residents and 5 to 68 cases per 100000 female residents (2002-2007 estimate)[2-4].

Although cSCC is mostly a benign tumor, it can locally infiltrate and metastasize. The 10-year survival rate of patients with cSCC is over 90%, but when metastasis occurs, the survival rate drops sharply[5]. The frequency of lymph node metastasis is about 4%, and the mortality is close to 2%. Because of the high incidence of cSCC, it has a significant impact on the overall mortality[6]. Furthermore, most cSCCs can be completely removed by surgery. cSCC of the popliteal fossa skin, which is a very rare site, is closely related to the knee joint and important neurovascular system, posing a surgical challenge for reconstruction. Herein, we report an exceedingly rare case of giant cSCC (maximum diameter > 5 cm), which presented as skin invasion of the popliteal fossa that was excised with optimal clinical result.

CASE PRESENTATION

Chief complaints
Three-year history of pain and mobility problems due to a progressively enlarged integumentary tumor located on the left popliteal fossa.

History of present illness
In June 2020, a 64-year-old woman presented with a 3-year history of pain and mobility problems due to a progressively enlarged integumentary tumor located on her left popliteal fossa.

History of past illness
This patient had no history of chronic diseases, such as hypertension, hyperuricemia, hyperlipidemia, and coronary heart disease.

Personal and family history
The patient was a non-smoker and had no family history of cSCC.

Physical examination
Physical examination showed an erythematous, nodular, protruding, ulcerative, mainly necrotic, foul smelling, cauliflower-like, firm skin tumor measuring 15 cm × 20 cm on the left popliteal fossa (Figure 1A). However, no significant lymph node or distant metastases were identified.

Laboratory examinations
The laboratory results revealed that the level of squamous cell carcinoma antigen was 20 ng/mL, the C-reactive protein level was 15.5 mg/L, and the erythrocyte sedimentation rate was 42 mm/h. Other laboratory results were within the normal range.

Imaging examinations
Computed tomography showed that the tumor had infiltrated deep into the muscular layer of the left popliteal fossa, but not the skeletal layer (Figure 1B).
Figure 1 Before the surgery. A: A huge erythematous nodular ulcerative skin tumor, measuring approximately 15 cm × 20 cm, was located on the left popliteal fossa; B: Computed tomography scan of the popliteal fossa.

FINAL DIAGNOSIS
Giant cSCC of the popliteal fossa skin.

TREATMENT
After popliteal fossa tumor excision and skin grafting, the tumor was totally excised. The tumor infiltrated the muscular layer and a 4 cm margin of muscular tissue was excised with the tumor. The final surgical defect measured 15 cm × 25 cm (Figure 2A and B). The surgical defect was repaired with a full-thickness skin graft from the lower left quadrant of the abdomen.

OUTCOME AND FOLLOW-UP
After surgery, the patient’s condition significantly improved (Figure 2C and D). Hematoxylin and eosin-stained section of the surgical specimen revealed an invasive, infiltrative well-differentiated cSCC (Figure 3). The patient was discharged 1 mo after operation, and had no recurrence and good wound healing after surgery. The patient was followed for one year after surgery (Figure 2E), without recurrent symptoms.

DISCUSSION
Although most cSCC cases have a good prognosis after surgical resection,[7] 3.7%-5.2% of patients have lymph node metastasis, and 1.5%-2.1% of patients die of cSCC.[8]. Although these incidences are relatively low compared with those of many other malignant tumors, the absolute number of cSCC patients with lymph node metastasis is estimated to be 5604 to 12572 in the United States alone.[9]. In addition, the estimated number of cSCC-related deaths per year is between 3932 and 8791, and its upper limit is close to the number of melanoma-related deaths per year. Thus, it is important to identify such aggressive cSCC cases in time, which can guide additional testing and treatment to improve the prognosis.[7]

Old age, fair skin, long-term sun exposure, long-term immunosuppression, and previous skin cancer diagnosis are all important risk factors for cSCC.[10]. In addition, long-term skin inflammation seems to contribute to the development of cSCC, such as chronic wound, ulcer, sinus tract, burn, or scar.[11]. This patient developed cSCC mainly due to repeated skin ulceration, leading to local chronic inflammation and popliteal squamous cell carcinoma, which not only affects the functional recovery of knee joint but also increases the probability of malignant degeneration and the difficulty of popliteal defect reconstruction.
Figure 2 After extirpating the tumor, the final surgical defect on the left popliteal fossa measured 25 cm × 15 cm. A: The surgical defect in the left popliteal fossa was 25 cm long; B: The surgical defect in the left popliteal fossa was 15 cm wide; C: As seen on day 4 after reconstruction, the surgical defect on the left popliteal fossa was repaired by full-thickness skin grafting; D: Appearance of the full-thickness skin repair of the left popliteal fossa on day 15 after reconstruction; E: Appearance of the full-thickness skin repair of the left popliteal fossa at the 1-year follow-up.

Besides Bowen disease, keratoacanthoma (KA), and invariant cSCC classic variant described above, the pathological tissues of cSCC also have several types, such as fibroproliferative, spindle cell, keratolytic, pseudovascular, verrucous, wedge-shaped epithelioma, adenosquamous cell and neurotrophic cSCC[12]. Disordered maturation of atypical keratinocytes, single cell keratinization, nuclear pleomorphism, atypical mitosis, and multi-nucleated tumor cells appear in all epidermal layers, but the basal layer remains unchanged[13]. KA is a symmetrical keratinocyte hyperplasia with limited proliferation, and its central horn plug and epidermis extend to the tumor. Histologically, invasive cSCC is characterized by atypical and abnormal keratinocytes, hyperchromic and pleomorphic nuclei, and atypical mitotic cells. Well-differentiated cSCC usually has horny pearls and single cell keratinization, while poorly differentiated cSCC usually lacks keratinization, and has many atypical mitoses and mixed inflammatory infiltration.

Pathological examination showed numerous squamous cells with keratosis and mitotic infiltration [13]. Considering that it was invasive cSCC with keratosis and no lymph node metastasis was found in our case, we performed surgery for complete tumor resection and skin grafting, and advised the patient to undergo regular postoperative reexamination.

The resection of cSCC at the popliteal fossa involves joint movement and numerous blood vessels and nerves. Therefore, it is critical to protect the important neurovascular system and prevent secondary scar contraction based on extensive activities of the popliteal fossa, which may be manifested as external aesthetic distortion and popliteal fossa retraction, thus seriously damaging the shape and function[14]. We chose a full-thickness skin graft from the lower left quadrant of the abdomen to repair the popliteal fossa defect. Full-thickness skin graft can survive on fresh sterile wounds or infected granulation wounds due to its characteristics of thin skin and strong vitality[15]. Additionally, the donor area is scar-free and cannot be easily infected[16]. In the present case, the patient could perform normal daily activities, without severe postoperative pain or any complications. Therefore, full-thickness skin repair is suitable for patients with popliteal cSCC who need extensive tumor resection, with fewer complications and faster postoperative recovery.

CONCLUSION

Full-thickness skin graft is a good alternative for the repair of popliteal fossa defects.
Figure 3 Photomicrographs of the tumor. A: Scattered squamous cells with dyskeratosis and mitotic infiltrates (H&E staining, 40 × magnification); B: Numerous squamous cells with dyskeratosis and mitotic infiltrates (H&E staining, 100 × magnification); C: Squamous cells in the periphery of the tumor (H&E staining, 400 × magnification).

FOOTNOTES

Author contributions: Wang K and Li Z collected the clinical data and drafted the manuscript; Wu XW formulated the clinical treatment programs and guided the manuscript preparation; Chao SW participated in the clinical treatment; all authors read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for the publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Chen YL
L-Editor: Wang TQ
P-Editor: Chen YL
REFERENCES


Right time to detect urine iodine during papillary thyroid carcinoma diagnosis and treatment: A case report

Shi-Chang Zhang, Cheng-Jing Yan, Yun-Fei Li, Ting Cui, Mei-Ping Shen, Jie-Xin Zhang

BACKGROUND
This is the first documentation of a spontaneous and nonspecific chemical reaction of an iodinated contrast media with ammonium persulfate used in $\text{As}^{3+}$-$\text{Ce}^{4+}$ catalytic spectrophotometry for urine iodine concentration (UIC) detection.

CASE SUMMARY
We herein report an incidental case who had a dual source computed tomography examination for papillary thyroid carcinoma diagnosis. Serial spot urine specimens were collected during her hospitalization and were measured by $\text{As}^{3+}$-$\text{Ce}^{4+}$ catalytic spectrophotometry on a Beckman Coulter AU5800. The reacted solutions were "brownish", and the results showed extremely high iodine concentrations despite serial dilutions. The patient claimed no dietary habit of iodized salt or iodine-containing medical history, which strongly pointed to iodinated contrast media (ICM) via intravenous injection. Even with 0.01% ICM, its interruption is still profound on the desired urine iodine reaction with ammonium persulfate, leading to inaccurate UIC and possibly inappropriate treatment.

CONCLUSION
The following laboratory suggestions should be considered: (1) $\text{As}^{3+}$-$\text{Ce}^{4+}$ catalytic spectrophotometry is only suitable for UIC measurement after confirmed ICM renal clearance; (2) A mass spectrometry-based method can be applied as an alternative during the ICM clearance period; and (3) The UIC baseline can be confirmed after ICM injection by consecutive detection for at least 2 mo.

Key Words: Papillary thyroid carcinoma; Urine iodine concentration; Iodinated contrast media
media; As\(^{3+}\)–Ce\(^{4+}\) catalytic spectrophotometry

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Core Tip: There has been no report on the nonspecific chemical reaction of an iodinated contrast media with ammonium persulfate used in As\(^{3+}\)–Ce\(^{4+}\) catalytic spectrophotometry thus far. We herein report a typical case, which might contribute to improving our understanding of the biochemistry mechanism as well as interpretation of the results of UIC detection during papillary thyroid carcinoma (PTC) diagnosis and treatment. This report also serves as a reminder to establish an individual flowchart to evaluate prognosis during PTC follow-up.

Citation: Zhang SC, Yan CJ, Li YF, Cui T, Shen MP, Zhang JX. Right time to detect urine iodine during papillary thyroid carcinoma diagnosis and treatment: A case report. World J Clin Cases 2022; 10(30): 11010-11015
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11010.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11010

INTRODUCTION

As the most widely used marker to assess the plasmatic iodine pool, urine iodine concentration (UIC) measurement is recommended to assess the iodine status of a population\cite{1,2}. With the increased use of iodinated contrast media (ICM) for chest and neck computed tomography (CT), excess iodine exposure has increased in patients with thyroid disease (TD). Several studies suggest that ICM increases the total body iodine stores for at least 3 mo following contrast exposure and, in some situations, for as long as 2 years. The introduction of approximately 0.1% inorganic iodine free from ICM into serum might compete with radioactive iodine or disturb thyroid function due to the Wolff-Chaikoff effect\cite{3,4}. Considering that accurate UIC detection is very important to guide radioactive iodine treatment in patients with TD, it is necessary to understand the effect of excess iodine exposure on UIC after ICM injection in patients with TD.

CASE PRESENTATION

Chief complaints
A 39-year-old female patient was admitted to our hospital on January 11, 2020 for a re-examination of a thyroid nodule.

History of present illness
The thyroid nodule was found 1 year ago. Ultrasound examination revealed a 6.1 cm × 4.9 cm × 6.7 cm hypoechoic area in the right lobe of the thyroid gland. The lesion was classified by the thyroid imaging reporting and data system (TI-RADS) as TI-RADS 4C (highly suspected malignancy).

History of past illness
The patient had a medical history that was free of previous illness.

Personal and family history
The patient had no personal or family history.

Physical examination
Upon physical examination, a solid mass was found in the right lobe of the thyroid gland.

Laboratory examinations
The patient’s laboratory blood test results on January 13, including AFP and thyroid function indicators (free triiodothyronine, free thyroxine, thyroid stimulating hormone, thyroid peroxidase antibody, thyroglobulin antibody, thyroglobulin, and parathyroid hormone), were all within the reference ranges. However, the spot UICs (sUICs) determined on January 14 were reported as errors (Figure 1A–C). We contacted her doctor to obtain new spot urine specimens on January 15 (preoperation) and 17 (1 d before discharge). Each specimen was serially diluted (10-fold, 50-fold, and 100-fold). All sUICs were extremely high (> 3 mg/L, Figure 2). Nevertheless, the reaction curves gradually changed when
Figure 1 Spot urine iodine concentration detected by As$^{3+}$-Ce$^{4+}$ catalytic spectrophotometry on January 14 by on a Beckman Coulter AU5800. A and B: Appearances of the reacted solution of the original urine specimen (A) and its 2-, 5-, 10-, and 20-fold serial dilutions after digestion at 100 °C for 60 min (B); C: Ce$^{4+}$ absorbance curve of the original urine specimen.

Comparing the same dilution ratio between different specimens over time and finally became valid in 100-fold dilution on January 17. The results indicated that the iodine concentration in the patient was actually dropping.

**Imaging examinations**

On January 13, 2020, the patient underwent dual source CT of the thyroid, and the result indicated a low density, ground-glass enhanced lesion near the back side of the right lobe. No obvious abnormality was found in the left lobe or the isthmic portion. There were multiple nodules in the II, III, IV, and VI regions of the bilateral neck with normal shapes that showed no early-stage enhancement.

**FINAL DIAGNOSIS**

The final diagnosis of the presented case was PTC.

**TREATMENT**

The patient underwent radical thyroidectomy on January 15, 2020. Histological examination of the frozen sections from the resected lesion confirmed PTC.
Figure 2 Ce⁴⁺ absorbance curves of two specimens during admission-discharge procedures to calculate the actual spot urine iodine concentrations. A-C: Original random urine specimen on January 15 (preoperation) (A) and its 10- (B) and 100-fold (C) dilutions; D-F: Original random urine specimen on January 17 (1 d before discharge) (D) and its 10- (E) and 100-fold (F) dilutions.

OUTCOME AND FOLLOW-UP

The patient had a good recovery. Her thyroid function indicators were normal until this article is written.

DISCUSSION

For the determination of iodine in urine, As³⁻-Ce⁴⁺ catalytic spectrophotometry is recommended as the standard assay according to WS/T 107.2-2016 by the National Health and Family Planning Commission in China. The protocol is as follows: (1) Add 600 μL ammonium persulfate to 200 μL urine and digest the mixture for 60 min in a 100 °C incubator; (2) Transfer the digested mixture to a Beckman Coulter AU5800; (3) Add 120 μL reagent 1 containing As³⁻ to 25 μL digested mixture; (4) Add 36 μL reagent 2 containing Ce⁴⁺ to reduce the yellow Ce⁴⁺ to colorless Ce³⁺; and (5) The decreasing absorbance curve of Ce⁴⁺ at a wavelength of 410 nm is positively proportional to the concentration of iodine over a designated period of time[5]. On January 14, we incidentally found that the digested solution of a spot urine specimen as well as its 2-fold dilution was “brownish”. We contacted the patient, and she recalled that the specimen was collected within 1 h after intravenous ICM injection on January 13. The ICM was iohexol (35 g I/100 mL). We tested iohexol instead of urine in serial dilutions. The results strongly indicated that a chemical reaction immediately started once iohexol was mixed with ammonium persulfate, even prior to digestion (Figure 3A), and we perfectly reproduced the “brownish” solution as well as the solid purple precipitates (Figure 3B). We believe that this automatic chemical reaction would disrupt the desired reaction of urine iodine with ammonium persulfate and cause inaccurate sUIC values.

There are three important studies that provide convincing and detailed data on urine iodine clearance [6-8]. In general, if a patient undergoes intravenous contrast CT examination, it will take at least 1 mo for the UIC to return to the baseline level. Unfortunately, there is a lack of data for the Chinese population to date. As³⁻-Ce⁴⁺ catalytic spectrophotometry has a sensitivity of 10 μg/L and a reportable range of 0-3000 μg/L in our laboratory. Notably, the color shade of the spot urine specimen on January 14 was between those of 35 mg iohexol (100% renal clearance assuming 200 mL urine output) and 3.5 mg iohexol (90% renal clearance). More importantly, as shown in Figure 1B, the color faded for the 2-fold dilution and disappeared for the 5-fold dilution, which allowed us to speculate that the original urine specimen probably contained at least 17.5 mg iohexol (50% renal clearance). This value was very different from that calculated on January 14, which was 1.05 mg/L (Figure 1C). We also checked the Ce⁴⁺ absorbance curve for 3.5 mg iohexol. Consistent with the curve of the 5-fold dilution of urine specimens on January 14, there was a background optical density value indicating a nonspecific reaction (Figure 3C and D). Therefore, the spontaneous and nonspecific chemical reaction of ICM with ammonium persulfate used in As³⁻-Ce⁴⁺ catalytic spectrophotometry can interfere with the accuracy of
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CONCLUSION

We suggest that the following scenarios should be considered for PTC patients who may have UIC measurement: (1) Pre-examination quality control of urine specimen. As$^3+$-Ce$^{4+}$ catalytic spectrophotometry is only suitable for the determination of the sUIC as well as the 24-h UIC after confirmed ICM renal clearance; (2) Appropriate laboratory methods for UIC detection. A mass spectrometry-based method can be applied as a favorable alternative during the ICM clearance period to evaluate potential ICM impairment; and (3) Optimal UIC detection intervals. The UIC should be detected for at least two consecutive months to confirm the baseline after ICM injection.

FOOTNOTES

Author contributions: Yan CJ and Li YF participated in data collection; Cui T and Shen MP gave expertise advice; Zhang SC and Zhang JX conceived and coordinated the study; all authors participated in manuscript writing.

Supported by the “The Six Top Talent Project” of Jiangsu Province, No. WSW-004; the Key Laboratory for Laboratory Medicine of Jiangsu Province of China, No. ZDXK2016005.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by
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S-Editor: Chang KL
L-Editor: Wang TQ
P-Editor: Chang KL

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Two novel mutations in the VPS33B gene in a Chinese patient with arthrogryposis, renal dysfunction and cholestasis syndrome 1: A case report

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Abstract

BACKGROUND
The VPS33B (OMIM: 608552) gene is located on chromosome 15q26.1. We found a female infant with autosomal recessive arthrogryposis, renal dysfunction and cholestasis syndrome 1 (ARCS1) caused by mutation in VPS33B. The child was diagnosed with ARCS1 (OMIM: 208085) after the whole exome sequencing revealed two heterozygous mutations (c.96+1G>C, c.242delT) in the VPS33B gene.

CASE SUMMARY
We report a Chinese female infant with neonatal cholestasis disorder, who was eventually diagnosed with ARCS1 by genetic analysis. Genetic testing revealed two new mutations (c.96+1G>C and c.242delT) in VPS33B, which is the causal gene. The patient was compound heterozygous, and her parents were both heterozygous.

CONCLUSION
This study extends the mutational spectrum of the VPS33B gene to provide a molecular basis for the etiological diagnosis of ARCS1 and for genetic counseling of the family.

Key Words: Arthrogryposis, renal dysfunction and cholestasis syndrome 1; VPS33B gene; Children; Heterozygous mutation; Case report
Core Tip: We report a Chinese female infant with neonatal cholestasis disorder, who was eventually diagnosed with arthrogryposis, renal dysfunction and cholestasis syndrome 1 by genetic analysis. Genetic testing revealed two new mutations (c.96+1G>C, c.242delT) in VPS33B, which are the causal genes. The patient was compound heterozygous, and her parents were both heterozygous. Our paper will expand the mutational spectrum of VPS33B.

INTRODUCTION
Arthrogryposis, renal dysfunction and cholestasis syndrome 1 (ARCS1, OMIM: 208085 and 613404) is an autosomal recessive disorder caused by mutations of the VPS33B (OMIM: 608552) and VIPAR (OMIM: 613401) genes[1,2]. We report a patient from a non-consanguineous family with ARCS1, who presented with two main symptoms (arthrogryposis and cholestasis) and ichthyosis at birth.

CASE PRESENTATION

Chief complaints
A 14-d-old female infant presented with jaundice for 5 d, with transcutaneous bilirubin (level 12.1 mg/dL).

History of present illness
The child was brought to the hospital because she had cholestatic jaundice since she was 9-d-old. No special treatment was given, and there was no progressive exacerbation or significant regression. The patient’s body weight was decreasing, and she had a loss of appetite, light yellow stools, and normal urine volume. Probiotics were given, but no improvement was seen. On September 26, 2021, she came to our hospital. There were no obvious abnormalities observed after routine blood examination. Liver function showed: total bilirubin (TBiL), 229.7 µmol/L; direct bilirubin (DBil), 152.4 µmol/L; and total bile acid (TBA), 50.6 µmol/L. Neonatal jaundice was diagnosed.

History of past illness
The child was delivered at 39 + 6W, G2P1. Cesarean section was performed because of unstable fetal heart rate. Her birth weight was 3.1 kg. The child did not have asphyxia or hypoxia at birth. Her mother had premature rupture of membranes. There was no meconium-stained amniotic fluid, intrauterine distress or abnormalities in the umbilical cord or placenta. The Apgar score was unknown.

Personal and family history
The parents denied consanguineous marriage. Her father was Han Chinese, 26-years-old and healthy. Her mother was also Han Chinese and 27-years-old with a history of Mediterranean anemia and hypothyroidism and was receiving oral levothyroxine.

Physical examination
On physical examination at 13 d after birth, her weight was 2.68 kg, length was 50 cm and cranial circumference was 32 cm. The systemic skin mucosa was yellow and dry with ichthyosis. No hemorrhagic spot. The anterior fontanelle was flat and had normal tension. Both pupils were equal in size and were sensitive to light. There was no edema in either eyelid and no congestion in the conjunctiva of either eye. Neonatal hearing screening revealed bilateral deafness. The oral mucosa was smooth. Heart sounds were strong and regular; no pathological murmur was found in the valve areas. The abdomen was soft, no rebound pain was experienced, and the liver or spleen were normal. She had joint contracture and could not stretch straight, with low muscle tone in the limbs. The ends of the limbs were warm, and capillary filling time was approximately 2 s. Primitive reflex could be elicited (Figure 1).
Yang H et al. Two mutations in VPS33B gene

Figure 1 The child had yellow, dry skin with joint contracture and could not straighten her limbs.

Laboratory examinations
After admission, we examined the patient thoroughly. The patient was blood type O, Rh-positive, and coagulation function was normal. Thalassemia genetic test showed: deletion type: genotype: α4.2/αα. Her white blood cell count was markedly elevated (356.10/L), urine bilirubin, protein and glucose were positive, and leukocyte esterase was positive (3+). She had a suspected Gram-positive bacterial urinary tract infection. Hepatitis A IgG antibody was positive. Total bilirubin was 157.6 µmol/L, direct bilirubin was 98.7 µmol/L, and total bile acid was 50.6 µmol/L. Urine acid and blood urea nitrogen were normal. Creatinine clearance rate was normal. Thyroid function was evaluated: triiodothyronine, 1.08 nmol/L; total thyroxine, 124.0 nmol/L; free triiodothyronine, 3.39 pmol/L; free thyroxine, 10.60 pmol/L; and thyroid-stimulating hormone, 7.73 mU/L. There were no obvious abnormalities in blood metabolism. The levels of urine organic acids were not raised. Cerebrospinal fluid analysis showed no abnormalities.

Imaging examinations
Small-organ color Doppler ultrasound showed a bilateral choroid plexus cyst. No significant abnormalities were observed in the abdominal color Doppler ultrasound. Cardiac color Doppler ultrasound showed an atrial septal defect. Brain magnetic resonance imaging showed signs of small cysts in the bilateral ventricles. Active electroencephalography showed that background activity was normal, with no abnormal electrical episodes.

High throughput whole-exome sequencing and mitochondrial sequencing
Informed consent was obtained from the parents on behalf of the proband for whole-exome sequencing (WES), mitochondrial sequencing and for publication of photographs. DNA samples were extracted from peripheral blood taken from the child and her parents to detect WESs and whole-genome copy number variations (CNVs). For analysis of genomic DNA, 2 mL of peripheral blood were extracted. WES and whole genome sequencing analysis of CNVs was performed by MGExome.

The second generation sequencer Illumina NextSeqTM 500 (Illumina, San Diego, CA, United States) was used to sequence the captured region at two ends, with a reading length of 150 bp. After sequencing the target region, splicing and low-quality data were removed from the sequencing data. Parental genetic investigation by Sanger sequencing revealed two heterozygous mutations (c.96+1G>C and c.242delT) in the VPS33B gene of the patient.

DNA was obtained from peripheral blood samples from the patient and her parents on October 1, 2021. The American College of Medical Genetics and Genomics sequence variation interpretation standards and guidelines were used for a comprehensive evaluation of the pathogenicity of mutation sites. Other gene mutations associated with the patient’s phenotype were not detected.

Gene detection results and pathogenicity analysis
WES showed that there were two compound heterozygous mutations of the VPS33B gene in this patient, c.96+1G>C and c.242delT, which were unreported before. The mutation, c.96+1G>C in exon 1, inherited from the father, is a novel variant. It causes a splicing mutation in aminophenol and might lead to a loss of gene function. The frequency of the variation in the normal population database is unknown, and it is a low-frequency variation. The results of protein function prediction are unknown and are not reported in the Human Gene Mutation Database (HGMD) database. According to Sanger sequencing, the variation originated from the child’s father, and her mother was wildtype (Figure 2). According to the American College of Medical Genetics and Genomics (ACMG) guidelines, the mutation was pathogenic.
Two mutations in VPS33B gene

Figure 2 Splicing mutations found in the neonate. The DNA chromatograms highlighted the mutations. A: c.96+1G>C in the proband; B: c.96+1G>C in the father; C: No abnormality in the mother.

The other was a frameshift mutation c.242delT (p.L81Cfs*33), a deletion of one thymine (T) in exon 4 (Figure 3), and is a rare variant found in < 0.1% of the general population. The mutation was a low-frequency mutation. The results of protein function prediction are unknown and are not reported in the HGMD database. This mutation was heterozygous in the mother, and the paternal gene was wildtype. According to the ACMG guidelines, the clinical significance of the variation was pathogenic.

**FINAL DIAGNOSIS**

Laboratory results showed there were two compound heterozygous mutations in the VPS33B gene. Based on clinical presentation, laboratory tests and gene sequencing results, the clinical phenotype of the patient was ARCS1.

**TREATMENT**

Routine blood examination follow-up during hospitalization indicated anemia, and thyroid-stimulating hormone was significantly elevated. Suspensions of red blood cells, levothyroxine and vitamins A, D and E were given to provide symptomatic treatment.

**OUTCOME AND FOLLOW-UP**

After 25 d of treatment, the child’s weight decreased to 2.71 kg. The whole body skin was still yellow. She had low muscular strength in the limbs; but the symptoms of anemia and hypothyroidism were better than before. The child was alive at age 4 mo. Her skin was still yellow, her weight had not increased, her joints could not straighten, she still had contractures, and she could only slightly raise her head.
two mutations in VPS33B gene

The VPS33B gene is located on chromosome 15q26.1, is 23.9 kb long, contains 23 exons and encodes a homolog of the class C yeast Vps33 gene, which contains a Sec1-like domain important in the regulation of vesicle-to-target SNARE complex formation and subsequent membrane fusion[3,4]. VPS33B contributes signaling between cell compartments. VPS33B is ubiquitously expressed in human tissues including both liver and kidneys. A proposed mechanism for the pathogenesis of VPS33B mutations includes failed intracellular trafficking, resulting in abnormal hepatocyte polarity leading to cellular damage and dysfunction[5]. The VPS33B is involved in intracellular protein sorting and ubiquitously expressed in human tissues. Mutations cause widespread errors in protein trafficking and membrane fusion, leading to dysfunction in multiple organ systems[6]. VPS33B dysfunction may lead to disruption of cell polarization in many organs, resulting in multisystem diseases. It can cause life-threatening conditions including serious dehydration, recurrent infection, metabolic acidosis and internal bleeding [7].

Mutation of the VPS33B gene can lead to ARCS1 (OMIM: 208085 and 613404). It is a congenital malfunction with autosomal recessive inheritance with poor prognosis. ARCS1 is an autosomal recessive disorder caused by mutations of the VPS33B and VIPAR (OMIM: 613401) genes[8]. The pathogenesis of ARCS1 was first described by Gissen et al.[1] in 2004. VIPAR is another causative gene of ARCS1. It is believed that VPS33B is altered in 75% of cases[9,10]. Additional features of ARCS1 include nephrogenic diabetes insipidus, failure to thrive, anomalies of the corpus callosum with neurodevelopmental delay, ichthyosis, platelet dysfunction, recurrent infections, dysmorphic features, congenital heart disease, hypothyroidism and keratitis[11].

We reported a patient with ARCS1 in China, and the patient carried two novel mutations in the VPS33B gene, which were the causative variations. The child was admitted for neonatal jaundice with clinical symptoms including joint contracture, weight loss, anemia and hypothyroidism. After vitamins, levothyroxine and other treatments, the child’s condition improved, but it was still below normal. Although she had a family history of hypothyroidism, it does not explain all symptoms. To clarify the etiology and provide better treatment, we performed WES in the child.

In our patient, ARCS1 was not clinically suspected initially. The delay in clinical diagnosis was due to the absence of renal dysfunction. The mutation c.95+1G>C in exon 1 inherited from the father, causing a splicing mutation in aminophenol, might lead to a loss of gene function. The other was a frameshift
mutation c.242delT (p.L81fs*33), a deletion of one thymine (T) in exon 4, which is a rare variant found in < 0.1% of the general population[12].

Compared with the previously reported ARCS1 patients, our child developed manifestations of neonatal jaundice and joint contracture. She had no significant abnormalities in renal function, which was distinguished from the typical symptoms of ARCS1[13-15].

We found that although it is not the typical symptom of ARCS1, ichthyosis has been reported in many previous cases, and it was present in our patient. The child had anemia, which may be associated with thalassemia gene mutations, but ARCS1 can also be accompanied by abnormal blood cell morphology. Therefore, the cause could not be defined. The child had hypothyroidism, and considering the medical history of her mother, there is also no clear evidence that this was an accompanying symptom of the disease.

Treatment of ARCS1 is mainly supportive, consisting of ursodeoxycholic acid and fat-soluble vitamin administration, maintenance of water, acid–base and electrolyte equilibrium and treatment of concurrent infections. For joint contracture in some patients, surgical correction can restore some joint function; however, due to the poor immune function of children with ARCS1, active orthopedic surgery is not recommended[16,17].

CONCLUSION

We herein reported a patient with ARCS1 caused by two new VPS33B mutations in China. We suggest that VPS33B should be considered in individuals with cholestatic jaundice, hypothyroidism and arthrogryposis features. The identification of compound heterozygotes encourages clinicians to consider ARCS1 in patients with similar clinical features and an unrelated family history. As there is no treatment for this syndrome, early identification and genetic diagnosis are essential to counsel and select for the affected families.

ACKNOWLEDGEMENTS

We would like to thank the child and her family members for agreeing to participate in this study.

FOOTNOTES

Author contributions: Yang H and Lin SZ collected and analyzed all clinical data and wrote the manuscript; Guan SH participated in collation of the literature and the chart research; Zhang SL was involved in the genetic diagnosis and treatment of the patients; Lin SZ, Wang WQ, Li JY and Yang GD substantially participated in drafting and revising the manuscript for important intellectual content; All authors involved have read and approved the final manuscript.

Supported by the Hainan Province Clinical Medical Center, No. (2021)75 and (2021)276.

Informed consent statement: Informed consent has been obtained from the patient’s family for all information mentioned in this report.

Conflict-of-interest statement: All the authors of this article have stated that there is no conflict of interest and have signed the relevant documents.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Zhang H
L-Editor: Filipodia
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Effect of electroacupuncture for Pisa syndrome in Parkinson's disease: A case report

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BACKGROUND
Pisa syndrome (PS) refers to marked lateral flexion of the trunk with a Cobb angle greater than 10°, which is typically mobile and can be resolved by lying down. PS is one of the most common postural deformities secondary to Parkinson's disease (PD) and can aggravate scoliosis in the advanced stages of PD.

CASE SUMMARY
Here, we present the case of a 53-year-old woman who presented with lateral curvature for 6 mo. Full spine X-ray films in the correct position showed that the thoracolumbar spine was bent to the right without any rotation of the vertebrae. The patient was diagnosed with Pisa syndrome. After receiving a month’s treatment with electroacupuncture, the Cobb angle decreased from 18.14° to 13.41°.

CONCLUSION
This case demonstrates that electroacupuncture can effectively improve Pisa syndrome secondary to PD with few side effects and a low risk of recurrence. Additionally, early accurate diagnosis and timely intervention are meaningful for the prognosis of PS.

Key Words: Pisa syndrome; Scoliosis; Parkinson disease; Electroacupuncture; Postural deformities; Case report
Core Tip: Pisa syndrome is common in Parkinson’s disease (PD) patients, can progress to scoliosis and may even be disabling. Currently, there is still a lack of effective treatments without side effects. We propose a new method, electroacupuncture, which may improve lateral curvature by relaxing the paraspinal muscles and modulating brain metabolism. This can ameliorate Pisa syndrome and delay the progression of PD by simultaneously treating the symptoms and disease. Thus, electroacupuncture may be an effective and beneficial treatment option for patients with Pisa syndrome.

INTRODUCTION

Parkinson’s disease (PD) is the second most common neurodegenerative disease and is characterized by resting tremor, bradykinesia, muscle rigidity and postural instability[1]. When PD is in the moderate or late stages, postural instability can progress to postural deformities which are a disabling complication in patients with PD. Approximately 33.33% of patients with PD experience postural deformities, including bell deformity, anterior cervical deformity, Pisa syndrome (PS) and scoliosis[2]. PS is one of the most common postural deformities and in the advanced stages of PD, it aggravates scoliosis[3]. The pathogenesis of PS is indeterminate, probably multifactorial and may be associated with central and peripheral pathogeneses[4]. As PS is reversible and its aggravation might decrease the quality of life of patients with PD, clinicians should recognize this condition and correct the curvature as early as possible.

Therapeutic measures for PS are limited because patients with PD generally have high muscle tension and low bone quality making conventional treatments for spinal deformity unsuitable for patients with PD[5]. However, electroacupuncture is also effective in the treatment of myotonia and spinal diseases.

Here, we report the case of a patient diagnosed with PS secondary to PD and treated with electroacupuncture who experienced a favorable result with no side effects. Her Cobb angle decreased from 18.14° to 13.41° after 1 mo, with other motor symptoms further improving.

CASE PRESENTATION

Chief complaints

A 53-year-old woman with a 4-year history of PD and lateral curvature for 6 mo presented to the acupuncture department in July 2021.

History of present illness

The patient was diagnosed with PD in January 2017. In January 2021, she experienced low back pain, stiff waist muscles and tremors. Stiffness tended to occur more frequently and seriously, and the spine could not remain upright and bent to the right. Her medication comprised of 125 mg of levodopa and benserazide tablets four times a day, pramipexole 0.375 mg once daily, piribedil 50 mg three times a day, amantadine 100 mg once a day and entacapone 100 mg four times per day.

History of past illness

The patient had a medical history of PD for 4 years and did not have diabetes, hypertension or other underlying diseases.

Personal and family history

The patient denied any family history of PD.

Physical examination

The patient’s hands trembled and she walked slowly. The patient’s head and lower limbs shook involuntarily. The spine was bent to the right (Figure 1), but this bending was alleviated when the patient adopted the supine position. Her Unified Parkinson’s Disease Rating Scale (UPDRS) score was 43, UPDRS III (motor function) score was 19 and Hoehn Yahr stage was 2.5. The muscle on the right side...
of her lower back was taut and rigid. The muscle tone of the right limb was slightly strengthened, and the tendon reflex of the limbs and Ashworth scale scores were 3.

**Laboratory examinations**
The patient’s laboratory examination results were unremarkable.

**Imaging examinations**
The erect position full-spine X-ray films showed that the thoracolumbar spine was bent to the right, the density of the vertebral body was decreased, the T10 vertebral body was suspicious of wedge-shaped changes and the full spine was degenerative. The Cobb angle at presentation was 18.14° (Figure 2A). Supine position full spine X-ray films showed that the T10 vertebral body was wedge shaped. In this position, the Cobb angle was 9.05° (Figure 2B).

**FINAL DIAGNOSIS**
Pisa syndrome secondary to PD.

**TREATMENT**
The patient underwent electroacupuncture on July 15, 2021. Along the center of the spine, 1.5-inch (0.30 mm × 40 mm) acupuncture needles were used, punctured from the twelfth thoracic vertebra to the fifth lumbar vertebra (Dumai). The needle feeding angle was 15° and the needle feeding depth was 30 mm. Six needles were evenly spaced and the feeding position of each needle was connected to the tip of the needle. Sanjiao Shu (BL 22), Shen Shu (BL 23), Qihai Shu (BL 24), and Dachang Shu (BL 25) were targeted at the right-side straight-needle (Figure 3). After acupuncture, a g-6850 electroacupuncture therapeutic instrument was used to connect the lumbar acupoints. A density wave was used and the current intensity was based on the patient’s tolerance. The needle was maintained for 30 minutes and the treatment was performed three times per week for 4 wk.

**OUTCOME AND FOLLOW-UP**
After 4 wk of treatment, the problems with leaning forward and bending to the right -side during walking significantly improved (Figure 4). Walking was more flexible than before and the patient experienced no special discomfort. Radiography of the whole spine revealed that the amplitude of lumbar scoliosis was lower than that in the anterior position. Her Cobb angle had decreased to 13.41° (Figure 5) and the UPDRS-III (motor function) score was 9 points. After 1 mo of follow-up, no aggravation of scoliosis was observed.
DISCUSSION

PS refers to a marked lateral flexion of the trunk with a Cobb angle greater than 10°[5]. Patients are typically mobile and their condition can be resolved by lying down[5]. At presentation, the patient’s Cobb angle was 18.14° which decreased in the supine position. Radiography of the entire spine did not show any rotation of the vertebrae which confirmed the diagnosis of PS. PS may be a precursor to the development of scoliosis in PD[6]; thus, it is necessary to distinguish between PS and scoliosis. Scoliosis is defined as a lateral curve of the spine with a Cobb angle of ≥ 10° in the coronal plane, usually combined with rotation of the vertebrae[7]. A previous study showed that scoliosis and Pisa syndrome were not the same, as PS is not always structural and may be caused by intrinsic muscle and soft tissue changes while scoliosis usually involves rotation and collapse of the vertebrae[6].

The mechanisms of PS are likely multifactorial and may be associated with dopamine, basal ganglia, sensorimotor dysfunction, body schema, perception and cognition, and trunk muscles[3]. Studies have shown that PS is correlated with the initiation or change in the dose of dopamine agonists in patients with PD[8,9]. According to movement disorders, central hypotheses play a key role in the pathogenesis of PS, particularly asymmetry in basal ganglia output and altered sensorimotor integration[4]. Tinazzi et al[10] found two different EMG patterns in the trunk muscles of parkinsonian patients under both static and dynamic conditions. The first pattern was characterized by hyperactivity of the lumbar paraspinal muscles contralateral to the leaning side, and the second pattern was thoracic paraspinal hyperactivity,
which was contralateral in all the patients. Both patterns indicated that there were bilateral spinal muscle imbalances[10].

There are no specific guidelines for the treatment of patients with PS; therefore, some challenges remain. One study recommended that Parkinson’s drug revision and adjustment should be considered as the first-line intervention. Second-line interventions may include pharmacological, non-pharmacological and surgical strategies[3]. PS has been associated with the initiation and dose changes of anti-Parkinsonian medication[8]; thus, adjusting the administration of medication may be effective. However, there is uncertainty regarding the adjustment of anti-parkinsonian medication, as levodopa may not only reduce Pisa symptoms[11] but can also possibly induce dyskinesias[12]. Current studies have suggested that botulinum toxin injections are effective in small cohorts as a pharmacological treatment for PS[13,14]; however, the effectiveness of botulinum toxin injections for PS is inconsistent between patients and lacks large and multicenter randomized clinical evidence[3,15]. Bartolo et al[16] observed improvements in axial posture and trunk mobility through a 4-wk rehabilitation program; however, trials of this treatment have only been performed in small cohorts and data on the long-term effects are inconsistent[3]. Surgical treatment is the last choice for PS. Currently, effective surgeries include deep brain stimulation (DBS) and spinal realignment surgery[3]. Only a few studies have addressed the effects of DBS on posture because dystonia is the underlying mechanism, but PS is not always related to dystonia; therefore, no definitive studies have yet proven that DBS is efficient for PS[17]. When a PS patient suffers from severe impairment in daily life, surgical intervention can be
considered[18]. However, spine surgery should accept the possibility of high rates of complications and reoperations due to muscle dystonia and poor bone quality[19]. In terms of cost, surgical treatment requires a large monetary investment of thousands of dollars which may cause enormous economic burden on patients. In this case, the patient was advised to undergo DBS surgery but refused because of the cost and concerns regarding surgical risks. Therefore, the patient was advised to undergo acupuncture.

No report of acupuncture treatment for PS has yet been published; however, some studies have suggested that acupuncture may be helpful in the management of scoliosis. Liu reported a case treated with acupuncture that achieved a 10° reduction in the Cobb angle[20]. Weiss et al[21] found that acupuncture could influence the deformity of patients with scoliosis by no more than 35 degrees. Both chose the Backshu acupoints to condition the zang-fu and relax the spinal muscles, similar to our study. Additionally, researchers found that acupuncture may reduce neurodegeneration in dopaminergic neurons and regulate the balance of the dopaminergic circuit to delay the progression of PD[22]. As the mechanisms of PS are strongly associated with dopaminergic neural circuits[8], acupuncture may promote the lateral curvature of PS. In addition, acupuncture may ameliorate back pain and tightness by relaxing the paraspinal muscles[23], thus reducing bending. Previous studies have shown that α-synuclein plays critical roles in PD pathogenesis[24]. Researchers have investigated the effect of electroacupuncture on abnormal neurochemical changes and motor symptoms in a mouse neurodegenerative disease model and concluded that electroacupuncture can enhance both anti-inflammatory and antioxidant activities, regulate neuronal autophagy, suppress aberrant glial activation in the diseased sites of the brain and possesses the ability to ameliorate motor abnormalities[1,25]. Based on the results of previous studies[20,21,25], we chose electroacupuncture aimed at the Backshu and Dumai acupoints on the back. The patient received a 4-wk treatment, reducing the Cobb angle by nearly 5°, which cost less than 200 dollars and induced no discomfort. After treatment, her back pain and tightness decreased, and her body movements became more flexible and gradually returned to a normal rhythm. During treatment, there were no adverse events, such as needle fainting and stagnation.

In this case, electroacupuncture improved the lateral curvature by relaxing the paraspinal muscles and balancing the dopaminergic circuit, thus preventing the curvature from developing into scoliosis which may cause disability or being bed-bound. The most important advantage of electroacupuncture is that it not only improves the lateral curvature but also delays the progression of PD[22]. Simultaneously, the cost of electroacupuncture is low and the manipulation is simple, reducing the economic burden on patients. The curvature was well maintained when she visited our clinic for postoperative review 1 mo after the end of treatment.

CONCLUSION

In conclusion, Pisa syndrome is common in patients with PD, can progress to scoliosis and can even be disabling. Currently, there is a lack of effective treatments without side effects. We propose a new method, electroacupuncture, which may improve lateral curvature by relaxing the paraspinal muscles and modulating brain metabolism. This can ameliorate PS and delay the progression of PD by simultaneously treating the symptoms and disease. Therefore, electroacupuncture may be an effective and beneficial treatment option for patients with PS.

ACKNOWLEDGEMENTS

We express our gratitude to the patients for their contribution to this case report. We also thank the Parkinson's Clinic of the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine for their support in this treatment.

FOOTNOTES

Author contributions: Yan MY and Fan JQ completed the treatment of the case and collected all the data related to the case report; Lu WJ, Mukaida K, Zhuang LX and Wang LL contributed to the writing and revising of the manuscript; all authors have read and approve the final manuscript.

Supported by National Natural Science Foundation of China, No. 82174486.

Informed consent statement: Both study participants and their legal guardians provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.
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Neonatal Cri du chat syndrome with atypical facial appearance: A case report

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BACKGROUND
Cri du chat syndrome (CdCS), also known as 5p deletion syndrome (5p-) is a syndrome caused by partial deletion of the 5p chromosome in human beings. The incidence accounts for 1/50000 and the cause of CdCS is related to partial deletion of chromosome 5 short arm (p). CdCS is a sporadic event. Only one case of CdCS was detected by chromosome screening in 125 and 170 pregnant Iranian women [1]. The most prominent clinical manifestations of CdCS are typical high-pitched cat calls, severe mental retardation or mental retardation and is most harmful to both language and growth retardation[2]. CdCS is a chromosome mutation disease which occurs during embryonic development and the symptoms of some cases are extremely atypical. It is difficult to make an early diagnosis and screening in clinic. We can suspect the disease from its atypical manifestations in the weak crying of cats, and chromosome karyotype analysis can find some questionable gene deletion fragments to assist the clinical diagnosis and prognosis of CdCS.

CASE SUMMARY
A 2-d-old male child who was admitted to our hospital with a poor postnatal reaction and poor milk intake. The baby's crying and sucking is weak, reaction and feeding time is poor and the baby has nausea and vomiting. Karyotype analysis showed that the chromosomes were 46, XY, deletion (5) p15. Whole
genome microarray analysis (named ISCN2013) showed that the chromosomes of the child were male karyotypes and contained three chromosomal abnormalities. Among them, loss of 5p15.2pter (113576-13464559) was associated with cat call syndrome. After 3 mo of follow-up, the child still vomited repeatedly, had poor milk intake, did not return to normal growth, had developmental retardation and a poor directional response.

CONCLUSION
Therefore, when cat crying and laryngeal sounds occur in the neonatal period, it should be considered that they are related to CdCS. Chromosome karyotype and genome analysis are helpful for the diagnosis of CdCS.

Key Words: CdCS; Gene; Chromosome karyotype; Neonatal; Case report

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INTRODUCTION
In 1963, French physician and geneticist Jerome Lejeune first described Cri du chat syndrome (CdCS) as a partial chromosome deletion syndrome with an incidence of about 1/15000-1/50000. Among the population with IQ (Intelligence Quotient) values less than 50, the proportion could reach 1:350\(^2\). CdCS is caused by a partial or total deletion of the short arm of chromosome 5. The size of CdCS is about 10-45 Mb and only about 12% of CdCS deletion is caused by an unbalanced translocation or recombination of the chromosome of one parent. The main clinical manifestations of this syndrome are as follows: Crying like a cat in infancy, severe mental retardation and retardation of development, microcephaly, round face, wide eye spacing, hypotropia of cleft eye, low ear position, epicanthus, penetrating hand, etc. We report a case of neonatal CdCS, who lacked typical round face features and only had a weak cry like a cat. Finally, CdCS was diagnosed by chromosome karyotype detection and genomic analysis.

CASE PRESENTATION

Chief complaints
Poor postnatal reaction and poor milk intake.

History of present illness
The intrauterine pregnancy 39 + 1w, G1P1A0, spontaneous delivery. Birth weight was 2690 g (between 3 and 10 percentiles, Fenton curve), head circumference of 31.5 cm (below 3 percentiles), length of 48 cm. After birth, the baby's cry is weak, reaction is poor with poor feeding and weak sucking with nausea and vomiting.

History of past illness
Early pregnancy has a history of fetal protection and mild anemia. Prenatal premature rupture of membranes which lasted about 11 h.
Personal and family history
Normal healthy parents of the child. Non-inmate marriage, deny any family genetic history, no special maternal contact history.

Physical examination
Body temperature 37.0 ℃, respiratory rate 68 bpm, blood pressure 70/52 mmHg, blood oxygen saturation 92%, weight 2520 g, head circumference 31.5 cm, body length 48 cm, poor stimulation response. The cry was weak, hoarse and catlike. The skin and sclera were yellow stained. The front fontanel was flat and the tension was not high and there was no facial deformity. Respiratory shortness of breath, inspiratory laryngeal ringing, heart rate 118 bpm, no murmur was heard in the valves on auscultation. Muscles tension have a slightly lower, weak sucking reflex, weak foraging reflex, normal grip reflex and incomplete hug reflex.

Laboratory examinations
White blood cell count: 6.4 × 10^9/L; Red blood cell count: 5.33 × 10^12/L; Hemoglobin: 190 g/L; Platelet count: 159 × 10^9/L; NE: 40.5% and Lymphocyte level: 49.9%; Procalcitonin level: 0.78 ng/mL. Karyotype analysis showed that the chromosomes were 46, XY, del (5) p15[20] (Figure 1). Whole genome microarray analysis (named ISCN2013) showed that the chromosomes of the child were male karyotypes and contained three chromosomal abnormalities. Among them, loss 5p15.2pter (113576-13464559) was associated with cat call syndrome, while gain (14q32.33) and loss (14q11.2) were benign cytomegalovirus changes and no pathological reports were found (Table 1 and Figure 2).

Imaging examinations
Craniocerebral ultrasound showed an intraventricular hemorrhage absorption period, cardiac ultrasound showed foramen ovale and patent ductus arteriosus, other examination results were normal.

FINAL DIAGNOSIS
Cri du chat syndrome.

TREATMENT
The child was given symptomatic treatment and discharged after their clinical symptoms improved.

OUTCOME AND FOLLOW-UP
After 3 mo of follow-up, the child was still vomiting repeatedly, had poor milk intake, 38 cm head circumference, 5000 g body weight, 55 cm body length (all below 3%), did not return to normal growth and development retardation, and had poor directional response. After stimulation, the crying of the child still resembled high-profile cat calls, with no special facial changes. After 12 mo of follow-up, the growth and development of the child were normal, but they could not make laughter or sound. They could only blur out a single syllable and react slowly to external stimuli.

DISCUSSION
Lejeune first described CdCS as the first chromosome partial deletion syndrome in 1963. The incidence of CdCS was 1/50000[3]. The cause was related to the partial deletion of the short arm (p) of chromosome 5. Typical clinical symptoms of CdCS are high-profile cat crying in infancy, growth retardation, small head with a round face deformity and mental retardation[4]. High-pitched cat calls in infancy are a typical clinical phenotype of the disease, which may be related to laryngeal development. Hassink G found that MARCH6 (TEB4) (9035025-9546120) is an E3 ubiquitin ligase located in the endoplasmic reticulum and a key gene associated with high-profile cat calls in children with 5p deletion. MARCH6 (TEB4) is involved in the protein degradation pathway. In gene expression experiments of animal embryos, it was found that MARCH6 is highly expressed in the chest and scalp tissues. It is speculated that MARCH6 (TEB4) may be involved in the cat barking sound[5]. 5p ranges from 5791886 to 7539901 in a 1.7 Mb area, 10361807 to 15728105 in a 5.4 Mb area, 22178 to 5539182 in a 5.5 Mb area and are all related to high-pitched cat calls[6]. This case was diagnosed by a genetic test because of the suspected high-profile cat calls. A notable clinical phenotype of CdCS is developmental retardation, but lack of clinical specificity[7]. In infants, poor feeding, frequent gastroesophageal reflux,
Table 1 Peripheral blood whole genome microarray analysis the results showed that the patient's chromosome was male karyotype, and there were three chromosomal abnormalities

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Exception type</th>
<th>Chromosome abnormal zones and genome coordinates (ISCN2013)</th>
<th>Abnormal size in kbp</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Loss</td>
<td>arr (hg19) 5p 15.2 pter (113576-13464559) × 1</td>
<td>13351</td>
<td>Abnormal correlation of hereditary diseases</td>
</tr>
<tr>
<td>14</td>
<td>Loss</td>
<td>arr (hg19)14q 11.2 (22510337-22969566) × 1</td>
<td>459</td>
<td>Benign CNV changes</td>
</tr>
<tr>
<td>14</td>
<td>Gain</td>
<td>arr (hg19) 14q 32.33 (106251069-106751178) × 3</td>
<td>500</td>
<td>-</td>
</tr>
</tbody>
</table>

CNV: Choroidal neovascularization.

Figure 1 Karyotype analysis of peripheral blood cells. A total of 20 metaphase phase cells were detected, and the results showed a deletion of chromosome 5 (orange arrow), namely 46, XY, del(5)(P15), which was a partial monosomic 5P syndrome (Cri du chat syndrome).

and suffocation can also occur. This affects both growth and development of the child. The clinical phenotype associated with CdCS is hTERT (1253166-1295625)[8]. The infant's birth weight was 2690 g and head circumference was 31.5 cm which was below the 10th percentile. There was intrauterine growth retardation, slow feeding, repeated breast-feeding, growth retardation, postnatal weight index of 2.43, body length/head circumference was 1.52 and other indicators are lower than those of normal newborns. These manifestations are consistent with the clinical manifestations caused by the deletion of this gene's phenotype.

Small head and round face deformity in infancy CdCS is more obvious which is manifested by a small head and round face deformity, widened eye cracks and low nasal bridge equality. This facial feature gradually becomes longer and narrower as the age increases to adolescence and adulthood and the facial features may become less obvious[3]. This case lacks the typical facial features but exhibits cat-like crying, inspiratory laryngitis and slow action which are difficult to diagnose. The serious harm of this disease is that it causes severe mental retardation and language development disorders which can assist early recognition of CdCS[9]. The most common deletion of the key genes of SEMA5A (9035025-
Figure 2 Analysis of 24 human chromosomes by whole genome microarray in peripheral blood. Autosomes 1-22 and sex chromosomes X and Y were detected. The results of chromosomal abnormalities showed deletion of chromosome 5 (orange), amplification of chromosome 5 (blue), and heterozygous deletion of chromosome 23 (purple).

9546120) and CTNND2 (10971951-11904154) in children with CdCS is related to the development of the nervous system. The deletion of these genes exists in the 5p15.2 region which will affect brain development and lead to neurodevelopmental retardation[10,11]. We consulted the OMIM website and identified TERT (1253166-1295625)[12], SEMA5A (9035025-9546120)[13], MARCH6 (10353638-10440387) [14], CTNND2 (10971951-11904154)[15], which is a single dose sensitive gene. The prognosis of CdCS is unsatisfactory, mainly due to language and mental retardation. During the follow-up of this case, mental retardation, language disorders and nervous system development retardation were found in the same age infants.

CONCLUSION
Therefore, the diagnosis of neonatal CdCS should be considered when cat crying and laryngeal sounds occur in the neonatal period. Chromosome analysis and gene screening can identify CdCS early. Its clinical phenotype and prognosis are related to the difference of deleted CdCS gene fragments.

ACKNOWLEDGEMENTS
The authors are grateful to the family members and patients for their participation in this study.

FOOTNOTES
Author contributions: Bai MM and Meng L carried out the data collection and drafted the manuscript; Sang YF, Cui YJ and Feng HY carried out the editing of the manuscript and contributed to review of the data; Li W, Zong ZT and Zhang HB conceived the study, participated in its design, coordinated and frequently edited the manuscript; All authors read and approved the final manuscript.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.
CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Xing YX
L-Editor: Filipodia
P-Editor: Xing YX

REFERENCES


Complete colonic duplication presenting as hip fistula in an adult with pelvic malformation: A case report

Xuan Cai, Jing-Tao Bi, Zhi-Xue Zheng, Ya-Qi Liu

**CASE REPORT**

**BACKGROUND**
Alimentary tract duplication (ATD) is a rare congenital anomaly. Thus, a case of ATD with a complete colonic duplication isolated in the abdominal cavity with a fistula and multiple malformations is very distinctive. These characteristics show the variability of this disease and explain why it tends to be challenging to diagnose and treat.

**CASE SUMMARY**
A 25-year-old woman with a history of a fistula opening in her right hip since birth presented with the irregular discharge of foul fluid from the fistula and intermittent abdominal pain. Contrast-enhanced computed tomography and magnetic resonance imaging findings revealed a duplicated tube isolated in her abdominal pelvic cavity along with a pelvic malformation and double ureter. Right foot radiographic examination showed pes cavus. During surgery, the tube appeared to be an almost complete colonic structure and was verified to be connected to the fistula. All of the involved tissue and fistula were removed, and the defect in the pelvic floor was closed by suturing after surgery. After 8 mo, the postoperative follow-up has been uneventful.

**CONCLUSION**
ATD may be a differential diagnosis in sinus tract cases. Laparoscopy combined with open surgery is a viable treatment option.

**Key Words:** Abdominal pain; Colonic duplication; Computed tomography; Hip fistula; Pelvic malformation; Laparoscopy; Case report

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Core Tip: This report is an uncommon case even among the rare alimentary tract duplication (ATD) cases. An entire colonic duplication without any connection to the digestive system was isolated in the abdomen pelvic. The presence of chronic sinus and several abnormalities appearing in a single case is extremely unique. There is little understanding of this disease with no consensus on the diagnosis and treatment. Additionally, the variable clinical features often lead to misdiagnosis. Here we present a successful diagnosis and treatment approach to improve the knowledge for the care of ATD cases.

Citation: Cai X, Bi JT, Zheng ZX, Liu YQ. Complete colonic duplication presenting as hip fistula in an adult with pelvic malformation: A case report. World J Clin Cases 2022; 10(30): 11037-11043
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11037.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11037

INTRODUCTION
Alimentary tract duplication (ATD) is a rare congenital anomaly characterized by a local cyst or a section of a tube-like intestine. In most cases, the duplicated tract is connected with an area of the normal digestive system[1,2]. The malformation has been reported to occur anywhere along the gastrointestinal tract from the mouth to the anus. According to clinical data, the ileum is the most common site, accounting for approximately 80% of cases. However, colonic duplication is unusual, accounting for approximately 6%-7% of cases. To the best of our knowledge, there are no previous reports or research on cases involving a body fistula combined with a pelvic malformation[3,4]. This disease usually manifests as abdominal pain, distension, hematochezia, constipation, obstruction, perforation, and even intestinal twisting. Given that more than 80% of patients can undergo treatment before the age of 2 years, adult cases are rare[4,5].

We report a case of colonic duplication presenting as a hip fistula in a 25-year-old woman with pelvic malformation. This is also a rare presentation of ATD and to our knowledge, has never been reported in the literature. To help improve medical care for ATD, the case presented here includes detailed patient history, diagnostic information, and details of treatment.

CASE PRESENTATION

Chief complaints
A 25-year-old woman with a fistula opening in her right hip since birth presented with intermittent pain in her abdomen for 3 years.

History of present illness
The patient complained of irregular dirty stool-like fluid discharge from the fistula and a pronounced limp while walking since she was a child. Additionally, scar tissue was found next to the fistula, which was a recurrent infection and abscess that had occurred and healed in the past. In addition, she had newly started experiencing intermittent abdominal pain frequently for the last 3 years without special signs, such as hematochezia, which was relieved by conservative treatment by oral or intravenous administration of antibiotics.

History of past illness
No local medical institutions were able to provide radical treatment to the patient owing to the complexity and high risk of complications of the disease. Severe acute abdominal pain was treated with intravenous antibiotics in the emergency department. Unfortunately, the patient cannot provide more detailed information concerning these treatments.

Personal and family history
The patient was of a yellow race and worked as a radiology technician in a local medical institution her height and weight were 155 cm and 43 kg, respectively. During adolescence, the menstrual cycle of the patient was irregular, and the bleeding lasted longer than normal. She experienced occasional constipation and had no history of trauma or surgery. She had no history of hypertension, coronary artery disease, diabetes, or any other chronic and infectious disease. No family history was identified.

Physical examination
The fistula appeared as a neoplasm located in her right hip nearby (approximately 5 cm) to a scar with round features (Figure 1A). A belly bulge on the right abdomen could be observed in the supine
position. Abdominal palpation revealed a tubular structure. There was no tenderness, rebound tenderness, or tension.

**Laboratory examinations**

Routine blood tests, such as blood routine examination, renal and liver function, electrolyte, coagulation function, and tumor markers did not reveal any abnormalities except mild anemia (90 g/L, 115–150 g/L). Given the patient’s history of the menstrual disorder and her compressed uterus and ovary, the serum levels of sex hormones were also evaluated and were found to be within the normal range.

**Imaging examinations**

Combined contrast-enhanced computed tomography (CT) with contrast epistolography revealed a large, dilated lumen structure with a large number of stored feces in the abdominal pelvic cavity (Figure 1B). The organs around the duplicated tract were compressed and the fistula, which connected with the distal tubular structure, was clearly shown by contrast enhancement (Figure 1C). It is possible that there was another sinus tract connecting to the proximal tubular structure with the recurrent infection area on the hip. Both CT and magnetic resonance imaging revealed abnormal morphology of the sacrum and absence of bone structures (Figure 1D). Ultrasonography showed that the uterus and ovary had normal morphologies. A double ureter and renal pelvic on the right side could be observed using contrast-enhanced CT. The right foot radiograph showed a pes cavus (Figure 1E). The colonoscope and gastrografin did not find any communication between the duplicated and normal tract.

**FINAL DIAGNOSIS**

A multidisciplinary conference was convened to clarify the diagnosis, make a treatment plan, and assess surgical risks and prognosis, especially concerning her reproductive system. Hence, the departments involved were general surgery, urology, spine surgery, obstetrics-gynecology, anesthesiology, and intensive care unit. Based on the investigation and discussion, they achieved a consensus that the final diagnosis was ATD, a special type of tubular colonic duplication with multiple anatomical abnormalities, such as pelvic malformation, pes cavus, and double ureter.
TREATMENT
A laparoscopic exploration and duplicated tract resection surgery were performed under general anesthesia. We located the double ureter and fully free the duplicated tract in the abdominal pelvic cavity under laparoscopic view. Thereafter, the patient’s operative position was changed to right supine. Methylene blue solution was injected into the duplicated tract from the right hip fistula to guide the extent of excision. This method is also commonly used in pilonidal sinus surgery cases[6,7]. After the closure of the fistula with sutures, a shuttle shape incision was made to remove the tract from the skin of the pelvic cavity along the blue-staining wall that bordered the fistula and normal tissue (Figure 2A). Finally, the tract met the fistula and the pelvis, and the entire duplicated tract was removed from the abdominal cavity through a rectus abdominal incision (Figure 2B). A tough non-absorbable stitch was used to close the defect left by the removed tract in the pelvic floor muscle layer.

Operative findings
The duplicated track was the length of the colonic tube in the retroperitoneal space of the right abdominal cavity and was covered by a sac-like peritoneal structure. We found the duplication of the ureter from the right kidney crossing the sac (Figure 2C and D). The blood supply was from an artery branching from the aortaventralsis, between the inferior mesenteric artery and the cross of the iliac vessels. Distally, the tract eventually entered into the muscular layer of the pelvic floor and terminated as a hip fistula, while proximally the tract had a blind side that had a clear border around its tissue and no connection with the body surface. The surgical specimen was a large luminal structure that appeared like a whole section of the colon (Figure 3A). After opening the lumen, a large amount of fecal slag-like secretion and a substantial portion of the tract components were found (Figure 3B).

Pathology findings
Pathology showed that duplicated tract was well-structured; the serosa, muscular, and mucous layers were similar to that of the intestinal canal. Upon hematoxylin and eosin staining, the mucous layer exhibited chronic inflammation with a large number of leukomonocytes (Figure 4A). The sinus tract was covered by squamous cells and intestinal mucosa and was infiltrated by lymphocytes (Figure 4B).

OUTCOME AND FOLLOW-UP
The patient had an uneventful recovery without short-term complications. At the 8-mo follow-up visit after surgery, the patient was still doing well. There was no pelvic floor hernia observed on the abdominal pelvic CT findings (Figure 5).

DISCUSSION
ATD is an exceedingly rare congenital deformity. Thus far, despite several theories and hypotheses, there is no clear pathogenesis. Attempts have been made to categorize it based on morphology and source of the duplicated tube. However, there has never been a consensus that could provide a definition, classification, and mechanism to describe the main characteristics of this disease in literature [8-10]. Therefore, we could not definitively diagnose this case as ATD.

This case was unique as the duplicated tube contained an entire anatomical structure resembling the colon. Additional, there were no connections between the normal digestive tract and the duplicated tube. We also could not identify any double tube or Y-shaped tube as observed in a previously reported case[1]. In our case, the duplicated tract was located in the right retroperitoneal space as a separate entity from the abdominal cavity. Therefore, it is difficult to place this into any previous classification. Based on the patient’s history, we suspected that the sinus tract in the right hip may have formed along with the duplicated tube in the abdominal pelvic cavity, which may have led to abnormalities of the ipsilateral pelvis. However, the observed pes cavus could not be explained as a consequence of this process, and could not find any link between these two. We also hypothesized that the duplicated colonic tube and sinus tract may be another complete colorectum and anus. However, there were no structures, such as sphincters, found in the sinus tract during operation or any record of functions, such as contraction and diastole in the patient’s history. The development of the duplicated tract, in this case, is definitely worth further investigation and conclusion.

ATD is usually accompanied by digestive system symptoms, such as abdominal pain, distention, diarrhea, constipation, hematochezia, obstruction, and even volvulus[4]. As a result, in most cases, it is detected and treated early, usually in childhood. A distinctive feature of our case was that the patient did not present with any digestive symptoms in her childhood as there was no connection between the normal bowel and the duplication. The only early presentation was related to the hip fistula with discharge. Colonoscopy and barium radiography, the examinations of choice for this disease, were
Figure 2 Images captured during the surgery demonstrating the process of treatment. A: Removing the fistula in the hip, after methylene blue staining; B: The duplicated tubular structure was removed from the abdominal pelvic cavity; C: The double ureter located during the operation (blue arrow); D: Freeing the duplicated colon. The blue arrow indicates the narrow pelvic floor, while the green arrow shows the complete colonic duplication under laparoscopic view.

Figure 3 Specimens of the duplicated colon. A: Complete surgery specimen; B: Mucosa of the duplicated tubular structure indicated by the blue arrow; the content of the lumen is a large amount of fecal slag-like secretion (yellow arrow).

Figure 4 Microscopy of the specimen with hematoxylin and eosin staining. A: Under 40 × magnification, the layers of the duplicated tubular structure are mucous, muscular mucosae, submucous, muscular, and serosa as shown by black arrows from top to bottom; B: Under 100 × magnification, numerous lymphocytes gather in the mucous layer are presented by the black arrow.

unrevealing[11]. As a result, the diagnosis and treatment for alimentary tract malformation were delayed. Therefore, in our opinion, for patients with sinus tracts not caused by trauma or nosocomial damage, ATD must be considered a differential diagnosis. Considering that the fistula and neoplasm may be hip bursitis or commonly infected sinus tract can easily lead to missing further inspection and delayed treatment. In most cases, an ultrasound examination may help detect the problem and exclude most differential diagnoses[12]. Additionally, diagnosis also requires multiple modes of examination and multidisciplinary involvement. It is difficult to appreciate the whole anatomical structure of the duplicated tube through routine imaging, including gastro-and-enteroscopy, which also provides a negative result. Thus, an exploratory laparotomy must be conducted.

Undoubtedly, based on both the literature and specialist’s opinion, surgery remains the only option for a cure and should be performed within a limited period, because of the malignant potential of the duplicated tube[13,14]. Owing to the tract traversing the peritoneal reflection to the pelvic floor, we used laparoscopic devices to operate. Laparoscopy combined with open surgery can be performed
under a clear and magnified field of vision, which can help identify and detect abnormal structures, such as the double ureter in this patient (Figure 2C), and can ultimately protect the normal tissue. Moreover, the instruments have an advantage over open surgery in deep and narrow spaces such as the pelvic floor. Finally, only a small incision is required to remove the pathological specimens. Because of these advantages, in the last decade, an increasing number of cases have reported the application of laparoscopy in the treatment of this disease\[15,16\]. For outcomes of treatment, there was no definitive result and high-level evidence to indicate that the laparoscopy involved in the surgery is a better choice, even in colon cancer\[4\]. However, compared to open operation, a smaller incision was an obvious advantage. The potential risk of pelvic floor hernia was also discussed, as the surgery cannot improve or reconstruct the abnormal morphology of the sacrum. However, during the operation, we found that the muscular strength in the pelvic floor was normal. Additionally, the defect had already been closed by a non-absorbable suture (2-0 prolene) following the fistula removal. Therefore, the prophylactic mesh was not considered in this case. Long-term follow-up still requires constant evaluation, especially for pregnancy. According to the above results, we can adjust the treatment strategy.

CONCLUSION
In ATD, adult cases always have a long history. Additionally, cases tend to be complex, each with unique features. This also contributes to the uncertainty of treatment. Therefore, the development of a treatment strategy should be thorough and meticulous. Multi-disciplinary consultation and careful diagnosis are essential for treatment. As in this case, surgical laparoscopy is recommended as part of the treatment.

ACKNOWLEDGEMENTS
We thank the patient and the members of our team.

FOOTNOTES
Author contributions: Cai X was responsible for gathering, analyzing, and interpreting the patient data regarding this case, and was a major contributor to writing the manuscript; Bi JT, Zheng ZX, and Liu YQ participated in the treatment; All authors read and approved the final manuscript.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection before study enrolment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-
REFERENCES


Autoimmune encephalitis with posterior reversible encephalopathy syndrome: A case report

Shu-Juan Dai, Qiu-Jian Yu, Xiao-Yan Zhu, Qun-Zhu Shang, Ji-Bo Qu, Qing-Long Ai

Specialty type: Neuroimaging
Provenance and peer review: Unsolicited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0
P-Reviewer: Beran RG, Australia; Jensen-Kondering U, Germany; Teragawa H, Japan
Received: May 6, 2022
Peer-review started: May 6, 2022
First decision: July 29, 2022
Revised: August 9, 2022
Accepted: September 23, 2022
Article in press: September 23, 2022
Published online: October 26, 2022

Abstract

BACKGROUND
Posterior reversible encephalopathy syndrome (PRES) is a neuroimaging-based syndrome and is associated with multifocal vasogenic cerebral edema. Patients with PRES frequently demonstrate headache, seizure, encephalopathy, altered mental function, visual loss and so on. We here report a patient who showed persistent neurologic deficits after PRES and was ultimately diagnosed with autoimmune encephalitis (AE).

CASE SUMMARY
This case exhibits a rare imaging manifestation of anti-casper 2 encephalitis which was initially well-matched with PRES and associated vasogenic edema.

CONCLUSION
AE should be further considered when the etiology, clinical manifestations, and course of PRES are atypical.

Key Words: Autoimmune encephalitis; Posterior reversible encephalopathy syndrome; Neuroimaging; Immunotherapy; Blood-brain barrier; Case report
Core Tip: Posterior reversible encephalopathy syndrome (PRES) is associated with many diverse clinical comorbid, the most common of which are hypertension, eclampsia, renal failure and immunosuppressive treatment. PRES is a neuroimaging-based syndrome and is associated with multifocal vasogenic cerebral edema. Patients with PRES are frequently manifested by headache, seizure, encephalopathy, altered mental function, visual loss, etc. We here report a patient who showed persistent neurologic deficits after PRES and was ultimately diagnosed with autoimmune encephalitis.

INTRODUCTION

A 37-year-old man visited the Department of neurological care unit in the First Affiliated Hospital of Kunming Medical University complaining of a general fatigue for 1 wk, aggravated with disturbance of consciousness for 1 d. He had no past medical history. When admitted to the hospital, his Glasgow Coma Scale (GCS) score was 9 (E4/V1/M4), he showed a normal blood pressure, no cervical resistance, increased muscle tone, hyperreflexia and hyperactivity ankle clonus. At presentation, brain magnetic resonance imaging (MRI) showed bilateral multifocal vasogenic edema especially in his bilateral occipital lobes, which is compatible with posterior reversible encephalopathy syndrome (PRES) (Figure 1A). Spot-like microbleeds were found on susceptibility weighted imaging (SWI) mapping (Figure 1C). During admission, follow-up MRI at 1 wk showed reduced vasogenic edema in both cerebral hemispheres considerably, with less prominent microbleeds on SWI (Figure 1B and D). Serum and cerebrospinal fluid (CSF) autoantibody tests using a cell-based immunocytochemistry kit (Shaanxi MYBiotech Co., Ltd.) showed the presence of anti-Casper 2 antibody with tilter of 1: 3.2 in CSF and 1: 100 in blood serum. The patient’s CSF profile was otherwise normal (red blood cell 20/μL; white blood cell 1/μL; protein 0.25 g/L; and glucose 4.5 mmol/L) with no evidence of infection. The patient finally diagnosed as an anti-Casper 2 autoimmune encephalitis (AE). After intravenous immunoglobulin (IVIG) for 5 d (400 mg/kg/d), his GCS score increased to 10 (E4/V1/M5), which means patient’s movement was improved. Unfortunately, due to economic problem, he didn’t perform electroencephalography (EEG) and electromyography (EMG). After 3 wk, he was transferred to local hospital.

CASE PRESENTATION

Chief complaints
A general fatigue for 1 wk, aggravated with disturbance of consciousness for 1 d.

History of present illness
There is no special illness except the chief complaints.

History of past illness
There is no history of past illness.

Personal and family history
There is no personal and family history.

Physical examination
The patient’s GCS score was 9 (E4/V1/M4), he showed a normal blood pressure, no cervical resistance, increased muscle tone, hyperreflexia and hyperactivity ankle clonus.

Laboratory examinations
Serum and CSF autoantibody tests using a cell-based immunocytochemistry kit (Shaanxi MYBiotech Co., Ltd.) showed the presence of anti-Casper 2 antibody with tilter of 1: 3.2 in CSF and 1: 100 in blood serum. The patient’s CSF profile was otherwise normal (red blood cell 20/μL; white blood cell 1/μL; protein 0.25 g/L; and glucose 4.5 mmol/L) with no evidence of infection.
Figure 1 Brain magnetic resonance imaging showed bilateral multifocal vasogenic edema especially in bilateral occipital lobes. A: Compatible with posterior reversible encephalopathy syndrome; B and D: Follow-up magnetic resonance imaging after 7 d showed significantly reduced vasogenic edema in both cerebral hemispheres, with decreased microbleeds on susceptibility weighted imaging (SWI) mapping; C: Spot-like microbleeds were found on SWI mapping.

**Imaging examinations**

Brain MRI showed bilateral multifocal vasogenic edema especially in his bilateral occipital lobes, which is compatible with PRES (Figure 1A). Spot-like microbleeds were found on SWI mapping (Figure 1C). During admission, follow-up MRI at 1 wk showed reduced vasogenic edema in both cerebral hemispheres considerably, with less prominent microbleeds on SWI (Figure 1B and D).

**FINAL DIAGNOSIS**

Anti-Casper 2 AE.

**TREATMENT**

IVIG for 5 d (400 mg/kg/d).

**OUTCOME AND FOLLOW-UP**

After intravenous immunoglobulin (IVIG) for 5 d (400 mg/kg/d), his GCS score increased to 10 (E4/V1/M5), which means patient’s movement was improved. Unfortunately, due to economic problem, he didn’t perform EEG and EMG. After 3 wk, he was transferred to local hospital.
DISCUSSION

This case exhibits a rare imaging manifestation of anti-Casper 2 encephalitis which was initially well-matched with PRES and associated vasospasm. Generally, PRES is predicted to be both clinically and radiologically reversible and especially has a good prognosis. One of the major causes of PRES is acute hypertension. Patients with normal BP who accompanied with systemic autoimmune disorders can also produce features of classic PRES radiologically. Tetsuka and Ogawa\[1\], proposed a case of PRES patient with anti-LGI 1 antibody whose MRI showed apparent vasospasm edema. It is presumed that factors such as tumor necrosis factor alpha (TNF-\(\alpha\)) and interleukin-1 (IL-1), that lead to PRES can activate the immune system and release other cytokines. These cytokines produce expression of adhesion molecules (vascular cell adhesion molecule 1 and intercellular adhesion molecule 1), which cooperate with leukocytes and lead them to produce reactive oxygen species (ROS) and proteases that result in endothelial damage and consequent fluid leakage. TNF-\(\alpha\) and IL-1 can furthermore stimulate astrocytes to secret vascular endothelial growth factor (VEGF), which deteriorates the form of junctions of the brain vasculature. These cascades result in vasogenic edema. In conclusion, endothelial hypotheses may be considered the most relevant in PRES patients with autoimmune disorders\[2\]. Meanwhile, PRES might cause the breakdown of blood-brain barrier (BBB) and the dis-organization of brain tissue\[3\]. In this case, it can be either presumed that BBB breakdown could uncover neuronal membrane antigen epitopes, such as Caspr 2, and further induce a process of autoimmune inflammatory encephalitis. More experiments should be taken in vitro and in vivo to further test the pathogenesis associated PRES-AE. Clinical diagnosis should also be made cautiously when a patient original has PRES neuroradiological features. PRES has been reported in patients with acute demyelinating encephalomyelitis (ADEM), multiple sclerosis (MS), other systemic autoimmune encephalitis (e.g. Hashimoto's disease, systemic lupuserythematosus, Behcet's disease), and paraneoplastic encephalitis\[4\].

CONCLUSION

In the present case, the patient was diagnosed as Caspr 2 AE rather than PRES due to the effectiveness of immunotherapy. In conclusion, AE can mimic PRES radiologically. AE should be further considered when the etiology, clinical manifestations and course of PRES are atypical. Persistent encephalopathic symptoms, imaging abnormalities in the multiple cortical and subcortical areas, and specifically, autoantibody analysis can be the evidences of AE. At last, immunotherapy and relevant systemic supportive treatment such as antiepileptic treatment, can lead to a better prognosis.

FOOTNOTES

Author contributions: All authors contributed to the article, critically revised the manuscript and approved the submitted version.

Supported by National Natural Science Foundation of China, No. 8216050484.

Informed consent statement: The study participant's legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Xing YX
L-Editor: A
P-Editor: Xing YX
REFERENCES


Hypophysitis induced by anti-programmed cell death protein 1 immunotherapy in non-small cell lung cancer: Three case reports

Yun Zheng, Chen-Yu Zhu, Jing Lin, Wang-Shan Chen, Yu-Jie Wang, Hong-Ye Fu, Qiong Zhao

Abstract

BACKGROUND
Hypophysitis induced by programmed cell death 1 protein (PD-1) immune checkpoint inhibitors is rare and poorly described. We report three patients with non-small cell lung cancer who developed hypophysitis after anti-PD-1 immunotherapy.

CASE SUMMARY
Both case 1 and case 2 presented with common symptoms of fatigue, nausea, and vomiting. However, case 3 showed rare acute severe symptoms such as hoarse voice, bucking, and difficulty in breathing even when sitting. Following two cycles of immunotherapy in case 3, the above severe symptoms and pituitary gland enlargement were found on magnetic resonance imaging at the onset of hypophysitis. These symptoms were relieved after 10 d of steroid treatment. Case 3 was the first patient with these specific symptoms, which provided a new insight into the diagnosis of hypophysitis. In addition, we found that the clinical prognosis of patients with hypophysitis was related to the dose of steroid therapy. Case 3 was treated with high-dose hormone therapy and her pituitary-corticotropic axis dysfunction returned to normal after more than 6 mo of steroid treatment. Cases 1 and 2 were treated with the low-dose hormone, and dysfunction of the pituitary-corticotropic axis was still present after up to 7 mo of steroid treatment.

CONCLUSION
The clinical symptoms described in this study provide a valuable reference for the
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Key Words: Programmed cell death protein 1; Immunotherapy; Hypophysitis; Lung cancer; Case reports

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Core Tip: Hypophysitis induced by programmed cell death 1 protein (PD-1) inhibitor treatment in non-small cell lung cancer (NSCLC) was rarely reported. In this study, we report three patients with NSCLC who developed hypophysitis induced by PD-1 immune checkpoint inhibitor treatment. Our study suggested that unexpected fatigue, appetite decreases, nausea, vomiting, hoarse voice, bucking, and difficulty breathing were largely correlated with immune-related hypophysitis. We also found that the clinical prognosis of patients with hypophysitis was related to the dose of steroid therapy. This work provided a reference for the diagnosis and timely treatment of hypophysitis in the clinic.

URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11049.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11049

INTRODUCTION

Immunotherapy of tumors has become a new treatment method in addition to traditional malignant tumor treatment such as surgery, radiotherapy, and chemotherapy. Recently, immune checkpoint inhibitors (ICIs) have attracted more and more attention due to their more favorable clinical outcome than conventional therapy in terminal cancer. ICIs can enhance anti-tumor activity by targeting key points in the immune system, such as cytotoxic T-lymphocyte protein 4 (CTLA4), programmed death 1 (PD-1), and its ligand programmed cell death 1 ligand 1 (PD-L1)[1]. Several immunotherapeutic drugs have been approved for the treatment of melanoma, lung cancer, and urinary tract cancer[2].

Due to the regulatory effect of ICIs on the immune system, they may induce several immune-related adverse events (irAEs) as they lack specificity and result in generalized immune activation. The irAEs occur in various organs such as the skin, gastrointestinal tract, and liver, and induce frequent dysfunction of the endocrine system[3]. Thyroid dysfunction is the most common side effect in the endocrine system; 6.5% of patients treated with ICIs developed hypothyroidism and 2.9% developed hyperthyroidism[4]. Thyroid dysfunction commonly occurs in patients treated with PD-1 or PD-L1 inhibitors. Immune-related hypophysitis (IRH) is the second most common adverse event caused by ICI treatment, which is largely induced by CTLA4 inhibitors with an incidence between 5.6% and 13.6%[5]. However, it is less common with PD-1 inhibitors (0.5%-1.1%)[6] and PD-L1 inhibitors (less than 0.1%).

Hypophysitis induced by CTLA4 inhibitors has been well documented. However, PD-1 and PD-L1 inhibitor-induced hypophysitis has been newly proposed and poorly described, probably because these drugs were approved later than CTLA4 inhibitors[7]. In the present study, we retrospectively analyzed 56 patients with advanced non-small-cell lung cancer (NSCLC) treated with an anti-PD-1 drug from 2019 to 2020 at Shulan (Hangzhou) Hospital. Three cases were diagnosed with IRH. We report these three cases of hypophysitis induced by anti-PD-1 treatment to provide new insights into its diagnosis and treatment.

CASE PRESENTATION

Chief complaints

Case 1: A 57-year-old man was diagnosed with lung squamous cell carcinoma (pT2N3M0, stage IIIB). He then received the anti-tumor treatment but he presented fatigue (grade 1 according to CTCAE version 4.0), decreased appetite (grade 1), and liver damage (grade 1).

Case 2: A 74-year-old man was diagnosed with lung adenosquamous carcinoma (pT2bN2M1, stage IV). After receiving the anti-tumor treatment, he presented severe nausea and vomiting (grade 3).

Case 3: A 54-year-old female patient was diagnosed with lung adenocarcinoma and bone metastases (pT4N2M1, stage IV). After treatment, the patient complained of fatigue, hoarse voice, bucking, and
difficulty in breathing even when sitting (grade 3).

History of present illness
Case 1: The patient refused radiotherapy and underwent four cycles of combination treatment with chemotherapy (docetaxel 75 mg/m² plus nedaplatin 80 mg/m² and anti-PD-1 drug (toripalimab 240 mg). He then received maintenance therapy with the anti-PD-1 drug only.

Case 2: The patient was treated with adjuvant combination chemotherapy (docetaxel 75 mg/m² plus nedaplatin 80 mg/m²) and an anti-PD-1 drug (pembrolizumab 200 mg) for 4 cycles. The patient did not receive continuous maintenance therapy with pembrolizumab as he developed immune-related pneumonia. He was then followed every 3 mo without any treatment. Four months later, he was taken to hospital due to severe nausea and vomiting (grade 3).

Case 3: After the patient was diagnosed, she was treated with a combination of chemotherapy (pemetrexed 500 mg/m² and nedaplatin 80 mg/m²), targeted therapy (bevacizumab 7.5 mg/kg), and anti-PD-1 (toripalimab 240 mg) therapy. Two cycles later, chest computed tomography (CT) reexamination demonstrated that the lung lesions had diminished and the curative effect was considered a significant partial remission. Unfortunately, the patient complained of fatigue, hoarse voice, bucking, and difficulty in breathing even when sitting.

History of past illness
Case 1: The patient had no history of autoimmunity.

Case 2: The patient underwent radical resection of the left lung cancer and presented with pleural metastasis.

Case 3: The patient did not have a history of autoimmunity.

Personal and family history
All patients have no family history of autoimmune disorders.

Physical examination
Case 1: The Eastern Cooperative Oncology Group (ECOG) score was 1 and Nutritional Risk Screening (NRS) score was 0. Murphy’s sign was negative. Other physical examination was unremarkable.

Case 2: The ECOG score was 1 and NRS score was 0. Murphy’s sign was negative. Other physical examination was unremarkable.

Case 3: The ECOG score was 1 and NRS score was 1. The psychological reflection was normal and no pathological reflection was induced. Other physical examination was unremarkable.

Laboratory examinations
Case 1: The patient had no epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements. Thyroid stimulating hormone (TSH), free thyroxine (FT4), adrenocorticotropic hormone (ACTH), and cortisol levels were all normal before immunotherapy in 2020. The levels of TSH and FT4 were slightly abnormal (Figure 1E, January 29, 2020) after anti-PD-1 treatment.

Case 2: The patient had no EGFR mutations or ALK rearrangements and no history of autoimmunity. The PD-L1 tumor proportion score was greater than 50%. The levels of TSH and FT4 were normal (Figure 2E, April 15, 2020).

Case 3: After the patient was diagnosed, the patient presented no EGFR mutations or ALK rearrangements. When the symptoms such as fatigue and hoarse voice appeared, the levels of ACTH (5.37 pg/mL) and cortisol (2 μg/dL) were lower than the normal range (Figure 3F).

Imaging examinations
Case 1: Magnetic resonance imaging (MRI) showed that the pituitary morphology (Figure 1A) was normal before immunotherapy in 2020. When the patient first exhibited fatigue, decreased appetite, and liver damage, the pituitary enlargement was also not found (Figure 1B).

Case 2: We performed cranial MRI and lumbar puncture, but no pituitary abnormalities (Figure 2A) or meningeal metastasis were found.

Case 3: The baseline chest CT is presented in Figure 3A. When the symptoms such as fatigue and hoarse voice appeared, we performed a 3T laryngoscopy but found no vocal cord disorders. We then performed pituitary MRI, and found that the pituitary gland was slightly enlarged (Figure 3D) compared with that at baseline (Figure 3C).
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Figure 1 Pituitary magnetic resonance imaging and laboratory examination results in case 1. A: The pituitary was normal before starting immunotherapy (November 30, 2019); B: Pituitary enlargement was not found at the onset of immune-related hypophysitis (July 26, 2020); C: The pituitary was normal after steroid treatment (December 18, 2020); D: The levels of adrenocorticotropic hormone and cortisol; E: The levels of thyroid stimulating hormone and free thyroxine. ACTH: Adrenocorticotropic hormone; TSH: Thyroid stimulating hormone; FT4: Free thyroxine.

FINAL DIAGNOSIS

Case 1: The patient was diagnosed with hypothyroidism and secondary adrenal insufficiency induced by hypophysitis due to anti-PD-1 treatment according to his medical history, clinical features, and laboratory measurements.

Case 2: According to his treatment history and clinical symptoms, the patient was diagnosed with hypothyroidism induced by anti-PD-1 treatment.

Case 3: Following a multidisciplinary consultation, the diagnosis of IRH was made after excluding all other possible cause.
Figure 2 Pituitary magnetic resonance imaging and laboratory examination results in case 2. A: The pituitary was normal when the patient developed nausea and vomiting for the first time; B: Pituitary enlargement was not found when the patient complained of nausea and vomiting for the second time; C: The pituitary was normal after 2 mo of steroid treatment; D: Adrenocorticotropic hormone and cortisol levels; E: Thyroid stimulating hormone and free thyroxine. ACTH: Adrenocorticotropic hormone; TSH: Thyroid stimulating hormone; FT4: Free thyroxine.

TREATMENT

Case 1: When the patient first exhibited fatigue, decreased appetite, and liver damage, we decreased the frequency of toripalimab administration. After one cycle of maintenance treatment, he was hospitalized again due to increased fatigue, severe nausea, and vomiting (grade 3). The patient discontinued anti-PD-1 maintenance treatment. The frequency of anti-PD-1 treatment was then adjusted and the patient was continuously treated for 6 mo, but the levels of TSH and FT4 were still abnormal (July 31, 2020). We also found abnormal levels of ACTH (3.66 pg/mL) and cortisol (0.9 μg/dL) (Figure 1D) at this time, suggesting that the symptoms were caused by secondary adrenal insufficiency. The patient was subsequently treated with hormone and thyroxine replacement therapy. He took oral hydrocortisone 50 mg/d and then given oral prednisone 25 mg/d. The dose of prednisone was then tapered to 1 tablet every 14 d, and finally reduced to 1 tablet.
Figure 3 Imaging examination and laboratory results in case 3. A: Chest computed tomography (CT) image at baseline; B: Chest CT image after two cycles of combination therapy; C: The pituitary was normal before combination therapy (June 9, 2020); D: Pituitary enlargement was found after two cycles of combination therapy (August 8, 2020); E: The pituitary was normal after nearly 2 mo of steroid treatment (September 27, 2020); F: Adrenocorticotropic hormone and cortisol levels; G: Thyroid stimulating hormone and free thyroxine. ACTH: Adrenocorticotropic hormone; TSH: Thyroid stimulating hormone; FT4: Free thyroxine.

Case 2: After the patient visited our hospital, we treated the patient with an antiemetic agent and his discomfort was relieved but prone to recurrence. After 3 mo of antiemetic treatment, he complained of nausea and vomiting exacerbation and a 5 kg weight loss. Pituitary MRI was performed again, but revealed no enlargement of the pituitary (Figure 2B). However, an empty sella was found on the
pituitary MRI. At the same time, the levels of ACTH (3.66 pg/mL) and cortisol (2.5 μg/mL) were abnormally lower than the normal range (Figure 2D). Obvious dysfunction of the pituitary-thyroid axis was not found. He subsequently received hormone therapy. Oral prednisone was administered at a dosage of 2.5 mg bid.

**Case 3:** The patient received hormone shock therapy. First, 200 mg/d methylprednisolone was injected for 4 d, and then 160 mg/d and 120 mg/d methylprednisolone for 3 d, respectively. After hormone therapy, the patient’s discomfort was gradually relieved. Next, we discontinued anti-PD-1 treatment and the patient received continuous administration of combined chemotherapy and targeted therapy for two cycles. Pemetrexed and bevacizumab were then administered as uninterrupted maintenance therapy. We also adjusted the administration of hormone therapy. Methylprednisolone 80 mg/d was given for 8 d and 5 g/d allotype for 5 d. Although her discomfort completely disappeared, the levels of ACTH and cortisol were not obviously changed. The dose of methylprednisolone was then reduced by 20%-30% every 7 d to 5 mg/d.

**OUTCOME AND FOLLOW-UP**

**Case 1:** When the patient took oral hydrocortisone for 1 wk, his discomfort was significantly reduced. After 1 mo of steroid treatment, the levels of TSH and FT4 were found to be in the normal range (September 2, 2020). In addition, dysfunction of the pituitary-gonadal axis and abnormality of pituitary morphology (Figure 1G) were not found. However, function of the pituitary-adrenal axis was abnormal for an extended period (Figure 1D).

**Case 2:** After 2 wk of hormone treatment, the patient’s symptoms were significantly relieved. Four months later, the pituitary gland was normal (Figure 2C), but the pituitary-corticotropic axis was still abnormal after 7 mo of steroid treatment (ACTH = 4.85 pg/mL).

**Case 3:** After almost 2 mo of hormone therapy, pituitary enlargement diminished (Figure 3E). Three months later, the level of ACTH (10.36 pg/mL) returned to normal, and cortisol level (10.3 μg/dL) also returned to normal after more than 4 mo of hormone therapy. No dysfunction of the pituitary-thyroid axis (Figure 3C) or the pituitary-gonadal axis was observed during the treatment period.

**DISCUSSION**

It is acknowledged that several human cancers can escape immune surveillance through the expression of PD-1. PD-1 is able to inhibit T-cell action against tumor cells; therefore, anti-PD-1 treatment has become an effective therapy by promoting the anti-tumor immune response. However, the main function of PD-1 in the healthy body is to suppress the autoimmune response, and inhibition of this system also triggers the T-cell inflammatory response against any susceptible healthy tissues [8]. Despite anti-PD-1 treatment having a remarkable impact on advanced cancers, it also induces wide-ranging irAEs.

The mechanism of irAEs remains unknown. Dysfunction of the endocrine system is one of the most common irAEs caused by anti-PD-1 treatment. It was reported that hypothyroidism frequently occurs in patients treated with anti-PD-1 drugs. In addition, hypophysitis was commonly found in patients treated with CTLA4 inhibitors [6,9]. This difference may be supported by the fact that there is no ectopic PD-1 expression in normal hypophysis tissue [10,11]. In the present study, only one case presented with hypothyroidism. IRH is a pituitary disorder with one or multiple anterior pituitary hormone deficiencies (mostly ACTH and/or TSH) [12]. In our study, three cases all displayed isolated ACTH insufficiency after anti-PD-1 treatment, which was consistent with a previous study [13]. It is worth mentioning that combination therapy with PD-1 and CTLA4 inhibitors increased the occurrence of hypophysitis, which ranged from 8.8% to 10.5% [14,15]. The frequency of hypophysitis occurrence may be under-estimated in oncological trials that did not systematically screen for this adverse event that has a non-specific clinical presentation [16].

The general symptoms associated with IRH are fatigue, decreased appetite, nausea, and vomiting. These common symptoms were also present in cases 1 and 2 in the present report. However, the symptoms including hoarse voice, bucking, and difficulty in breathing even when sitting in case 3 are rare, and this is the first case showing such specific symptoms in our clinical experience. This may provide oncologists with a new understanding of the symptoms caused by IRH. The adverse event of immune-mediated hypophysitis commonly occurs within 8-12 cycles after the initiation of anti-PD-1 therapy [17]. In the present study, it occurred after eight cycles of immunotherapy in case 1 and after four cycles in case 2. Whereas, case 3 developed hypophysitis after two cycles of immunotherapy. This may be related to the insufficient sample size and heterogeneity between patients. Heterogeneity is derived from the patient’s constitution, treatment profile, psychological pressure, and so on.
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MRI is an imaging technique used in the diagnosis of pituitary inflammation. Pituitary enlargement is usually found in patients diagnosed with hypophysitis. However, due to a lack of experience among clinicians, brain or pituitary MRI is not performed at baseline before immunotherapy. Pituitary MRI is generally performed following the development of hypophysitis. Therefore, clinicians are not able to fully assess hypophysitis. It was found that 25% of patients showed a normal pituitary MRI during the acute phase of pituitary inflammation[18-20]; therefore, hypophysitis is easily misdiagnosed if the clinician lacks experience. In this study, the pituitary gland was enlarged in case 3 when hypophysitis developed, but was still considered to be in the normal range. Although pituitary enlargement is not found in most patients at the onset of hypophysitis, pituitary MRI is necessary at baseline before immunotherapy. In addition, the clinician should inform the radiologist of the patient’s medical history in order to make the correct diagnosis.

In terms of treatment for IRH, hormone replacement is commonly administered by clinicians. After treatment, thyroid function can return to normal, but dysfunction of the pituitary-gonadal axis and pituitary-corticotropic axis may still persist[21,22]. Our study also confirmed this situation. Thyroid function in case 1 recovered soon after almost 1 mo of steroid treatment, but function of the pituitary-corticotropic axis in cases 1 and 2 was still abnormal after up to 7 mo of steroid treatment. However, the pituitary-corticotropic axis in case 3 returned to normal after more than 6 mo of steroid treatment. The reason for this difference may be related to the dose of hormone administered, as case 3 was treated with high-dose hormone therapy while cases 1 and 2 were treated with the low-dose hormone therapy. Our study provides a reference for the treatment of IRH. A previous study reported that the overall survival of patients with IRH was not improved by steroid therapy[23]. We speculate that the poor prognosis may be related to the dose of steroid therapy.

Besides the focus on the side effects caused by PD-1 inhibitors, the expression rate of PD-1 and PD-L1 is also important. It has been reported that the expression rate was correlated with the disease types and subtypes[24]. In addition, the inflammatory cytokines can affect the PD-1 or PD-L1 expression. Ribas and Hu-Lieskovan[25] reported that inflammatory cytokines induced the PD-L1 expression, and particularly, the involvement of interferon-γ in immune checkpoint induction has been reported[26]. At present, no research reported the involvement of inflammatory cytokines in related hypophysitis caused by PD-1 expression. The investigation of inflammatory cytokines might be conducive to monitoring the hypophysitis caused by PD-1 inhibitor treatment.

CONCLUSION

This study describes three patients receiving anti-PD-1 treatment for NSCLC who ultimately developed hypophysitis, simultaneously leading to hypothyroidism and/or isolated ACTH deficiency. PD-1 inhibitor induced-hypophysitis presented with less obvious clinical and radiological signs, and the lack of a clinical presentation can lead to delayed diagnosis. It is necessary to perform a systematic and regular hormonal evaluation in patients treated with ICIs. When unexpected fatigue, decreased appetite, nausea, vomiting, hoarse voice, bucking, and difficulty in breathing develop, IRH should be considered.

FOOTNOTES

Author contributions: Zheng Y and Zhu CY designed the study, drafted the manuscript, and reviewed the manuscript; Zheng Y, Zhu CY, and Lin J performed the literature review; Lin J was involved in supervision and manuscript review and editing; Chen WS contributed to the data curation and investigation; Wang YJ and Fu HY conducted the study and suggested pertinent modification; Zhao Q supervised the study process and reviewed the manuscript; Zheng Y, Zhu CY, and Lin J performed the literature review; Lin J was involved in supervision and any accompanying images.

Informed consent statement: Informed written consent was obtained from the patients for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Country/Territory of origin: China
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10.1186/s40425-019-0729-3


Different intraoperative decisions for undiagnosed paraganglioma: Two case reports

Dongho Kang, Bo-eun Kim, Minjae Hong, Joungmin Kim, Seongtae Jeong, Seongheon Lee

**Abstract**

**BACKGROUND**
Paragangliomas may be preoperatively misdiagnosed as non-functioning retroperitoneal tumors and are sometimes suspected only at the time of intraoperative manipulation. Without preoperative alpha blockade preparation, a hypertensive crisis during tumor manipulation and hypotension after tumor removal may result in critical consequences. Therefore, primary consideration should be given to the continuation or discontinuation of surgery on the basis of the possibility of gentle surgical manipulation and hemodynamic stabilization. We report two cases of paragangliomas detected intraoperatively.

**CASE SUMMARY**
A 65-year-old woman underwent laparoscopic small-bowel wedge resection. A hypertensive crisis occurred during manipulation of the mass, and an unrecognized catecholamine-producing paraganglioma was suspected. The surgeon and anesthesiologists believed that tumor excision could be performed with minimal manipulation of the tumor because the tumor was in a favorable location. Serious hemodynamic instability did not occur with aggressive use of vasoactive drugs. A week later, a 54-year-old man underwent open resection of a 3-cm-sized retroperitoneal mass and showed the same findings during mass manipulation. For this patient, continuous manipulation of the mass seemed inevitable due to adhesion between the right adrenal gland and the mass in a narrow surgical field. The surgeon and anesthesiologists decided to cancel the surgical procedure and planned to perform a reoperation after alpha blockade therapy. Two weeks later, the tumor was uneventfully removed with small doses of vasoactive drugs.

**CONCLUSION**
When an undiagnosed paraganglioma is suspected intraoperatively, reoperation after adequate preparation should be considered as an option to avoid fatal
outcomes.

**Key Words:** Paraganglioma; Undiagnosed diseases; Hypertensive crisis; Preoperative alpha blockade; Surgery cancellation; Neuroendocrine tumors; Case report

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**Core Tip:** Undiagnosed paragangliomas may be suspected at the time of intraoperative manipulation. Tumor removal without preoperative alpha blockade preparation can lead to serious hemodynamic instability. The present case report describes different intraoperative decisions for two patients with undiagnosed paragangliomas. Intraoperative cancellation of surgery may not always be feasible or practical, but it should be considered as an option in cases requiring frequent manipulation of the tumor.

**Citation:** Kang D, Kim BE, Hong M, Kim J, Jeong S, Lee S. Different intraoperative decisions for undiagnosed paraganglioma: Two case reports. *World J Clin Cases* 2022; 10(30): 11059-11065

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i30/11059.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i30.11059

**INTRODUCTION**

Paragangliomas are rare neuroendocrine tumors derived from extra-adrenal chromaffin cells, which are catecholamine-producing postganglionic sympathetic neurons[1-3]. Similar to pheochromocytomas, these tumors can show life-threatening complications such as hypertensive crisis and hemodynamic instability during surgery. To reduce these complications, preoperative preparation with an adrenal blockade is essential. However, paragangliomas may be preoperatively misdiagnosed as non-functioning retroperitoneal tumors since patients have no specific preoperative symptoms, such as palpitation. In these patients, paragangliomas may be suspected at the time of intraoperative manipulation.

Previous reports of undiagnosed catecholamine-producing tumors have described successful operations with careful surgical resection and intensive anesthetic management[4-6]. However, most cases involved a hypertensive crisis, which was followed by severe postoperative hypotension. The patients may even show intraoperative acute catecholamine cardiomyopathy and sudden cardiac arrest [7]. Adequate preparation may prevent these lethal situations. Therefore, when a catecholamine-producing paraganglioma is suspected during surgery, primary consideration should be given to the continuation or discontinuation of surgery. Surgeons and anesthesiologists should discuss the possibility of gentle surgical manipulation, intraoperative hemodynamic stabilization, and postoperative complications.

We report two cases of intraoperatively detected paragangliomas.

**CASE PRESENTATION**

**Chief complaints**

**Case 1:** A 65-year-old woman was admitted for laparoscopic small-bowel wedge resection of a 6-cm-sized mass suspected to be a small-bowel gastrointestinal stromal tumor (GIST). During laparoscopic manipulation of the mass, systolic blood pressure suddenly increased to 250-280 mmHg.

**Case 2:** A 54-year-old man was admitted for open resection of a 3-cm-sized retroperitoneal mass suspected to be leiomyosarcoma. During careful dissection of the mass superior to the right adrenal gland, systolic blood pressure and pulse rate increased to 200-230 mmHg and 130-150 bpm, respectively.

**History of present illness**

**Case 1:** The patient’s blood pressure was 178/85 mmHg, and her heart rate was 65 bpm on arrival to the operating room. General anesthesia was induced and maintained with propofol and remifentanil. The mass became visible 20 min after the start of laparoscopic surgery. When the surgeon manipulated the mass, systolic blood pressure suddenly increased to 250-280 mmHg. Repeated doses of nicardipine (1-mg doses with a total dose of 3 mg) were administered, and the systolic blood pressure decreased to 120 mmHg. Within 5 min, the blood pressure increased again, and the patient showed tachycardia (110-130 bpm). Nicardipine and esmolol were then administered repeatedly, and the anesthetic depth was increased by
increasing the doses of propofol and remifentanil. However, adequate control of blood pressure could not be achieved.

**Case 2:** The patient’s blood pressure and heart rate on arrival to the operating room were 136/82 mmHg and 79 bpm, respectively. General anesthesia was maintained with desflurane and remifentanil after anesthesia induction with propofol. The mass became visible 35 min after the start of the operation. When the surgeon manipulated the mass, the systolic blood pressure suddenly increased to 185 mmHg. After administration of nicardipine (0.5 mg), the blood pressure normalized. Anesthetic depth was also increased by increasing the doses of desflurane and remifentanil. However, systolic blood pressure and pulse rate increased to 200-230 mmHg and 130-150 bpm, respectively, during careful dissection of the mass superior to the right adrenal gland. The blood pressure and heart rate were not adequately controlled by administering multiple doses of nicardipine and esmolol.

**History of past illness**

**Case 1:** The patient had been receiving an angiotensin-2 receptor blocker and thiazide for the treatment of hypertension from 2016. Her blood pressure was well controlled until the morning of the surgery. She had been in a euthyroid state with levothyroxine medication after undergoing total thyroidectomy in 2006.

**Case 2:** The patient was receiving clopidogrel owing to a history of deep vein thrombosis. Clopidogrel was withheld for 5 d before surgery. The patient had no history of hypertension.

**Personal and family history**

None of the two patients had any relevant personal or family history.

**Physical examination**

**Cases 1 and 2:** The results of preoperative physical examination were unremarkable. During general anesthesia, the depth of anesthesia and arterial blood pressure were continuously monitored. No prominent elevation of blood pressure or heart rate was observed during tracheal intubation, skin incision, or laparoscopic port insertion. Deep neuromuscular blockade was maintained with continuous infusion of rocuronium under neuromuscular monitoring.

**Laboratory examinations**

The results of preoperative laboratory tests and electrocardiography were normal.

**Imaging examinations**

**Case 1:** Abdominal computed tomography (CT) showed an approximately 6-cm-sized well-circumscribed heterogeneously enhancing mass around the duodenal flexure ([Figure 1A](#)). The initial radiographic impression was a GIST.

**Case 2:** Abdominal CT showed an approximately 3-cm-sized heterogeneously enhancing mass in the retrocaval space ([Figure 1B](#)). The mass pushed the inferior vena cava forward and abutted the liver in the lateral portion. The initial radiographic impression was a leiomyosarcoma with possible invasion of the liver.

**FINAL DIAGNOSIS**

An unrecognized catecholamine-producing paraganglioma was highly suspected based on the high blood pressure and heart rate induced by intraoperative manipulation of the mass.

**TREATMENT**

The surgeon was asked to stop the manipulation of the tumor to prevent further hypertensive crises. Surgical procedures involving undiagnosed paragangliomas without adequate preoperative preparation may lead to increased morbidity and mortality. Therefore, the surgeon and anesthesiologists discussed whether to proceed with the surgical procedure or cancel it.

**Case 1**

The surgeon thought that tumor excision could be performed with minimal manipulation of the tumor because the tumor seemed to have a relatively clear margin without invasion to the surrounding tissue. The anesthesiologists then agreed to resume the surgical procedure and prepare cardiovascular drugs for intensive hemodynamic control. For quick and safe excision, the laparoscopic procedure was...
converted to open surgery in accordance with the surgeon’s decision.

During tumor excision, esmolol and nicardipine were continuously infused with intermittent bolus injections to minimize severe hypertension and tachycardia. The mass was completely removed 70 min after the start of surgery. Following mass removal, systolic blood pressure decreased to 75 mmHg. Aggressive fluid resuscitation was performed with continuous administration of dopamine and norepinephrine until the patient was hemodynamically stable.

**Case 2**
Continuous manipulation of the mass seemed inevitable due to adhesion between the right adrenal gland and the mass in a narrow surgical field. The possibility of the inferior vena cava invasion and massive bleeding also could not be ruled out. The surgeon and anesthesiologists decided to cancel the surgical procedure and planned to perform a reoperation after adequate preparation a few weeks later.

An endocrinologist in the general ward evaluated the patient. The results of 24-h urinary metanephrine and catecholamine (metanephrine 2700 µg/d, norepinephrine 133.8 µg/d, and epinephrine 79.2 µg/d) strongly suggested the presence of a catecholamine-producing paraganglioma. We decided to proceed with reoperation after an alpha-1 adrenergic receptor antagonist (doxazosin mesylate) regimen for two weeks.

**OUTCOME AND FOLLOW-UP**

**Case 1**
The patient was transferred to the intensive care unit (ICU) after surgery for close monitoring of vital signs. All vasopressors were stopped 7 h after ICU admission. She was transferred to the general ward on postoperative day (POD) 2 and discharged without any complications on POD 4. The mass was histopathologically confirmed as an extra-adrenal paraganglioma.

**Case 2**
The patient returned to the operating room after alpha blockade therapy for two weeks. Anesthesia induction was uneventful. During tumor manipulation, the increase in blood pressure was easily controlled with small doses of nicardipine. Modest hypotension (85/40 mmHg) occurred after tumor excision and was treated with short-term infusion of norepinephrine and fluids. The patient was transferred to the ICU after surgery and was hemodynamically stable without any vasopressors. He was transferred to the general ward on POD 1 and discharged without any complications on POD 12. The mass was histopathologically confirmed to be an extra-adrenal paraganglioma.

**DISCUSSION**
The present case report describes different intraoperative decisions for two patients with undiagnosed paragangliomas. We aimed to clarify the decision-making regarding continuation of surgery when a paraganglioma was identified intraoperatively. This issue has not been emphasized in previous literatures.
Patients with paragangliomas do not always show catecholamine-related symptoms, making proper preoperative diagnosis difficult. The incidence of headache, palpitations, perspiration, pallor, and hypertension has been reported to be 26%, 21%, 25%, 12%, and 64%, respectively [8]. Although the first patient had hypertension, her preoperative blood pressure was well-controlled. The second patient had no history of hypertension and did not show any symptoms associated with catecholamine-secreting tumors. Therefore, the possibility of paraganglioma was overlooked and hormonal studies were not conducted in either case.

When an adrenal or retroperitoneal mass without clinical symptom is incidentally detected, results of imaging studies may sometimes indicate the need for biochemical screening for catecholamine-producing tumors. Therefore, previous images should be interpreted with caution, taking into consideration of additional imaging studies. For example, degree of attenuation on unenhanced CT images [9, 10] or signal intensity on T2-weighted magnetic resonance (MR) images [11, 12] of the mass could provide presumptive criteria to characterize production of catecholamine. Functional imaging such as scintigraphy with metaiodobenzylguanidine (MIBG) or positron-emission tomography (PET) scanning is also effective in localizing metastatic disease or multiple paragangliomas [13-15].

Elective surgery in patients with undiagnosed paragangliomas or pheochromocytomas can be life-threatening. Previous studies have reported the occurrence of a hypertensive crisis primarily during tumor manipulation and/or induction of anesthesia. The complications arising from alarmingly high blood pressure include cerebrovascular hemorrhage, hypertensive encephalopathy, neurological deficits, severe arterial spasms causing unconsciousness, metabolic acidemia, heart failure, arrhythmias, and myocardial infarction [16]. Severe hypotension after tumor removal, rather than hypertension during tumor manipulation, can lead to even more disastrous consequences, including cardiac arrest and death. In the cases described in this report, serious complications related to hypotension did not occur. However, severe hypotension developed after tumor removal in the first patient (case 1), who was not treated preoperatively. Conversely, modest and transient hypotension was observed after tumor removal in the second patient (case 2), who was treated with doxazosin. This finding emphasizes the importance of appropriate preoperative preparation in patients with suspected catecholamine-producing tumors.

The clinical practice guidelines for pheochromocytoma and paraganglioma issued by the Endocrine Society continue to recommend alpha-adrenergic blockade for at least 7 d preoperatively to prevent unpredictable instability in blood pressure during surgery [12]. Although the concept of adrenergic blockade-free management is evolving [17, 18], there is no consensus supporting this approach [15]. High levels of catecholamines in patients with paraganglioma/pheochromocytoma produce chronic vasoconstriction and a subsequent decrease in blood volume. Therefore, in combination with the use of alpha-adrenergic receptor blockers, preemptive fluid replacement is essential for gradual restoration of catecholamine-induced blood volume contraction [12] and can reduce the risk of severe and sustained hypotension after tumor removal [19].

Paragangliomas are frequently found in areas that are difficult to resect, as observed in the second patient. Although intraoperative cancellation of the surgery was not an easy decision, the surgeon and anesthesiologists believed that continuous manipulation of the tumor without adequate preparation might result in disastrous consequences. Fortunately, the mass in the first patient was in a favorable location, and serious hemodynamic instability could be avoided by minimal manipulation under aggressive use of vasoactive drugs.

CONCLUSION

Hemodynamic management of patients with catecholamine-producing tumors remains a challenge for anesthesiologists, especially when preoperative alpha blockade has not been established. When an undiagnosed paraganglioma or pheochromocytoma is suspected during surgery, immediate and coordinated responses by surgeons and anesthesiologists are required to avoid fatal outcomes. Intraoperative cancellation of surgery may not always be feasible or practical, but it should be considered as an option in cases requiring frequent manipulation of the tumor.

FOOTNOTES

Author contributions: Kang D and Kim B wrote the manuscript; Hong M and Kim J performed literature analysis; Jeong S was the anesthesiologist in charge of the patient; Lee S revised the manuscript for important intellectual content; all authors approved the final version of the manuscript to be submitted.

Informed consent statement: Informed written consents were obtained from the patients for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.
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Hepatic steatosis with mass effect: A case report

Na Hu, Shi-Jun Su, Jin-Ye Li, Hui Zhao, Shan-Feng Liu, Lin-Sheng Wang, Ruo-Zhen Gong, Chuan-Ting Li

BACKGROUND
Hepatic steatosis is a common radiologic finding. Some imaging inklings are the absence of a mass effect, and there is currently no report of hepatic steatosis with mass effect.

CASE SUMMARY
A 23-year-old female was admitted due to a liver mass for half a month. No obvious abnormalities were found in physical and laboratory examinations. Ultrasound, computed tomography, and magnetic resonance imaging showed a huge mass between the liver and stomach with a significant mass effect, and the caudate lobe and left lobe of the liver were involved. The signal on T2- and T1-weighted fat-saturated images of the mass was significantly reduced, and the enhanced scan showed inhomogeneous enhancement. Surgical and pathological findings indicated the diagnosis of hepatic steatosis. The operation and re-review of the patient's images showed that the lesion was supplied by the branch of the hepatic artery. The signal on T1-weighted out-of-phase images of the lesion was lower than on in-phase images, and there was no black rim cancellation artifact around the hepatic steatosis area on T1-weighted out-of-phase images. The dynamic enhancement pattern of the lesion was similar to that of the adjacent normal liver parenchyma. The above characteristics suggested that the lesion was hepatic steatosis. However, in this case, the lesion showed exogenous growth and was mass-like, with an obvious mass effect, which has not been reported previously.
**CONCLUSION**

Hepatic steatosis could grow exogenously and has an obvious mass effect. It needs to be distinguished from fat-rich tumors. The T1-weighted in- and out-of-phase images and dynamic enhanced scanning are valuable for differential diagnosis of this lesion.

**Key Words:** Hepatic steatosis; Computed tomography; Magnetic resonance imaging; In-phase and out-of-phase imaging; Case report

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**INTRODUCTION**

Hepatic steatosis is caused by the abnormal and excessive intracellular accumulation of fat (mainly triglycerides) in hepatocytes[1,2]. It is a common radiologic finding. There are six patterns of fat accumulation in the liver, including diffuse, geographic, focal, subcapsular, multifocal, and perivascular patterns[3-6]. Some imaging inklings are the absence of mass effect, stability in size over time, and enhancement similar to the hepatic parenchyma[7]. To the best of our knowledge, hepatic steatosis with mass effect has not been reported. It needs to be distinguished from liver tumors and other abdominal tumors containing fat. Here, we described a case of hepatic steatosis with exogenous growth and mass effect.

**CASE PRESENTATION**

**Chief complaints**

The patient was a 23-year-old female who was admitted due to a liver mass for more than half a month. The patient had no obvious symptoms.

**History of present illness**

The liver mass was found by computed tomography (CT) examination during routine physical examination in another hospital half a month ago.

**History of past illness**

She had chronic gastritis for more than 3 years and had taken medications (including omeprazole and hydrotalcite chewable tablets) intermittently.

**Personal and family history**

The patient’s family history was unremarkable.

**Physical examination**

No obvious abnormality was found during physical examination.

**Laboratory examinations**

The laboratory examination was unremarkable. Blood routine tests showed that red blood cell count was 4.40 × 10¹² / L; hemoglobin was 128 g/L; white blood cell count was 5.65 × 10⁹ / L; C-reactive protein level was 0.25 mg/L; D-dimer level was 0.57 μg/mL; and, low density lipoprotein level was 1.28 mmol/L, which were all within normal range. The results for viral hepatitis markers were negative. The
carninoembryonic antigen was 0.50 ng/mL; the alpha-fetoprotein was 2.17 ng/mL; and, the carbohydrate antigen 19-9 was 4.47 U/mL, which were all within normal range, indicating negative results for tumor markers.

**Imaging examinations**

Ultrasound showed a large hyperechoic mass with a size of 13 cm × 10 cm × 7 cm in the parenchyma of the caudate lobe of the liver, with clear boundary, irregular shape and inhomogeneous internal echo (Figure 1). CT examination showed an irregular mass in the caudate lobe of the liver with a size of about 12 cm × 6 cm × 10 cm, locally protruding beyond the liver outline. It had a clear boundary and inhomogeneous density. The unenhanced CT attenuation value was 5 - 31 HU (Figure 2A). The contrast-enhanced CT attenuation value was 21 - 44 HU in the arterial phase (Figure 2B), 39 - 66 HU in the portal vein phase (Figure 2C), and 21 - 59 HU in the delayed phase (Figure 2D). The dynamic enhancement pattern of the lesion was similar to that of the adjacent normal liver parenchyma, and the lesion was hypovascular compared with the background liver in all three contrast-enhanced phases. There were branches of the hepatic artery inside the mass (Figure 2E). The intrahepatic and extrahepatic bile ducts, hepatic arteries, and the trunk and branches of the portal vein were compressed and displaced (Figure 2F). The stomach and the duodenum were slightly compressed. One nodule in the mass was observed on CT images. The attenuation of the nodule on the unenhanced scan was the same as that of normal liver parenchyma (Figure 2G), and the dynamic enhancement-mode of the nodule was synchronous with that of normal liver parenchyma (Figure 2H).

Magnetic resonance imaging (MRI) examination: T2-weighted non-fat-saturated image showed slight hyperintensity (Figure 3A). The signal intensity was reduced on T2- and T1- weighted fat-saturated images (Figure 3B and C). T1-weighted in-phase image showed slight hyperintensity (Figure 3D), and the signal intensity of the T1-weighted out-of-phase image decreased obviously (Figure 3E). The degree of reduction of the T1-weighted out-of-phase image was higher than that of T1- weighted fat-saturated image. Diffusion-Weighted Imaging (b value = 800) showed slight hypointensity. Apparent diffusion coefficient mapping showed hyperintensity and isointensity. The enhancement pattern of MRI was the same as that of CT. No abnormality was found in the remaining liver parenchyma.

**FURTHER DIAGNOSTIC WORK-UP**

The fatty mass originating from the caudate lobe of the liver was removed completely by the caudate lobectomy, with the patient under general anesthesia. Surgical findings: the lesion was an exogenous mass with root in the caudate lobe of the liver and with soft texture similar to the liver tissue. It adhered closely to the left liver surface, crossed the hepatoduodenal ligament forward, and protruded behind the left lobe of the liver, with a size of about 12 cm × 8 cm. There was a fibrous capsule on the surface of the mass. The blood supply of the mass was rich. The supplying artery was from the left hepatic artery, and the drainage vein was connected with the inferior vena cava and portal vein.

The pathological results of the resected mass were analyzed. Macroscopically, the resected mass was 13 cm × 10 cm × 4 cm in size, with smooth surface and grayish red color. Most of the fibrous capsule was complete. The section of the mass was grayish-yellow, grayish red, solid, soft, and nodular. Microscopically, some normal structures of liver tissue disappeared. No obvious hepatic lobular
Figure 2 Computed tomography images of hepatic steatosis with mass effect. A: The unenhanced computed tomography (CT) showed irregular and inhomogeneous low-density lesion in the caudate lobe of the liver with clear boundary (arrow); B: Dynamic enhanced scanning showed mild enhancement of the lesion in the arterial phase (arrow); C: Dynamic enhanced scanning showed peak enhancement in the portal vein phase (arrow); D: Dynamic enhanced scanning showed lower enhancement in the delayed phase than in the portal vein phase (arrow). The dynamic enhancement pattern of the lesion was similar to that of the adjacent normal liver parenchyma, and the lesion was hypovascular compared with the background liver in all three contrast-enhanced phases; E: The minimum intensity projection (MinIP) in the arterial phase of contrast-enhanced scanning showed that the blood supply of the lesion was from the branch of the hepatic artery (arrow). There were branches of the hepatic artery inside the mass (arrowhead); F: The mass effect of the lesion was significant. The hepatic artery and branches were compressed and displaced; G: A focal nodule (arrow) in the lesion was observed on unenhanced CT; H: The focal nodule (arrow) in the lesion was also observed on contrast-enhanced CT. The attenuation of unenhanced CT and enhancement mode was similar to that of normal liver parenchyma.

structure was found. There was extensive steatosis in hepatocytes, intrahepatic vascular proliferation, local vascular dilatation, and a fibrous cell layer around the lesion (Figure 4A). Immunohistochemical staining results were as follows: Hep Par 1 (hepatocyte paraffin 1) (+) (Figure 4B), GPC-3 (glypican-3) (-) (Figure 4C), CD34 vascular (+), Cytokeratin 19 (CK19) focus (+), S-100 (-), HMB-45 (human melanoma black-45) (-), Melan-A (melanocyte antigen) (-), MDM2 (murine double minute 2) (-), CDK4 (cyclin-dependent kinase 4) (-) and Ki-67 index (2%) (Figure 4D).

**FINAL DIAGNOSIS**

Surgical and pathological findings suggested the diagnosis of hepatic steatosis.

**TREATMENT**

The patient received the caudate lobectomy to completely remove the mass.
Hepatic steatosis with mass effect

Figure 3 Magnetic resonance imaging of hepatic steatosis with mass effect. A: Coronal T2-weighted non-fat-saturated image revealed that the lesion (arrow) in the caudate lobe of the liver showed slight hyperintensity and locally protruding beyond the liver outline; B: The signal intensity was reduced on axial T2-weighted fat-saturated images; C: The signal intensity was also decreased on axial T1-weighted fat-saturated images; D: Axial T1-weighted in-phase image showed slight hyperintensity; E: The signal intensity of out-of-phase image decreased significantly. The degree of reduction of the T1-weighted out-of-phase image was higher than that of T1-weighted fat-saturated image.

OUTCOME AND FOLLOW-UP

After 10 mo of follow-up, the patient showed no signs of disease relapse.

DISCUSSION

Hepatic steatosis, also known as fatty liver, is a common radiologic finding. It is caused by the dysfunction of liver fat metabolism and the excessive accumulation of fat in hepatocytes[1,2,8]. Hepatic steatosis has no mass effect. Its size is stable over time, and its enhancement is similar to that of liver parenchyma[7]. Hepatic steatosis with mass effect has not been reported in the literature. In this report, the case had hepatic steatosis with exogenous growth and obvious mass effect. The signal intensity of hepatic steatosis in the T1-weighted out-of-phase images decreased significantly compared with in-phase images. The dynamic enhanced scanning mode is similar to the normal liver parenchyma. The T1-weighted in- and out-of-phase images and dynamic enhanced scanning have great value in differential diagnosis.

Fatty infiltration of the liver occurs in many forms, depending on the amount and distribution of liver parenchymal fat[9]. It can be divided into diffuse, geographic, focal, subcapsular, multifocal, and perivascular hepatic steatosis[3-6]. Clinically, diffuse hepatic steatosis is more common, which is characterized by a decreased diffusing density of the liver. Geographic hepatic steatosis is a frequently encountered variant. Different geographic hepatic steatosis can be attributed to specific causes. It may be secondary to an injury to the liver parenchyma[3]. The focal hepatic steatosis is characterized by the geographic location of the fat distribution such as adjacent to the falciform ligament or ligamentum venosum, in the porta hepatis, and the gallbladder fossa[3]. Subcapsular hepatic steatosis may present as small fat nodules or as a confluent peripheral region of fat confined to a subcapsular zone[4]. It is seen in patients with renal failure and insulin-dependent diabetes[6]. Multifocal hepatic steatosis involves multiple scattered foci of fat resembling true nodules. Perivascular hepatic steatosis is characterized by fat infiltration around the hepatic veins and portal veins. Focal and multifocal hepatic steatosis need to be differentiated from benign and malignant liver tumors. The absence of mass effect, stability in size over time, and enhancement similar to the hepatic parenchyma are the characteristics of hepatic steatosis[10]. The case in this report was hepatic steatosis in the caudate lobe, which was an exogenous mass with significant mass effect. The imaging findings of the case were different from those of the previous types.

The lesion of this case was located in the caudate lobe of the liver, obviously protruding beyond the outline of the liver. It was closely related to the left lobe of the liver, and compressed adjacent structures.
Pathological changes of hepatic steatosis with mass effect. The HE (hematoxylin and eosin) and immunohistochemical staining of resected specimen at × 100 magnification. A: HE staining of the specimen showed that some normal structures of liver tissue disappeared. No obvious lobular structure was found. There were extensive steatosis of hepatocytes (*), and fibrous cell layer around the lesions (arrow). B: Immunohistochemical staining: Hep Par 1 (hepatocyte paraffin 1) (+); C: Immunohistochemical staining: GPC-3 (glypican-3) (-); D: Immunohistochemical staining: Ki-67 index (2%).

The mass effect of the lesion was significant. The preoperative localization of the mass appeared to be in the hepatogastric space, and it involved the caudate lobe and left lobe of the liver. After operation and re-reviewing the images, it was found that the blood supply of the mass was from the branch of the hepatic artery. Ultrasound showed that the lesion was inhomogeneous hyperechoic. The characteristics of dynamic enhanced scanning of hepatic steatosis are similar to those of normal liver parenchyma[7]. The hepatic steatosis is hypovascular compared with the background liver[11]. The case reported in this study also has such characteristics. The nodule in the mass was observed on CT images. The attenuation of the unenhanced scan of the nodule was the same as that of normal liver parenchyma, and the dynamic enhancement-mode was synchronous with that of normal liver parenchyma. This sign is helpful for distinguishing hepatic steatosis from other lesions. The mass showed inhomogeneous low density, slight hyperintensity on T2-weighted non-fat-saturated image, and decreased signal intensity on T2- and T1-weighted fat-saturated images. These signs suggested that it contained fatty substances, which included adipose tissue and steatosis. The MRI findings of adipose tissue and steatosis are different. Adipose tissue shows hyperintensity on T1-weighted in-phase image, hyperintensity in the center of adipose tissue on T1-weighted out-of-phase image, with a black rim cancellation artifact. The signal on T2- and T1-weighted fat-saturated images of the mass is significantly reduced[12]. Steatosis shows isointensity or slight hyperintensity on T1-weighted in-phase image. The signal intensity of the T1-weighted out-of-phase image decreases significantly. The signal of fat-saturated images can be reduced, but the reduction range is often less than that of the T1-weighted out-of-phase image[8]. The MRI signal characteristics of this case were consistent with those of steatosis.

Pathological findings were most reliable in the diagnosis of this case. Immunohistochemistry was also helpful in making differential diagnosis. Although initially reversible, hepatic steatosis may progress into cirrhosis and hepatocellular carcinoma (HCC)[4]. Hep Par 1, GPC-3, and CD 34 are sensitive and specific markers for HCC[13,14]. Hep Par 1 is mainly strongly positive in HCC and can also be expressed in normal liver tissue. In a normal liver, immunohistochemistry for CD34 stains the endothelial cells of blood vessels in the portal tracts and the fibrous septa[15]. The case reported here was positive for Hep Par 1, negative for GPC-3 and positive for CD34 vascular, which ruled out the diagnosis of HCC. CK19 is a immunohistochemical marker of intrahepatic cholangiocarcinoma[15]. This case showed focal positivity, excluding the diagnosis of intrahepatic cholangiocarcinoma. MDM2 and CDK4 are immunohistochemical markers of liposarcoma, and they are positive in different degrees in liposarcoma[16]. This case was negative for MDM2 and CDK4, excluding liposarcoma. S-100 positive indicates the source of neural tissue, and this case was negative for S-100. HMB-45 and Melan-A are
important immunohistochemical markers in the diagnosis of melanoma[17]. This case was negative for HMB-45 and Melan-A, excluding the diagnosis of melanoma. The Ki-67 index was 2%, indicating that the cell proliferation of the lesion was inactive.

Hepatic steatosis with mass effect needs to be distinguished from liver tumors and other abdominal tumors containing fat. The following points are of great value in the diagnosis of hepatic steatosis with mass effect: The blood supply of the hepatic artery, the signal of the T1-weighted out-of-phase image significantly lower than that of the T1-weighted in-phase image, no black rim cancellation artifact around hepatic steatosis area on T1-weighted out-of-phase images, and dynamic enhanced scanning mode similar to the normal liver parenchyma. Because there is a lack of previous understanding of the hepatic steatosis with mass effect, the diagnosis of liver tumor was highly suspected based on imaging findings, and thus surgical resection was performed in this case. The diagnosis of hepatic steatosis with mass effect was made post-operatively. However, surgical resection is not recommended as the first choice for treatment of hepatic steatosis with mass effect. If similar imaging characteristics to this case are present but the diagnosis is not clear, tissue biopsy and pathological examination should be performed to facilitate clear diagnosis.

CONCLUSION

In summary, hepatic steatosis in this case could grow exogenously and has an obvious mass effect. It needs to be distinguished from fat-rich tumors. The T1-weighted in- and out-of-phase images and dynamic enhanced scanning play an important role in differential diagnosis.

FOOTNOTES

Author contributions: Hu N, Su SJ, Li JY, and Zhao H reviewed the literature and contributed to manuscript drafting; Liu SF and Wang LS performed the computed tomography and magnetic resonance imaging, and contributed to manuscript drafting; Gong RZ and Li CT were responsible for the revision of the manuscript regarding important intellectual content; All authors issued final approval for the version to be submitted.

Supported by the Medical and Health Science and Technology Development Plan of Shandong, China, No. 2018WS322, No. 202109010865, and No. 202009010992.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES


CASE REPORT

Bone marrow metastatic neuroendocrine carcinoma with unknown primary site: A case report and review of the literature

Xue-Bing Shi, Wen-Xia Deng, Feng-Xiang Jin

Specialty type: Oncology
Provenance and peer review: Unsolicited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0
P-Reviewer: Debaibi M, Tunisia; Sheikh Hassan M, Somalia; Zhang X, United States
Received: June 10, 2022
Peer-review started: June 10, 2022
First decision: June 27, 2022
Revised: July 8, 2022
Accepted: August 23, 2022
Article in press: August 23, 2022
Published online: October 26, 2022

Abstract
BACKGROUND
Metastatic neuroendocrine carcinoma (NEC) of bone marrow is uncommon. Here, we report a case of bone marrow metastatic NEC with an unknown primary site.

CASE SUMMARY
A 73-year-old Chinese woman was admitted to our hospital because marked chest distress and asthma lasting 1 d on March 18, 2018. She was initially diagnosed with pulmonary infection, cardiac insufficiency, thrombocytopenia and severe anemia. Following treatment with antibiotic therapy, diuresis and blood transfusion, the patient’s symptoms greatly improved. After bone marrow examinations, the patient was diagnosed with bone marrow metastatic NEC, bone marrow necrosis (BMN) and secondary myelofibrosis (MF). Further imaging workup did not show the primary tumor, we presumed that the primary site might regress spontaneously or merely be unexplored due to lack of positron emission tomography with gallium peptide. Everolimus (10 mg/d) was added to the treatment and the best supportive and symptomatic therapies were also administered. Unfortunately, the patient’s condition continued to deteriorate and she died on May 15, 2018.

CONCLUSION
Bone marrow invasion of NEC is rare and our patient who suffered from bone marrow metastatic NEC as well as secondary BMN and MF had an extremely poor prognosis. Bone marrow biopsy plays an important role in the diagnosis of solid tumors invading bone marrow.

Key Words: Neuroendocrine neoplasm; Bone marrow metastasis; Bone marrow necrosis; Myelofibrosis; Everolimus; Case report
Core Tip: Neuroendocrine carcinoma (NEC) rarely occurs in the bone marrow. We report a patient diagnosed with bone marrow metastatic NEC, bone marrow necrosis and secondary myelofibrosis. As extensive imaging examinations did not show the primary lesion, we speculated that the primary tumor might regress spontaneously or merely not be identified due to lack of positron emission tomography with gallium peptide. Because of the poor general physical condition with an Eastern Cooperative Oncology Group performance status of 3-4, chemotherapy was abandoned, and everolimus as well as the best supportive therapies were given. Unfortunately, the patient’s condition continued to deteriorate and finally passed away.

INTRODUCTION

Neuroendocrine neoplasms (NENs), account for 0.5% of all malignancies, they originate from neuroendocrine cells throughout the body, and are a group of relatively rare and highly heterogeneous neoplasms[1]. Most NENs occur in the gastrointestinal tract (62%-67%) and the lung (22%-27%)[2]. NENs are divided into well differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs)[2]. The clinical manifestations of NENs mainly depend on whether they are functional or non-functional and which hormones are secreted[3]. Bone marrow metastasis of NENs is extremely rare. Few studies on this topic have been published since 2000 and most of them are case reports[4-14]. We report a case of bone marrow metastatic NEC accompanied by bone marrow necrosis (BMN) and secondary myelofibrosis (MF). In this patient, no neoplastic lesions were found in the body except the bone marrow.

CASE PRESENTATION

Chief complaints

On March 21, 2018, a 73-year-old woman was admitted to the Department of Hematology and Oncology, Tongling People’s Hospital (Anhui Province, China) due to severe unexplained anemia and thrombocytopenia.

History of present illness

Initially, the patient was hospitalized in the emergency ward of internal medicine because of marked chest distress and asthma lasting 1 day on March 18, 2018. The concentrations of B-type natriuretic peptide, high-sensitivity C-reactive protein and procalcitonin were 853.90 pg/mL, 140.96 mg/L and 1.51 μg/L, respectively. Peripheral blood count showed a leukocyte count of 12.95 × 10^9/L, hemoglobin of 29 g/L, platelet count of 49 × 10^9/L and neutrophil count of 9.84 × 10^9/L. Chest computed tomography (CT) examination indicated bilateral pulmonary inflammation. The patient was preliminarily diagnosed with pulmonary infection, cardiac insufficiency, thrombocytopenia and severe anemia. She was treated with antibiotic therapy, diuresis and red blood cell transfusions. Following the above treatment, the symptoms of chest tightness and asthma were relieved. The etiology of anemia and thrombocytopenia was unknown, and the patient was hospitalized in our department for further hematological examinations.

History of past illness

The patient did not have a previous history of surgery, anemia or malignant neoplasms and was not taking any medication.

Personal and family history

She never smoked and her spouse and daughter were both healthy. Her family history of hematological malignancies and solid tumors was unremarkable.
Physical examination

Physical examination revealed anemia, scattered dry rales in both lungs, a few moist rales in the middle and lower lobe of the right lung and bilateral depressed edema of the lower limbs.

Laboratory examinations

The results of laboratory examinations with the exception of bone marrow tests are listed in Table 1. Both bone marrow aspiration and biopsy were carried out on the right posterior superior iliac spine. Bone marrow cytomorphologic examination revealed that most of the nucleated cells were dissolved and one type of cell characterized by small size, less cytoplasm, no granules in the cytoplasm, a round or irregular nucleus, loose chromatin and distinct nucleoli was discovered. Cytogenetic analysis using both the G-banding and R-banding technique demonstrated a karyotype of 45, XX, del (1) (p13p36.1), I (1) (p10), dup (4) (p15p16), add (6) (p23), der (6) del (6) (p21) del (6) (q23q25), der (7) t (7;11) (p10; q10), add (11) (p11.2), der (12) t (4;12) (q21;p11.2), -13, del (13) (q14), -16, -17, + mar1, + mar2 in 19/20 metaphases examined (Figure 1). Bone marrow biopsy showed that the marrow was characterized by extensive fibrosis and necrosis, moreover, nest-like distributions of small cells with less cytoplasm, round or irregular nuclei and coarse granular and dark stained chromatin were found in the stroma (Figure 2A). Additional immunohistochemistry of this specific category of cells exhibited CD56 (+) (Figure 2C), synaptophysin (+) (Figure 2D), Ki-67 (90% +), CK-pan (scattered and weak +), chromogranin A (-), S-100 (-), TdT (-), CD3 (-), CD5 (-), CD10 (-), CD19 (-), CD34 (-), TTF-1 (-), vimentin (-), and CD117 (-). Reticulin staining was positive (+++) (Figure 2B) and no Janus kinase 2 (JAK2) mutations were detected.

Imaging examinations

Extensive imaging workup including abdominal CT and 18F-Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT tumor metabolic imaging did not show the primary lesion (Figure 3).

FINAL DIAGNOSIS

The patient was diagnosed with bone marrow metastatic NEC with unknown primary site, BMN and secondary MF.

TREATMENT

The patient continued treatment with anti-infection medication, blood transfusion, diuresis as well as interleukin-11 after admission to our department. She was subsequently diagnosed with bone marrow metastatic NEC according to bone marrow biopsy and immunohistochemistry. In view of the patient’s poor general physical condition with an Eastern Cooperative Oncology Group performance status of 3-4, chemotherapy was abandoned and everolimus (10 mg/d) was added to the treatment on April 26, 2018.

OUTCOME AND FOLLOW-UP

Following supportive and symptomatic therapies, chest tightness and asthma improved. Hemoglobin was maintained above 60 g/L and platelets were maintained between 20 × 10⁹/L and 30 × 10⁹/L. The white blood cell count decreased with the lowest leukocyte count of 2.24 × 10⁹/L and neutrophil count of 1.15 × 10⁹/L following administration of everolimus. Unfortunately, during the treatment process, the patient became more and more emaciated and received repeated albumin infusions due to a significant decline in serum albumin level. Despite being treated with everolimus plus the best supportive treatment, the patient’s condition continued to deteriorate and she died on May 15, 2018.

DISCUSSION

Although NEN is an uncommon malignant tumor, the incidence of NEN has gradually increased over the past decades owing to continuous improvement in diagnostic methods and improved awareness of the disease[2,15]. The most common site of metastasis in NENs is the liver (40%-93%) followed by bone (12%-20%) and lung (10.8%)[16]. Metastatic NEN in bone marrow is extremely rare and most reported cases are NECs[4,8,11,12].

The main treatments in reported cases of bone marrow metastatic NECs consist of chemotherapy, peptide receptor radionuclide therapy (PRRT) and supportive care. Helbig et al[4] and Post et al[5] respectively reported a NEC patient with multiple metastases with bone marrow invasion. Both the...
Table 1 Laboratory examinations of our patient

<table>
<thead>
<tr>
<th>Testing items</th>
<th>Results</th>
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<tbody>
<tr>
<td>Reexamined peripheral blood count</td>
<td>Leukocyte 14.87 × 10^9/L, hemoglobin 65 g/L; platelet 20 × 10^9/L and neutrophil 12.46 × 10^9/L.</td>
</tr>
<tr>
<td>Peripheral blood smear</td>
<td>2% promyelocyte</td>
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<tr>
<td>Coombs test</td>
<td>Negative</td>
</tr>
<tr>
<td>LDH</td>
<td>1185 U/L</td>
</tr>
<tr>
<td>ALP</td>
<td>355 U/L</td>
</tr>
<tr>
<td>Coagulation function</td>
<td>Fibrinogen 1.09 g/L, D-dimer &gt;20000 μg/L</td>
</tr>
<tr>
<td>Serum tumor markers</td>
<td>Carbohydrate antigen 125 236.40 U/mL, ferroprotein &gt; 3000 ng/mL</td>
</tr>
</tbody>
</table>

LDH: Lactic dehydrogenase; ALP: Alkaline phosphatase.

Figure 1 Chromosomal karyotype analysis of bone marrow. Cytogenetic analysis using both the G-banding and R-banding technique demonstrated a karyotype of 45, XX, del (1) (p13p36.1), i (1) (p10), dup (4) (p15p16), add (6) (p23), der (6) del (6) (p21) del (6) (q23q25), der (7) t (7;11) (p10; q10), add (11) (p11.2), der (12) t (4;12) (q21; p11.2), -13, del (13) (q14), -16, -17, + mar1, + mar2 in 19 of 20 metaphases examined.

patients received multiple cycles of chemotherapy; however, no effect was observed[4,5]. Another bone marrow metastatic NEC case was offered best supportive care; however, the patient died 2 wk after diagnosis[8]. PRRT is recommended in advanced NEN patients with positive somatostatin receptors (SSTRs)[7]. After four cycles of PRRT with 177Lu-DOTA octreotate, a patient suffering from duodenal NEC with extensive metastases including bone marrow achieved a partial response and a progression-free survival (PFS) of 27 mo[6,7].

Multiple studies have indicated that the mammalian target of rapamycin (mTOR) pathway participates in the development of NENs and mTOR is expected to become a promising therapeutic target for NENs[17]. The clinical trials RADIANT-2 and RADIANT-4 revealed that advanced NEN patients might benefit from the mTOR inhibitor everolimus and achieve a longer median PFS[18,19].
Spontaneous regression (SR), an extremely rare phenomenon, is defined as the partial or complete disappearance of a tumor without any treatment[20]. The burned-out tumors represent tumors presenting SR followed by metastases[21,22]. With regard to NENs, SR of the tumor has been reported in Merkel cell carcinoma (MCC), bile duct NET, and both lung and gastric large-cell NECs[23-26]. Longo et al[27] reported a case of inguinal lymphadenopathy histologically corresponding to MCC. The lesion later spontaneously regressed and histopathological examination showed negative results. However, five months later, a nearby lymphadenopathy appeared which was diagnosed as MCC metastasis. Our patient was diagnosed with bone marrow metastatic NEC and further imaging examinations showed no other neoplastic lesions in the body. Similarly, Helbig et al[4] and Schlette et al[13] also reported 2 cases of bone marrow metastatic NENs without primary sites. We hypothesize that the primary tumors of such NENs which can be called burned-out tumors may be located in the gastrointestinal system, pancreas, lung or bile duct and develop SR in order to originate metastases. Furthermore, we did not perform PET with gallium peptide, which may have resulted in potential bias in our diagnosis. Therefore it should be taken into account that the unknown primary lesion was unexplored.

BMN is a relatively rare clinicopathological entity and most common in malignant tumors (80%-90%) [28-30]. Anemia (91%) and thrombocytopenia (78%) are the most frequent hematologic abnormalities in BMN and almost 50% of BMN patients have elevated lactate dehydrogenase and alkaline phosphatase levels[28]. It is reported that 30% of BMN cases are found in solid tumors[28]. As previously mentioned, a patient with BMN caused by a thymic NET died 2 wk after diagnosis[8], and another case of BMN secondary to gastric cancer passed away shortly after hospitalization[31]. Thus, the prognosis of patients suffering from solid tumors with BMN is significantly worse than that of patients with malignancies alone.

MF represents increased fibers in the bone marrow stroma and is usually caused by numerous reactive and neoplastic disorders. There are two types of MF: Primary and secondary. The former is often characterized by splenomegaly and mutations of JAK2, MPL or CALR. Our patient had no splenomegaly or mutations of the above genes, thereby excluding primary MF and the patient’s MF was due to bone marrow metastatic NEC. Secondary MF is very common in patients with bone marrow metastatic tumors. Xiao et al[32] reported that all 101 patients with bone marrow metastatic malignancies showed various degrees of MF and 17% of patients also had both anemia and thrombocyt-
openia. Patients with secondary MF, especially accompanied by anemia and decreased platelets, have very poor survival[33].

We report a case of bone marrow metastatic NEC with an unknown primary lesion accompanied by secondary BMN and MF. To our knowledge, few such cases have been reported in China to date. As the patient’s condition was very poor, chemotherapy was ultimately discontinued. According to published reports, NEC patients with multiple metastases including bone marrow infiltration may benefit from treatment with PRRT[6,7]. However, very few hospitals in China can carry out PRRT at present and our hospital is unable to implement SSTR detection and PRRT treatment; thus, we unfortunately failed to attempt PRRT in this patient. On the basis of relevant reports[18,19], the patient received everolimus treatment; however, the patient’s condition did not improve and she died 2 mo after admission.

CONCLUSION

Bone marrow metastasis of NENs is rare and patients suffering from bone marrow metastatic NEC as well as secondary BMN and MF may have an extremely poor prognosis. Bone marrow biopsy plays an important role not only in the diagnosis of hematological diseases, but also in the diagnosis of solid tumors invading bone marrow.

FOOTNOTES

Author contributions: Shi XB participated in the treatment of the patient, collecting and analyzing the clinical data, and writing the manuscript; Deng WX contributed to the treatment of the patient, data analysis, and revision of the manuscript; Jin FX was involved in guiding the treatment of the patient and designing the research; all authors read and approved the final manuscript.

Informed consent statement: Written informed consent was obtained from the patient’s offspring for publication of this case report.

Conflict-of-interest statement: The authors declare that they have no conflicts of interests.

CARE Checklist (2016) statement: We have read the CARE Checklist (2016), and this manuscript was prepared and revised according to the CARE Checklist (2016).

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REFERENCES


Child with adenylosuccinate lyase deficiency caused by a novel complex heterozygous mutation in the ADSL gene: A case report

Xing-Chen Wang, Ting Wang, Rui-Han Liu, Yan Jiang, Dan-Dan Chen, Xin-Yu Wang, Qing-Xia Kong

Abstract

BACKGROUND
Adenylosuccinate lyase (ADSL) deficiency is a rare autosomal-recessive defect of purine metabolism caused by mutation of the ADSL gene. It can cause severe neurological impairment and diverse clinical manifestations, including epilepsy.

CASE SUMMARY
Here, we describe a 3-year-old Chinese boy who had both psychomotor retardation and refractory epilepsy. Magnetic resonance imaging showed myelin hypoplasia. Electroencephalography findings supported a diagnosis of epilepsy. Whole-exon sequencing revealed the presence of a novel complex heterozygous mutation in the ADSL gene: The splicing mutation c.154-3C>G and the missense mutation c.71C>T (p. Pro24Leu). Considering the patient’s clinical presentation and genetic test results, the complex heterozygous mutation was predicted to prevent both ADSL alleles from producing normal ADSL, which may have led to ADSL deficiency. Finally, the child was diagnosed with ADSL deficiency.

CONCLUSION
We identified a novel complex heterozygous mutation in the ADSL gene associated with ADSL deficiency, thus expanding the known spectrum of pa-
thogenic mutations that cause ADSL deficiency. Additionally, we describe epilepsy that occurs in patients with ADSL deficiency.

**Key Words:** Adenylosuccinate lyase deficiency; Compound heterozygous mutations; Epilepsy; Pathogenic mutation; Case report

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**Core Tip:** A child presented with comprehensive developmental delay and epilepsy. Whole-exon sequencing revealed the presence of a novel complex heterozygous mutation in the adenylosuccinate lyase (ADSL) gene. Bioinformatics analysis suggested that the mutation caused ADSL deficiency.

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**INTRODUCTION**

Adenylosuccinate lyase (ADSL) deficiency is a rare deficiency of purine metabolism. More than 120 cases have been reported[1], and the global prevalence is 1 in 1.25 million[2]. The most common and prominent clinical manifestations are neurological symptoms, including acute encephalopathy, chronic encephalopathy, and behavioral abnormalities. Approximately half of affected patients have epilepsy [2]. Currently, there is no effective treatment for ADSL deficiency; thus, prenatal genetic testing is important for affected families.

ADSL participates in two purine nucleotide metabolic pathways. It catalyzes the conversion of succinylaminoimidazole carboxamide ribotide to aminoimidazole carboxamide ribotide as well as the conversion of adenylate succinate to adenosine monophosphate. ADSL deficiency results in the accumulation of succinylaminoimidazole carboxamide riboside (SAICAr) and succinyladenosine in various body fluids, particularly cerebrospinal fluid and urine[3]. ADSL deficiency is caused by ADSL gene mutations; two-thirds of confirmed cases involve complex heterozygous mutations[2]. Thus far, more than 150 ADSL gene mutations have been identified, most of which constitute missense mutations[1]; all mutations in the ADSL gene can cause ADSL deficiency.

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**CASE PRESENTATION**

**Chief complaints**

A 3-year-old boy was admitted to our clinic after he had experienced paroxysmal loss of consciousness for > 1 year.

**History of present illness**

The patient exhibited loss of consciousness, global lack of muscle tone and presence of cyanotic lips during seizures, and spontaneous remission after 2-3 min. Since the onset of the seizures, he had exhibited poor mentation, additional crying, ingestion of a semiliquid diet, reduced appetite, and worsened sleep. Convulsion episodes had continued after 2-3 min. Seizures were observed, and the patient appeared to be normal after 4 week later and sleep increased. Oxazepine was added on January 5, 2021. No seizures were observed, but a rash appeared 4 week later and sleep increased. Oxazepine was discontinued on February 25, 2021, and the rash abated. Perampanel, two tablets once daily, was added on February 26, 2021. However, the patient continued to experience seizures that manifested as sudden rapid head drop (myoclonus), sometimes accompanied by lip smacking, slow shaking of both upper extremities, and sudden freezing. These seizures often occurred after excitement and diminished after 1 min. At the time of admission, the patient was receiving sodium valproate 12 mL twice daily, topiramate 25 mg twice daily, and perampanel 8 mg once daily.

**History of past illness**

The patient had no abnormal birth history. He had a history of poor growth milestones (e.g., he began to
roll over slowly and could not sit unassisted at the age of 9 months) and had been diagnosed with developmental delay. At the time of admission, he could not sit unassisted, could not recognize people, could not speak, and exhibited unconscious pronunciation.

**Personal and family history**
The patient’s parents were healthy, non-blood relatives. The patient was the only child in his family, and neither parent had other offspring. There was no obvious family history of developmental delay or seizures.

**Physical examination**
Physical examination findings were temperature 37.3 °C, pulse 102 beats/min, respiration 24 breaths /min, and weight 17.7 kg. The patient exhibited a clear mind, poor spirit, frequent crying, limited development, moderate nutrition, pharyngeal congestion, coarse breath sounds in both lungs, and slightly elevated muscle tension.

**Laboratory examinations**
Laboratory findings were within normal limits.

**Genetic analysis:** Genomic DNA was isolated from peripheral blood that had been collected from the patient and his parents. Candidate mutation sites were examined by Sanger sequencing. Complex heterozygous mutations were found in the patient’s ADSL gene: The splicing mutation c.154-3C>G (present in his father; Figure 1A-C) and the missense mutation c.71C>T (p. Pro24Leu) (present in his mother; Figure 1D-F).

The bioinformatics software programs PSIPRED V4.0 (http://bioinf.cs.ucl.ac.uk/psipred/) and RaptorX (http://raptorx.uchicago.edu) were used to predict the secondary and tertiary structures, respectively, of mutant and wild-type ADSL proteins. The missense mutation c.71C>T causes an amino acid change from proline to leucine (p. Pro24Leu), possibly leading to a change in polarity (Figure 2). The splicing mutation c.154-3C>G was predicted to be pathogenic, according to the SD-Score Algorithm (Figure 3).

**Imaging examinations**
Magnetic resonance imaging in July 2020 showed bilateral external frontal temporal space widening and abnormal signals around the posterior horns of both lateral ventricles, suggestive of myelin hypoplasia; follow-up examination showed similar findings (Figures 4 and 5).

**Electroencephalography:** Electroencephalography performed in July 2020 revealed an abnormal electroencephalogram with slightly more medium-high amplitude in the left and right frontal regions, a few full-conduction irregular medium-high amplitude spikes, sharp slow waves, and a slow background rhythm. In July 2021, video electroencephalography revealed highly rhythmic patterns during most of the waking period and the entire sleep period. On the basis of irregular slow waves with full diffusion of 2-7 Hz, the patient exhibited multifocal slow waves, spiky slow waves, and polyspinous slow waves, with left and right asymmetry, asynchronous anterior and posterior findings, pronounced anterior activity, and an obvious sleep period (Figure 5).

**FINAL DIAGNOSIS**
Based on the patient’s clinical characteristics and the results of genetic tests and bioinformatics analyses, the child was diagnosed with ADSL.

**TREATMENT**
Oral valproate solution, topiramate, and perampanel tablet.

**OUTCOME AND FOLLOW-UP**
The patient was seizure-free for >1 year, but he did not show clinically significant improvements in intelligence or motor ability.
Figure 1 Mutations in the adenylosuccinate lyase genes of the three family members. A and B: The heterozygous mutation c.154-3C>G was present in the patient and his father; C: The wild-type sequence was present in his mother; D and E: The heterozygous mutation c.71C>T was present in the patient and his mother; F: The wild-type sequence was present in his father.

DISCUSSION

There are four types of ADSL deficiency, according to the clinical manifestations. The neonatal type is characterized by fatal neonatal encephalopathy, lack of autonomous movement, respiratory failure, and intractable epilepsy, leading to death within a few weeks after birth. Type I (the most common type) is characterized by severe psychomotor retardation, early epileptic seizures, microcephaly, and autistic features. Type II is a milder form in which symptoms usually develop within a few years after birth; affected patients usually exhibit mild to moderate psychomotor retardation and transient contact disturbances, sometimes accompanied by epilepsy. There is an additional phenotype that solely involves solitary psychomotor retardation or ataxia[1,4].

The phenotypic severity of ADSL deficiency may reflect the structural stability and residual enzymatic activity of the mutant ADSL enzyme complex. The pathogenic effects of biochemically benign and structurally stable mutations may be related to abnormalities that arise only under in vivo conditions in eukaryotic cells, rather than their intrinsic structural and/or catalytic properties[5]. Diffuse cortical atrophy and delayed myelination are the main neuroimaging findings in patients with ADSL deficiency[6].

Type II is a milder clinical phenotype of ADSL deficiency that involves slow disease progression and no specific symptoms. This phenotype was previously suspected to occur in approximately 15%-20% of patients with ADSL deficiency, but there is some evidence that it may be more common[7]. Patients with type II ADSL deficiency have only minor neurological involvement and a low incidence of epilepsy; they also have milder brain anomalies and generally do not exhibit microcephaly[7]. Our patient presented with comprehensive developmental delay and epilepsy, but he lacked autism or microcephaly. His magnetic resonance results were suggestive of myelin dysplasia, genetic analysis demonstrated a complex heterozygous mutation in the ADSL gene, and his clinical manifestations had not substantially progressed in recent years. Thus, he was diagnosed with type II ADSL deficiency.

The pathogenesis of ADSL deficiency is currently unclear. The underlying mutations are presumed to cause enzyme instability, which leads to the accumulation of SAICAr and succinyladenosine; the accumulation of SAICAr then produces neurotoxic effects. Other hypotheses regarding the pathogenesis of ADSL deficiency include a lack of the de novo purine biosynthetic pathway or the absence of a fully functional purine cycle in the muscles and brain[2]. We searched for common ADSL deficiency-related gene mutations in ADSLD (http://www1.lf1.cuni.cz/udmp/adsl) and PubMed (Table 1). c.1277G>A was the most common missense mutation, followed by c.340T>C; c.-49T>C was the most common splicing mutation. We speculate that the complex heterozygous mutation c.71C>T and c.154-3C>G in the ADSL gene, which is present in Chinese families, may be responsible for the phenotype in our patient. The c.71C>T mutation may cause a change in amino acid polarity, such that a hydrophobic
Table 1 Common genetic mutations that cause adenylosuccinate lyase deficiency

<table>
<thead>
<tr>
<th>Mutant protein</th>
<th>c.1277G&gt;A</th>
<th>c.340T&gt;C</th>
<th>c.-49T&gt;C</th>
<th>c.907C&gt;T</th>
<th>c.736A&gt;G</th>
<th>c.1187G&gt;A</th>
<th>c.569G&gt;A</th>
</tr>
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<tr>
<td>Number</td>
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<td>12</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 2 Structures of the wild-type and mutant adenylosuccinate lyase. A: The tertiary structure of wild-type mutant adenylosuccinate lyase (ADSL); B: The tertiary structure of mutant ADSL; C: The secondary structure of wild-type ADSL; D: The predicted results of amino acid polarity in wild-type ADSL; E: The secondary structure of p. Pro24Leu ADSL; F: The predicted results of amino acid polarity in p. Pro24Leu ADSL. The green regions in panels A and B indicate substantial changes in protein structure.

leucine replaces a small non-polar proline. This adversely affects ADSL function (Figure 2). c.154-3C>G is a splicing mutation in the intron before nucleotide 154 in the coding region, which may influence the heterogenous nuclear RNA splicing process and produce an altered form of ADSL (Figure 3). We hypothesized that the ADSL alleles in our patient could not produce normal ADSL, leading to the clinical manifestation of ADSL deficiency. Our report of a complex heterozygous mutation in the ADSL gene in a Chinese patient could help expand the known spectrum of mutations and provide guidance for genetic counseling.

Epilepsy is a common clinical manifestation of ADSL deficiency, such that it occurs in approximately half of patients with ADSL deficiency. Epilepsy phenotypes in patients with ADSL deficiency include...
Wang XC et al. A case report of ADSL deficiency

**Figure 3** SD-Score Algorithm predicted that the mutation would affect gene splicing. Ri: Information contents; CV: Position weight matrix; Δ SD-Score: Differences in the SD-Score; Δ Ri: Differences in the information contents; Δ CV: Differences in the position weight matrix.

**Figure 4** Brain magnetic resonance images findings. A and B: T2-weighted images; C and D: Diffusion-weighted images; E and F: Fluid-attenuated inversion recovery images. Magnetic resonance images showed bilateral external frontal temporal space widening and abnormal signals around the posterior horns of both lateral ventricles.

myoclonus, partial seizures, infantile spasm, and epileptic persistence[6]. In patients with type I ADSL deficiency, epilepsy tends to occur early and is mostly refractory. In patients with type II ADSL deficiency, epilepsy usually appears by 2-4 years of age and can be controlled with medication; the mildest forms of epilepsy generally are not accompanied by seizures[4]. Currently, ADSL-related epilepsy is mainly controlled by antiepileptic drugs, but the therapeutic effect depends on the type of seizure[2]. A ketogenic diet has been shown to reduce the frequency of seizures in patients with ADSL deficiency who exhibit refractory epilepsy[9].

There is currently no effective treatment for ADSL deficiency. The interval from onset to diagnosis of this disease is generally long. It is easy to miss the diagnosis or misdiagnose patients with other diseases. Therefore, ADSL deficiency should be considered, and genetic screening should be performed for children with neurological symptoms such as psychomotor retardation and refractory epilepsy along with magnetic resonance imaging findings of diffuse cortical atrophy and delayed myelination.

**CONCLUSION**

ADSL deficiency is a rare deficiency of purine metabolism. ADSL deficiency should be suspected in children with psychomotor retardation and refractory epilepsy as well as in patients with magnetic resonance imaging findings of diffuse cortical atrophy and delayed myelination. Genetic testing is
Figure 5  Electroencephalography findings.

necessary to confirm the diagnosis. Metabolic epilepsy caused by ADSL deficiency can be controlled by the administration of antiepileptic drugs.

ACKNOWLEDGEMENTS

We thank the patient and his parents for providing relevant information and allowing us to publish this information. We also thank the Affiliated Hospital of Jining Medical University for providing support and assistance with this work.

FOOTNOTES

Author contributions: Wang XC, Liu RH, and Kong QX designed the study; Chen DD, Jiang Y, Wang XY, and Wang T collected the data; Wang XC, Wang T, and Liu RH contributed to data analysis and interpretation; Wang XC drafted the manuscript; Kong QX and Liu RH contributed to revisions; all authors approved the final version of the manuscript.

Supported by the Natural Science Foundation of Shandong Province, No. ZR2019MH060.

Informed consent statement: Informed written consent was obtained from the patients for the publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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REFERENCES


Recovery of brachial plexus injury after bronchopleural fistula closure surgery based on electrodiagnostic study: A case report and review of literature

Young-In Go, Da-Sol Kim, Gi-Wook Kim, Yu Hui Won, Sung-Hee Park, Myoung-Hwan Ko, Jeong-Hwan Seo

BACKGROUND
Axillary thoracotomy and muscle flap are muscle- and nerve-sparing methods among the surgical approaches to bronchopleural fistula (BPF). However, in patients who are vulnerable to a nerve compression injury, nerve injury may occur. In this report, we present a unique case in which the brachial plexus (division level), suprascapular, and long thoracic nerve injury occurred after BPF closure surgery in a patient with ankylosing spondylitis and concomitant multiple joint contractures.

CASE SUMMARY
A 52-year-old man with a history of ankylosing spondylitis with shoulder joint contractures presented with right arm weakness and sensory impairment immediately after axillary thoracotomy and latissimus dorsi muscle flap surgery for BPF closure. During the surgery, the patient was positioned in a lateral decubitus position with the right arm hyper-abducted for approximately 6 h. Magnetic resonance imaging and ultrasound revealed subclavious muscle injury or myositis with brachial plexus (BP) compression and related neuropathy. An electrodiagnostic study confirmed the presence of BP injury involving the whole-division level, long thoracic, and suprascapular nerve injuries. He was treated with medication, physical therapy, and ultrasound-guided injections. Ultrasound-guided steroid injection at the BP, hydrodissection with 5% dextrose water at the BP and suprascapular nerve, and intra-articular steroid and hyaluronidase in-
jection at the glenohumeral joint were performed. On postoperative day 194, the pain and arm weakness were resolved, and a follow-up electrodiagnostic study showed marked improvement.

CONCLUSION
Clinicians should consider the possibilities of multiple nerve injuries in patients with joint contracture, and treat each specific therapeutic target.

Key Words: Brachial plexus; Electrodiagnosis; Physical therapy; Surgical flaps; Thoracotomy; Case report

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Core Tip: We report a rare case of brachial plexus (division level), suprascapular, and long thoracic nerve injury after axillary thoracotomy and latissimus dorsi muscle flap surgery for bronchopleural fistula. The patient was diagnosed via the clinical course, magnetic resonance imaging, ultrasound, and electrodiagnostic study. This case recommends that clinicians should pay attention to patients’ underlying conditions, which are related to nerve complications such as severe multiple joint contractures, and prevent the complications.

INTRODUCTION
The nerves susceptible to damage during thoracic surgery include the vagus nerve, recurrent laryngeal nerve, stellate ganglion or sympathetic trunk, and brachial plexus (BP), and the anatomical position of the nerve and the occurrence of perioperative nerve injury are closely related to each other[1]. The brachial plexus is responsible for the overall motor and sensory functions of the upper extremity, and when an injury occurs, it causes various symptoms, from minor sensory loss to large loss of functional ability; thus, an accurate understanding of anatomy during surgery is important[1]. There are various causes of BP injury during surgery; however, perioperative mechanical forces, such as stretching, compression, and laceration, are the representative contributors. Stretching and compression are typically caused by poor limb padding and positioning during surgery, excessive surgical retractor use, prolonged immobility, and hematoma around the nerve, while laceration is often caused by direct damage from the blade or needle[2]. The risk factors for intraoperative BP injury are inappropriate positioning, especially with arms abducted > 90°, old age (> 60 years), prolonged operation time (316 ± 62 min), hypotension, and hypothermia[3,4].

Axillary thoracotomy is a surgical method that approaches the axillary area, which includes the first rib or second and third rib resection, and smaller muscle transections are made compared to those in the original thoracotomy, which requires transection of the latissimus dorsi or serratus anterior muscle[5]. It is mainly one of the surgical methods for the apical lung, pleural cavity, thoracic cavity, heart, and esophagus and is performed by exposing the axilla by flexing the ipsilateral arm in the lateral decubitus position. In patients with bronchopleural fistula (BPF) due to complications of supplicative pleuropulmonary disease, along with medical treatments, surgical closure, including muscle flap, is performed to provide fistula coverage[6]. Axillary thoracotomy has a lower risk for muscle or nerve injury than the original thoracotomy, although there has been a case of injury to the intercostobrachial nerve or long thoracic nerve at the incision site or a very rare case of BP injury[7,8]. We report a patient who simultaneously suffered from BP injury, whole-division level, suprascapular nerve, and long thoracic nerve injury immediately following BPF closure surgery under general anesthesia in thoracic surgery. Herein, we examine the causes and mechanisms that cause nerve damage during surgery and review the related literature.

CASE PRESENTATION

Chief complaints
A 52-year-old man complained of muscle weakness and paresthesia in the right arm immediately after
BPF closure surgery.

**History of present illness**
During the surgery, the patient was placed in the left lateral decubitus position under general anesthesia, his right shoulder was abducted to approximately 90°, and his elbow was placed on a padded board with 90° of flexion and pronation. First, an incision was made in the right axillary region for entry, and subsequently, partial resection of the second and third ribs to expose the cavitary lesion and debridement were performed. An additional skin incision was performed to expose the latissimus dorsi muscle and dissect the muscle to a length that is sufficient to cover the cavity. After the latissimus dorsi myocutaneous flap was prepared, the wound cavity area was covered with this flap, and the surgical site was completely closed to complete the operation. The operation was performed for approximately 6 h, and there were no complications, such as excessive bleeding, hypotension, decreased oxygen saturation, or hypothermia during the operation.

**History of past illness**
The patient had a history of old pulmonary tuberculosis, newly detected aspergillosis at the BPF lesion, and asthma. In addition to pulmonary diseases, the patient was diagnosed with ankylosing spondylitis and underwent hip arthroplasty due to bilateral hip arthritis, and multiple joint angles were limited due to bilateral shoulder and elbow arthritis and bamboo spine.

**Personal and family history**
The patient had no personal or family history of neurologic diseases.

**Physical examination**
On the physical examination performed on postoperative day (POD) 1, the passive range of motion (ROM) of right shoulder flexion, extension, abduction, internal rotation, and external rotation were limited to 80°, 20°, 70°, 0°, and 30°, respectively. Manual muscle testing (MMT) scores were 1 for shoulder flexion and extension, elbow flexion and extension, wrist flexion and extension, and finger flexion and extension. Sensation was decreased throughout the right arm; in particular, the patient complained of hypoesthesia and paresthesia (visual analog scale of 4) over the medial side of the upper arm, forearm, and hand.

**Laboratory examinations**
The routine blood tests, including complete blood count, electrolyte profile, infection indexes, and routine urine tests, were within the normal range.

**Imaging examinations**
On BP magnetic resonance imaging (MRI) performed on POD 4, the signal intensity of the subclavius muscle was increased on T2WI, and heterogeneous enhancement was observed, suggesting myositis or muscle injury. In addition, the BP was compressed at the division level by the hypertrophied subclavius muscle (Figure 1). Similarly, in the musculoskeletal ultrasound performed on POD 6, clear hyperechogenicity was observed in the right subclavius muscle, and marked swelling was observed when compared to the left (Figure 2).

**FURTHER DIAGNOSTIC WORK-UP**

**Electrodiagnostic evaluation**
In the nerve conduction study (NCS) on POD 9 and needle electromyography on POD 14, the results showed right BP injury, whole-division level, right long thoracic nerve injury (severe degree), and right suprascapular nerve injury (moderate degree) (Tables 1 and 2).

**FINAL DIAGNOSIS**
The final diagnosis of the presented case was right brachial plexus injury (division level), suprascapular nerve, and long thoracic nerve injury based on MRI, ultrasound, and electrodiagnostic study.

**TREATMENT**
The patient received physical therapy five times a week from POD 2 to 28. Passive, active-assisted ROM exercises, strengthening exercises, and neuromuscular electrical stimulation were performed to improve
### Table 1 Results of the nerve conduction study in postoperative day 9

<table>
<thead>
<tr>
<th>Nerve conduction (motor)</th>
<th>Recording site</th>
<th>Stimulation site</th>
<th>Latency (ms)</th>
<th>Amplitude (mV)</th>
<th>Conduction velocity (m/s)</th>
<th>Nerve conduction (sensory)</th>
<th>Recording site</th>
<th>Stimulation site</th>
<th>Latency (ms)</th>
<th>Amplitude (mV)</th>
<th>Conduction velocity (m/s)</th>
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<tbody>
<tr>
<td>Right median</td>
<td>APB</td>
<td>Wrist</td>
<td>2.75</td>
<td>11.7</td>
<td></td>
<td>Right median</td>
<td>3rd finger</td>
<td>Palm</td>
<td>1.55</td>
<td>9.2</td>
<td>45.2</td>
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<tr>
<td></td>
<td></td>
<td>Elbow</td>
<td>7.00</td>
<td>10.1</td>
<td>56.5</td>
<td>Left median</td>
<td>3rd finger</td>
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<td>1.25</td>
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<td>Left median</td>
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<td>2.70</td>
<td>15.0</td>
<td></td>
<td>Left median</td>
<td>3rd finger</td>
<td>Palm</td>
<td>2.55</td>
<td>25.5</td>
<td>53.8</td>
</tr>
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Table 2 Results of needle electromyography

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<th>Muscle (right)</th>
<th>Abnormal spontaneous activity (positive sharp wave)</th>
<th>MUAP</th>
<th>Recruitment pattern</th>
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<td>Teres major</td>
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MUAP: Motor unit action potential.

Figure 1 A T2-weighted magnetic resonance coronal image of the brachial plexus. A: A reduced version; B: An enlarged version. The hypertrophied subclavius muscle is compressing the underlying brachial plexus, and elevated signal intensity throughout the brachial plexus is shown (arrows). C: Clavicle; S: Subclavius muscle.

right arm weakness and shoulder ROM. For neuropathic pain control, gabapentin was increased from an initial dose of 600 mg orally per day to 1200 mg/d. On POD 6, ultrasound-guided perineural injection at the right BP below the clavicle was administered with 5 mg of dexamethasone and 4 mL of normal saline. On POD 16, ultrasound-guided hydrodissection at the right BP below the clavicle and suprascapular nerve were performed with 10 mL and 5 mL of 277.53 mmol/L dextrose solution, respectively.
Figure 2 Musculoskeletal ultrasonography along the short axis of the subclavius muscle. A: Isolated hypertrophy of subclavius muscle (arrowhead) of the affected side; B: Normal finding of subclavius muscle (arrowhead) of the unaffected side.

OUTCOME AND FOLLOW-UP

After medication, ultrasound-guided injection, and physical therapy, right arm paresthesia was slightly improved, and the patient discontinued gabapentin on POD 62. However, right shoulder pain and the limited ROM of the right shoulder were continuously present, and an ultrasound intra-articular injection at the right shoulder was performed on POD 108. On the follow-up NCS performed on POD 61, the compound muscle action potential amplitude of the right long thoracic nerve was slightly improved, which was absent in the initial test. In addition, there was no significant difference (Table 3). Manual muscle testing scores improved to 2 for shoulder flexion and extension, 3 for elbow flexion and extension, 3 for wrist flexion and finger extension, and 4 for wrist extension and finger flexion. On POD 133, there was a marked improvement in MMT scores, which were 4 for flexion and extension of the whole right arm and limited ROM of the right shoulder joint. The grip power of the right hand, measured using a hand dynamometer, was 24 kg, which was improved compared to 12.7 kg on POD 17. On POD 194, the follow-up NCS showed recovery within the normal range (Table 4). The treatment was terminated because there was no significant hindrance to the patient’s daily activities.

DISCUSSION

In this study, we report a unique case of a patient with BPs injuries at the whole-division level, suprascapular, and long thoracic nerve, which presented various symptoms and severities, which occurred immediately after BPF closure. The well-known mechanisms of injury are compression by the clavicle during retraction in median sternotomy, compression by the thorax and humeral head in the lateral decubitus position, and stretching of the upper BP root by arm abduction and external rotation[2]. However, the pathology of the injury in the current patient is different from the known pathology because it is caused by hypertrophied subclavius muscle. BP passes through the root and trunk at the supraclavicular level based on the clavicle and is divided into cords and branches at the infraclavicular level[9], and this nerve bundle is located below the subclavius muscle in the costoclavicular space[10]. The subclavius muscle originates in the first rib and first costal cartilage and is inserted into the inferior middle third of the clavicle, which depresses the shoulder and pulls the clavicle in the anteroinferior direction[10,11]. During shoulder abduction, downward movement of the scapula and coracoid occurs, and upward movement of the clavicle causes traction of the subclavius muscle[12,13]. Hypertrophy may have occurred as a result of continuous excessive muscle tension while maintaining shoulder abduction posture during the operation period[14]. Ankylosing spondylitis is a chronic inflammatory rheumatic disease that mainly affects the axial skeleton, with shoulder involvement in approximately 7%-33% of patients[15]. The patient previously had severe shoulder joint ROM limitation, and a greater force would have been required to abduct the arm for > 90° during the surgery, and more stress would have been applied to the subclavius muscle. These conditions might cause secondary BP injuries due to the subclavius muscle injury during the surgery.

Suprascapular nerve palsy is caused by nerve entrapment by the anterior coracospinal ligament and suprascapular ligament, compression by a lipoma-like mass, intraosseous ganglion cyst, or paralabral cyst, and repetitive overhead activity; however, injuries that occur during surgery are rarely reported[16,17]. In this patient’s case, considering the incision site, the possibility of direct nerve transaction is relatively low. On the other hand, secondary nerve stretching due to the subclavius muscle injury might be considered according to imaging and electrodiagnostic studies. In particular, mechanical stretching due to nerve kinking from the origin of the upper trunk of the Erb’s point[18] or
<table>
<thead>
<tr>
<th>Nerve conduction (motor)</th>
<th>Recording site</th>
<th>Stimulation site</th>
<th>Latency (ms)</th>
<th>Amplitude (mV)</th>
<th>Conduction velocity (m/s)</th>
<th>Nerve conduction (sensory)</th>
<th>Recording site</th>
<th>Stimulation site</th>
<th>Latency (ms)</th>
<th>Amplitude (mV)</th>
<th>Conduction velocity (m/s)</th>
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<tr>
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APB: Abductor pollicis brevis; ADM: Abductor digiti minimi; EIP: Extensor indicis proprius.

Stretching (or compression) of the nerve by the superior transverse scapular ligament occurs at the suprascapular notch; the so-called sling effect\[19\] is the most likely mechanism. These nerve injuries are particularly vulnerable to shoulder hyperflexion, hyperabduction, and external rotation postures\[18-20\]. Furthermore, glenohumeral stiffness reportedly induces a compensatory wider scapulothoracic excursion, making the suprascapular nerve more susceptible to traction injury at the suprascapular notch and more easily irritated\[21\].

In the case of long thoracic nerve injury, direct nerve injury and traction injury were suspected during axillary thoracotomy or the latissimus dorsi muscle flap. The long thoracic nerve originates from the C5-C7 spinal nerve, passes down the clavicle and the first and second ribs, runs distally along the midaxillary line, and finally innervates the serratus anterior muscle\[22\]. Unlike other nerve injuries, considering the course of the nerve, the long thoracic nerve transaction may have occurred during the second and third rib resection (Figure 3). Alternatively, when flapping the latissimus dorsi muscle, transaction and traction damage in the process of exposing and dissecting the muscle to the flap may occur. The pattern was different from the BP injury or suprascapular nerve in that the response was absent on the initial NCS; however, it showed improvement on the follow-up NCS and was considered a partial nerve injury due to direct nerve transaction or traction.

As axonal regeneration of the peripheral nerve occurs at a rate of 1–2 mm/day in general, three months of conservative treatment is recommended for stretch/compression injury without laceration; however, exploration is recommended if there is no subsequent improvement\[23,24\]. In the case of peripheral nerve injury, early rehabilitation is important, and the main goal of treatment is to prevent muscle atrophy and secondary deformity of the upper arm and to improve pain and somatosensory deficit\[25\]. During the initial post-injury period, applying sling/splint and passive ROM exercises are recommended to maintain upper extremity joint mobility, and active assist or active ROM exercise is recommended.
Table 4 Results of the nerve conduction study in postoperative day 194

<table>
<thead>
<tr>
<th>Nerve conduction (motor)</th>
<th>Recording site</th>
<th>Stimulation site</th>
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APB: Abductor pollicis brevis; ADM: Abductor digiti minimi; EIP: Extensor indicis proprius.

optional depending on the patient’s strength gain. Strengthening exercise with electrical stimulation of the denervated muscle using direct-current stimulation is also recommended[25-27]. According to the Neuropathic Pain Special Interest Group guidelines and Canadian Pain Society guidelines, tricyclic antidepressants, gabapentin, and pregabalin are the first-line therapy for pain management, and opioid analgesics or tramadol are recommended as second- or third-line options[25,28]. If non-operative treatment fails, minimally invasive treatment can be attempted, and perineural injection using anesthetic medications with steroids, such as bupivacaine and methylprednisolone, help relieve symptoms, and glenohumeral joint hydrodilatation is helpful for patients with adhesive capsulitis[29,30].

In the electrodiagnostic study, Wallerian degeneration was observed in the area below the BP division level, in the suprascapular nerve, and in the long thoracic nerve, which showed progressive improvement in the follow-up examination. In T2WI on BP MRI, a signal increase due to compression of the BP at the division level was observed; thus, axonotmesis of the BP may have occurred according to the Seddon Sunderland classification[9,31]. Based on these studies, incomplete nerve injury was diagnosed, and axonal regeneration and spontaneous improvement could be expected. Ben-David and Stahl presented prognostic milestones for 1 wk and 6–8 wk for patients with intraoperative BP injury and noted a long-term residual neurological deficit if there is no sign of motor improvement within 6–8 wk[3]. In our patient, the motor showed gradual improvement on POD 61, and almost full motor recovery was observed on POD 133, which is consistent with the previous literature.

This case involved multiple nerve injuries of the ipsilateral arm immediately after axillary thoracotomy and latissimus dorsi muscle flap for pulmonary tuberculosis and BPF caused by aspergillosis in a patient with underlying ankylosing spondylitis and severe multiple joint contractures. Based on the initial symptoms alone, it can be misdiagnosed as a simple BP injury at the root level.
However, by observing the characteristics of the incision site, postoperative electrodiagnostic and imaging studies (musculoskeletal ultrasound and MRI), symptom progression, and prognosis, it was confirmed that suprascapular nerve and long thoracic nerve injuries occurred independently of BP injury. In addition, very rarely, compressive BP injury and whole-division level due to subclavius muscle swelling were observed. Along with ultrasound-guided injection, physical therapy, and drug treatment, numbness in the upper extremities and muscle weakness started to improve two months after the onset. Conversely, suprascapular nerve or long thoracic nerve injury did not show as much rapid improvement as BP in symptoms or electrodiagnostic study results and started to show improvement at three months after the onset of physical therapies and ultrasound-guided injections for each nerve.

**CONCLUSION**

In case of nerve damage after surgery, efforts should be made to find the cause using electrodiagnostic and imaging studies, and injection therapy, drug therapy, and physical therapy are needed according to the cause and pathophysiology of each nerve damage. In addition, if there are multiple joint angle restrictions due to underlying diseases, such as in this case, it is important to recognize the risk of nerve damage, especially during chest surgery, and efforts, such as intraoperative nerve monitoring, reducing the operating time, and excessive attention to patient posture, are needed to prevent nerve damage.

**ACKNOWLEDGEMENTS**

The authors thank all the members of the Department of Physical Medicine & Rehabilitation, Jeonbuk National University Hospital.

**FOOTNOTES**

**Author contributions:** Go YI performed the electrodiagnostic study and contributed to the manuscript drafting; Kim GW, Won YH, and Park SH contributed to the data analysis; Go YI, Ko MH, Seo JH, and Kim DS contributed to the final diagnoses; Kim DS was responsible for the manuscript revision and intellectual content; all authors issued final approval for the version to be submitted.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by
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S-Editor: Xing YX
L-Editor: A
P-Editor: Xing YX

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Severe *Klebsiella pneumoniae* pneumonia complicated by acute intra-abdominal multiple arterial thrombosis and bacterial embolism: A case report

Xiao-Li Bao, Nan Tang, Yang-Zhong Wang

**Abstract**

**BACKGROUND**

*Klebsiella pneumoniae* (*K. pneumoniae*) is a clinically common Gram-negative bacillus that can cause community- and hospital-acquired infections and lead to pneumonia, liver abscesses, bloodstream infections, and other infectious diseases; however, severe pneumonia caused by hypervirulent *K. pneumoniae* (*hvKp*) complicated by acute intra-abdominal multiple arterial thrombosis and bacterial embolism is rarely seen in the clinical setting and has not been reported in the literature.

**CASE SUMMARY**

A 51-year-old man was hospitalized with fever and dyspnea. Persistent mild pain in the middle and upper abdomen began at dawn on the 3rd day following admission and developed into persistent severe pain in the left upper abdomen 8 h later. Based on chest computed tomography (CT), bronchoscopy, bronchoalveolar lavage fluid metagenomic next-generation sequencing, abdominal aortic CT angiography (CTA), and culture of the superior mesenteric artery embolus, adult community-acquired severe *hvKp* pneumonia complicated by acute intra-abdominal multiple arterial thrombosis and bacterial embolism was diagnosed. Notably, he recovered and was discharged from the hospital after receiving effective meropenem anti-infection, endovascular contact thrombolytic, and systemic anticoagulant therapies and undergoing percutaneous thrombus aspiration. Ten days later, the patient returned to the hospital for abdominal CTA examination, which indicated blocked initial common pathway of the celiac trunk and superior mesenteric artery, and local stenosis. Therefore, celiac trunk artery stenting was performed in Chongqing Hospital, and postoperative recovery was good.

**CONCLUSION**
We report a case of hvKp severe pneumonia complicated by acute intra-abdominal multiple arterial thrombosis and bacterial embolism and suggest that clinicians should consider the possibility of a Gram-negative bacillus infection and conduct effective pathogen detection in a timely fashion when managing patients with severe community-acquired pneumonia before obtaining bacteriologic and drug sensitivity results. At the same time, when patients have severe pulmonary infection complicated by severe abdominal pain, an acute mesenteric artery embolism should be considered to avoid delays in treatment.

Key Words: Klebsiella pneumoniae; Severe pneumonia; Acute mesenteric ischemia; Superior mesenteric artery embolism; Case report

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Core Tip: The community-acquired Klebsiella pneumoniae (K. pneumoniae) infection rate is relatively low, but a hypervirulent K. pneumoniae infection can develop into a severe illness or even death, which deserves the attention of clinicians. At the same time, although current thrombolytic therapy for the arterial system complicated by infectious bacterial embolism is controversial, we believe that local thrombolytic therapy is still effective under effective anti-infection therapy and warrants further study.

Citation: Bao XL, Tang N, Wang YZ. Severe Klebsiella pneumoniae pneumonia complicated by acute intra-abdominal multiple arterial thrombosis and bacterial embolism: A case report. World J Clin Cases 2022; 10(30): 11101-11110
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11101.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11101

INTRODUCTION
Hypervirulent Klebsiella pneumoniae (hvKp) are highly virulent variants of K. pneumoniae, and these strains can cause purulent liver abscesses and bacteremia in the absence of biliary or intestinal pathology, as well as spread to the lungs, eyes, and central nervous system, and cause severe community-acquired infections in previously healthy and young people, such as liver abscesses, pneumonia, meningitis, endophthalmitis, and necrotizing fasciitis[1-3].

Acute mesenteric ischemia (AMI) is one of the most severe acute abdominal diseases encountered in vascular surgery. AMI is caused by obstruction of the mesenteric artery or vein, which leads to a sudden interruption of the blood supply or reflux, obstruction of the blood supply and malnutrition of the intestinal canal, and finally the loss of bowel function and necrosis. AMI has an insidious onset and rapid progression and causes severe consequences. If diagnosis and treatment cannot be made in a timely fashion, the fatality rate can reach 50%-70%[4].

CASE PRESENTATION
Chief complaints
A 51-year-old nonsmoking male chemical plant worker with normal immune function was hospitalized on March 28, 2021 with fever and dyspnea for 4 d.

History of present illness
Four days before admission, the patient developed a fever without any apparent trigger. His peak temperature was 39.3 °C, and he experienced progressive aggravation of dyspnea and fatigue. In addition, the patient had a paroxysmal, nonproductive cough.

History of past illness
Hypertension existed for 10 d. Amlodipine besylate tablets (5 mg/d) were taken orally for antihypertensive treatment daily.

Personal and family history
His personal and family histories were unremarkable.
**Physical examination**
The initial physical examination showed a heart rate of 107 beats/min, a respiratory rate of 33 breaths/min, a body temperature of 39.1 °C, and a blood pressure of 20.62/10.0 kPa. The body weight was 65 kg. Scratches were noted on both the forearms and hands, and skin ulcerations were occasionally observed (Figure 1). Coarse breath sounds and extensive rales were appreciated in both lungs. The remainder of the organ systems were unremarkable on physical examination.

**Laboratory examinations**
Laboratory testing revealed the following: WBC count, 20.30 × 10^9/L; neutrophil percentage, 84.4%; hemoglobin concentration, 116 g/L; procalcitonin, 2.03 ng/mL; C-reactive protein (CRP), 380.00 mg/L; interleukin-6 (IL-6), 408.4 pg/mL; serum albumin, 25.0 g/L; arterial blood gas (FiO_2, 33%; pH, 7.46; PaCO_2, 35 mmHg; PaO_2, 76 mmHg; HCO_3, 24.9 mmol/L; lactic acid, 1.1 mmol/L; and P/F, 230 mmHg. The following measures and indicators were normal: liver function; coagulation function; HIV; HBV; A/B virus antigen; cytomegalovirus IgM/IgG; Epstein-Barr virus IgM/IgG; blood lipids; blood glucose; lymphocyte subsets; IgM, IgG, IgA, IgE, IgD; renal function; autoantibody spectrum; anti-neutrophil cytoplasmic antibody spectrum; brain natriuretic peptide; myocardial injury markers; ECG; and routine defecation. In addition, there were no abnormalities detected in the heart, abdominal and lower limb deep veins by ultrasonography, or by bilateral carotid artery ultrasonography.

**Imaging examinations**
On the day of admission, chest computed tomography (CT) showed multiple patchy, nodular, flocculent high-density shadows in both lungs, with blurred edges and small voids in some lesions (Figure 2A).

**Initial diagnosis**
We made an initial diagnosis of adult community-acquired severe pneumonia and type I respiratory failure; however, the pathogenesis was not determined.

**Initial treatment**
After admission, the patient was administered high-flow nasal cannula supportive therapy, piperacillin/tazobactam (4.5 g intravenous infusion every 8 h), and linezolid (0.6 g intravenous infusion every 12 h).

**Deterioration of patient condition**
The patient had recurrent high fevers, and the P/F decreased to 152 mmHg. During this period, sputum and blood cultures were repeatedly performed, but no causative organisms were isolated. In addition, in the early morning of the 3rd day following admission, the patient began to develop persistent mild pain in the middle and upper abdomen, although no positive signs were elicited on the abdominal physical examination. The pain was not relieved by intravenous proton pump inhibitor therapy. Eight hours later, the patient developed persistent severe pain in the left upper abdomen; abdominal signs on physical examination were still negative.

**Further diagnostic work-up**
An emergency determination of myocardial injury markers, serum amylase, serum lipase, and re-examination of the cardiac and whole abdominal ultrasounds were normal, but the plasma D-dimer increased to 25.5 mg/L. The results of repeat chest and abdominal CT angiography (CTA) showed that the proximal segment of the celiac trunk and superior mesenteric artery were embolized, and the distal branch appeared reduced in size. The hepatic parenchyma around the gallbladder was enhanced in the arterial stage, with uneven local perfusion and a few calcified plaques in the abdominal aorta (Figure 3A). The bilateral lung lesions increased, and the solid parts around some nodules increased, with reverse halo signs and trophovascular signs (Figure 2B).

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**MULTIDISCIPLINARY EXPERT CONSULTATION**

Ke Li, MD, Professor and Chief, Department of General Surgery, Chongqing University Fuling Hospital
The patient had no signs of intestinal necrosis and peritonitis and no indications for a laparotomy; however, to avoid bowel resection, multiple intra-abdominal artery emboli require urgent restoration of the blood supply.
Wei Wei, MD, Assistant Professor of Interventional Vascular Radiology, Department of Radiology, Chongqing University Fuling Hospital

The acute intra-abdominal multiple arterial emboli were clear, and endovascular catheter treatment was recommended; however, the patient had severe pneumonia, and it is not clear what type the embolus was. Indeed, if the embolus is bacterial, thrombolytic therapy may cause systemic spread of bacteria, thus aggravating the patient’s overall status.

Yong-sheng Shi, MD, Attending Physician, Department of Vascular Surgery, Chongqing University Fuling Hospital

The patient was in an early stage of acute abdominal multiple artery emboli without obvious peritoneal irritation, and the lesions were located in the main trunk. Therefore, intracavity catheter therapy combined with systemic anticoagulation could be a first treatment choice; however, the patient had severe pneumonia, and if the intra-abdominal artery was bacterially embolized, thrombolitics increased the risk of systemic bacterial spread, resulting in further aggravation of the infection or life-threatening complications.

Wu Guo, MD, Professor and Chief, Department of Infectious Diseases, Chongqing University Fuling Hospital

The patient had severe pneumonia with acute intra-abdominal multiple arterial emboli; thus, his current condition was severe. Although the etiology was unknown, it is not possible to know whether there were bacterial emboli. If the blood supply was not restored in a timely fashion, irreversible loss of the intestinal canal would occur, further aggravating the patient’s condition. Therefore, endovascular catheter treatment and local intracatheter arterial thrombolysis were recommended on the basis of the patient undergoing strong anti-infection therapy. During the operation, aspirated emboli could be sent for culture. In addition, bronchoalveolar lavage fluid metagenomic next-generation sequencing (BALF-mNGS) was performed to further identify the pathogen(s) after the patient’s general condition improved.

FINAL DIAGNOSIS

We made a final diagnosis of community-acquired severe pneumonia with acute intra-abdominal multiple arterial emboli.

TREATMENT

We replaced the antibiotics with meropenem (1 g intravenously every 8 h) combined with vancomycin (1 g intravenously every 12 h) for anti-infection, initiated low-molecular weight heparin sodium (100 IU/kg subcutaneously for anticoagulation every 12 h), withheld food, and provided fluid rehydration.
and parenteral nutrition. We immediately performed artery digital subtraction angiography (DSA) and found that the embolus in the superior mesenteric artery opening had almost completely blocked the blood vessels.

We implanted a percutaneous endovascular catheter to aspirate the superior mesenteric artery emboli. The aspirated emboli were sent for microbial culture, and endovascular contact thrombolysis [urokinase (300000 U)] was performed. After surgery, urokinase was pumped with 100000 U arterial microbeam for 4 h, followed by a conventional heparin (1250 U) arterial micropump for 4 h by alternate intra-arterial catheter administration, and systemic low-molecular weight heparin was injected subcutaneously for anticoagulation.

Postoperative abdominal pain was significantly relieved, but abdominal distention appeared on the first day after surgery; thus, the alternate intra-arterial catheter administration of intra-arterial thrombolysis and anticoagulant was continued as before. After 72 h of thrombolytic therapy, intra-arterial thrombolytic therapy and intracatheter anticoagulation were discontinued due to positive fecal occult blood, but subcutaneous injection of 100 IU/kg low-molecular-weight heparin every 12 h was continued.

Figure 2: Chest computed tomography imaging examinations. A: Multiple patchy, nodular, and flocculent high-density shadows in both lungs, with blurred edges and small voids in some lesions; B: The bilateral lung lesions increased, and the solid parts around some nodules increased, with reverse halo and trophovascular signs; C: The bilateral lung lesions were significantly absorbed and reduced compared with previous imaging.
On the 5th day following admission, the superior mesenteric artery embolus culture suggested *K. pneumoniae* growth (PHOENIX100 Fully Automatic Microbial Analysis System, from BioMérieux, France). On the 7th day following admission, the patient still had intermittent fevers. Therefore, BALF-mNGS (Kingmed Diagnostics, China) was performed to further clarify the etiology, and the results showed that the sequence number of *Klebsiella* was 13636, among which the sequence number of *K. pneumoniae* detected was 4812. Therefore, we discontinued vancomycin and continued meropenem to fight the infection, and low-molecular-weight heparin 100 IU/kg subcutaneous injection was continued every 12 h during hospitalization.

**OUTCOME AND FOLLOW-UP**

The dyspnea was relieved, the body temperature returned to normal, the abdominal pain resolved, abdominal distension improved, and a semifluid diet was resumed. On the 23rd day following admission, a chest CT re-examination showed that the bilateral lung lesions were significantly absorbed and reduced compared with the former CT findings (Figure 2C). The patient's condition improved, and he was discharged home. He was treated with rivaroxaban (15 mg twice daily) and clopidogrel (75 mg once daily). Although the abdominal distention improved, he still had symptoms of abdominal distension after discharge.

Ten days later, the patient returned to the hospital for abdominal CTA examination, which indicated reperfusion of the proper hepatic artery, partial infarction of the spleen, cystic changes, blocked initial common pathway of the celiac trunk and superior mesenteric artery, and local stenosis (Figure 3B). Therefore, celiac trunk artery stenting was performed in Chongqing Hospital, and postoperative recovery was good.
DISCUSSION

In recent years, the *K. pneumoniae* detection rate has been increasing steadily. *K. pneumoniae* belongs to *Klebsiella Enterobacteriaceae*. According to its virulence and pathogenic characteristics, *K. pneumoniae* can be divided into classic *K. pneumoniae* (cKp) and hvKp[5]. One of its main characteristics is that cKp causes nosocomial infection and usually infects immunocompromised or immunocompromised people since cKp carry fewer virulence genes and are less virulent but can show high levels of multiresistance to antibiotics. However, hvKp often manifests as a community-acquired infection, which is more likely to cause disease in healthy people and is often accompanied by multisite invasive infection, which can be life-threatening in severe cases[6]. Compared with cKp strains, hvKp strains showed stronger virulence in various infection modes. Recent studies suggested the existence of hvKp strains with a negative string test. The K1 and K2 capsular serotypes *rmpA*, *rmpA2*, aerobactin and yersiniabactin are the common factors responsible for hypervirulent phenotypes[7].

hvKp was initially found mainly in Southeast Asia, but an increasing number of cases have been reported around the world, including in Europe and the United States, and China is a high-incidence area of hvKp infection[6]. A bloodstream source is currently the most recognized route of infection for hvKp. Due to the ability of hvKp to resist neutrophil phagocytosis, it can flow to various tissues and organs in the body through the blood circulation, thereby leading to infection[9].

Chest CT in patients with community-acquired *K. pneumoniae* pneumonia may show large, honeycomb, patchy consolidation shadows or be accompanied by abscesses, cavities, and liquefaction necrosis, and > 50% of patients have pleural effusions[10]. Pneumonia caused by hematogenous disseminated *K. pneumoniae* infections is similar to *Staphylococcus aureus* (*S. aureus*) infection, such as multiple nodules near the pleura of both lungs, or accompanied by hollow nodules, trophovascular signs, anti-halo signs, and other CT imaging features[11]. Therefore, there is a risk of failure of antibiotic therapy based only on the characteristics of chest CT images.

The patient presented herein was a healthy Asian man who worked as a cleaner in a factory. Before the disease onset, his skin was exposed to sewage pollutants due to touching it with both hands during cleaning, and the skin of his forearms and hands was scratched, resulting in local suppurative infections, after which he developed fevers and dyspnea. His procalcitonin, CRP, and IL-6 Levels were elevated. Chest CT showed multiple patchy, nodular, and flocculent bilateral lung high-density shadows, with blurred edges, and small cavities in some lesions. During chest and abdominal CTA, the lung lesions showed reverse halo and trophovascular signs.

An *S. aureus* infection was suspected as the initial clinical diagnosis, and treatment with piperacillin/tazobactam combined with linezolid failed. In recent years, mNGS has been shown to be able to rapidly and objectively detect various pathogenic microorganisms in clinical samples and conduct drug resistance gene detection of bacteria; thus, mNGS is widely used in clinical practice[12]. In our case, when early anti-infection treatment was ineffective, BALF was obtained for mNGS detection, and *K. pneumoniae* was detected, which was consistent with the results of the DSA aspiration embolus culture, proving that meropenem treatment was effective and reducing the adverse effects caused by the blind use of other broad-spectrum antibiotics.

Although the traditional research view is that high virulence and multidrug resistance do not overlap in the hvKp genome, most hvKp remain highly sensitive to commonly used antibiotics except ampicillin, and their resistance rate is extremely low[7,13]. However, with the extensive use of antibiotics, drug-resistant hvKp has emerged, especially carbapenem-resistant hvKp (CR-hvKp), which has brought great challenges to clinical treatment. Although our case was not detected as CR-hvKp, the antibiotics, drug-resistant hvKp has emerged, especially carbapenem-resistant hvKp (CR-hvKp), which has brought great challenges to clinical treatment. Although our case was not detected as CR-hvKp, the infection prevention and control measures to prevent the spread of CR-hvKp infection[14,15].

AMI has an insidious onset and rapid progression. Various causes lead to acute obstruction of the mesenteric artery or vein, which leads to sudden interruption of the blood supply or reflux, intestinal blood supply disorder and malnutrition, and eventually loss of function and necrosis[4]. Although clinical incidence is only 1%-2%, the fatality rate is very high[16,17]. Sixty-five percent of AMI patients have acute superior mesenteric artery emboli[18]. Mesenteric artery emboli mostly originate from the left atrium and are often associated with arrhythmias, such as atrial fibrillation, and can also be caused by heart valve dysfunction or bacterial emboli shedding. It has been reported that high-risk factors include atherosclerosis, dyslipidemia, hypertension, dehydration, diabetes, estrogen, and antiphospholipid syndrome[19].

Although the chief complaint of severe abdominal pain inconsistent with the physical examination findings is a classic presentation of early AMI, it is not sufficient for its diagnosis, and there are no specific biomarkers to confirm AMI[20]. CTA imaging technology has officially replaced angiography as the imaging examination of choice, with a sensitivity of 93%, a specificity of 100%, a positive rate of 94%, and an exclusion rate of 100%[21].

Currently, the "4R" treatment strategy (resuscitation, rapid diagnosis, revascularization, and reassessment of bowel) is recommended internationally for the treatment of AMI[22]. In patients with early acute arterial embolism or thrombosis, the onset of intestinal ischemia is < 12 h, intestinal injury is usually in the reversible stage without obvious peritoneal irritation, and the lesions are located in the...
main trunk or branches. Endovascular catheter therapy combined with systemic anticoagulation can be the first choice for treatment\cite{17,23}. In this case, the patient had acute abdominal pain, high blood pressure, and high-risk factors for dehydration, and the plasma D-dimer levels increased sharply.

After acute intra-abdominal multiple artery emboli were confirmed, although it was impossible to know whether there was bacterial embolism, timely intracatheter contact thrombolysis, percutaneous thrombosis aspiration, and systemic anticoagulation therapy were performed on the basis of strong anti-infection treatment, which avoided intestinal necrosis and diffuse peritonitis and improved the patient’s prognosis. Although hvKp infection can cause sepsis, the risk of infective endocarditis is very low\cite{1}, and the patient had no history of atrial fibrillation, which does not support mesenteric artery embolism due to shedding of infective endocarditis bacterial emboli.

Therefore, we speculated that hvKp entered his bloodstream through the damaged and exposed skin and then circulated to the mesenteric artery. Due to sepsis, high fever, and dehydration, the patient developed a hypercoagulable state, which resulted in the formation of bacterial emboli and thrombi. At present, the efficacy and safety of arterial thrombolysis are mainly reported for acute ischemic stroke secondary to infective endocarditis. Previously, infective endocarditis represented a classical contraindication to thrombolysis for acute ischemic stroke due to a potential increased risk of intracranial hemorrhage. However, some case reports have suggested the safety and potential efficacy of intravenous or intra-arterial thrombolysis in stroke related to infective endocarditis\cite{24-27}. Notably, McCollom and Zwirko\cite{28} reported a case of infected iliofemoral deep venous thrombosis that was successfully treated with catheter-directed thrombolysis, angioplasty, and stent placement. Although there are no reports of bacterial thrombolysis in mesenteric arteries, this case demonstrates that thrombolysis can be accomplished safely with adequate antibiotic coverage.

CONCLUSION

At present, community-acquired severe pneumonia complicated with acute intra-abdominal multiple arterial thrombosis and bacterial embolism caused by hvKp has not been reported in the literature, and there is no rapid and reliable clinical test to identify hvKp. In summary, we suggest that clinicians should consider the possibility of Gram-negative bacilli infection and conduct effective pathogen detection in a timely fashion, such as BALF or tissue mNGS, when managing patients with severe community-acquired pneumonia without waiting for bacteriologic and drug sensitivity results. At the same time, in cases of acute abdominal multiple artery embolism and organ dysfunction, thrombolysis and systemic anticoagulation need to be applied along with vascular radiologic intervention. Although thrombolytic therapy for the arterial system complicated with infectious bacteria thrombolysis is currently controversial, we believe that local thrombolytic therapy is still effective under effective anti-infection therapy; however, further research is warranted in the future.

ACKNOWLEDGEMENTS

We acknowledge the contributions of Mr. Xiu-Qing Liao, who endorsed the data and conclusions.

FOOTNOTES

Author contributions: Bao XL analyzed the data and wrote the manuscript; Tang N made suggestions; Wang YZ revised the manuscript; all authors have read and approve the final manuscript.

Supported by the Chongqing Regional Key Discipline Construction Project, No. zdkx201702.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and this manuscript was prepared and revised according to the CARE Checklist (2016).

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Bao XL et al. Severe pneumonia with intra-abdominal arterial emboli

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S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM

REFERENCES


Spontaneous bilateral femur neck fracture secondary to grand mal seizure: A case report

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Specialty type: Orthopedics

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Beran RG, Australia; Liu J, United States

Received: June 4, 2022
Peer-review started: June 4, 2022
First decision: July 29, 2022
Revised: July 29, 2022
Accepted: September 20, 2022
Article in press: September 20, 2022
Published online: October 26, 2022

Abstract

BACKGROUND
Spontaneous bilateral femur neck fracture is a rare entity in the general population.

CASE SUMMARY
A 17-year-old immobile, developmentally delayed male with the sequelae of cerebral palsy fractured both femoral necks during a grand mal epileptic seizure. He had been treated with valproic acid as an antiseizure medication for about 10 years; otherwise, he had no history of drug use. The laboratory analysis was normal except a marked vitamin D deficiency. Closed reduction and osteosynthesis with percutaneous cannulated screws were performed. Solid union was observed at 6 mo, and rapid postoperative rehabilitation was started.

CONCLUSION
A femoral neck fracture may occur in a person with epilepsy presenting with hip pain in the emergency department.

Key Words: Grand mal seizure; Bilateral femur neck fracture; Antiepileptic drugs; Immobile patient; Valproic acid use; Spontaneous fracture; Case report

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Core Tip: Spontaneous bilateral femoral neck fracture is a very rare entity and may develop in association with metabolic diseases, bone diseases, high-energy traumas, and epileptic seizures. It should be predicted that complications such as nonunion, loss of reduction, and avascular necrosis may develop secondary to these fractures, which are theoretically considered to be associated with metabolic diseases.
INTRODUCTION

Femoral neck fractures in young patients account for approximately 3% of all femoral neck fractures and are usually secondary to high-energy trauma\[1,2\]. Spontaneous bilateral femoral neck fracture is very rare and may occur in association with metabolic or bone diseases, high-energy trauma, and epileptic seizures\[3\]. Complications of these fractures include nonunion, loss of reduction, and avascular necrosis, which are potentially associated with metabolic diseases. Early anatomical reduction, fixation, and rehabilitation are the primary goals. Spontaneous bilateral femoral neck fractures have been rarely reported\[4,5\].

CASE PRESENTATION

Chief complaints

A 17-year-old developmentally delayed immobile male with epilepsy as a sequela of cerebral palsy was brought to the emergency service due to pain in both hips after a sudden generalized tonic-clonic seizure 3 d previously.

History of present illness

The patient had pain in both hips after a sudden generalized tonic-clonic seizure 3 d previously, as reported by his family (Figure 1).

History of past illness

The patient had epilepsy as a sequela of cerebral palsy, and he had been treated with the antiseizure medication valproic acid for 10 years.

Personal and family history

The patient had no history of drug use other than valproic acid.

Physical examination

On physical examination, both lower extremities were in external rotation and there was pain and tenderness with movement.

Laboratory examinations

The patient's vitamin D level was relatively low (9 nmol/L), because he lacked sun exposure due to immobility (Table 1).

Imaging examinations

The patient had bilateral femur subcapital Garden type 4 fracture as revealed by a direct pelvis anteroposterior radiograph (Figure 1A).

FINAL DIAGNOSIS

The patient was diagnosed as having bilateral Garden type 4 femur neck fracture secondary to a grand mal seizure.

TREATMENT

Both hips were reduced anatomically and fixed with three 6.5-mm titanium cannulated screws. The hip joint capsules were not opened during surgery. Acceptable reduction and fixation were confirmed in the anteroposterior and lateral planes in the postoperative radiographs (Figure 1C and D).
Senocak E. Epilepsy related femur neck fracture

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ALP: Alkaline phosphatase.

Figure 1 Images. A: Preoperative anteroposterior radiographic view of bilateral femur neck fracture of the patient; B: The patient’s surgery position; C and D: Postoperative anteroposterior and frog leg radiographic view of the patient.

OUTCOME AND FOLLOW-UP

A rapid rehabilitation program was initiated to prevent hip stiffness in the patient, who was normally immobile. After a neurology consultation, the antiseizure treatment was revised due to the potential osteoporotic effect of valproic acid. Maintenance treatment was started with phenytoin, which is a less osteolytic agent. Since his hormone levels were normal according to an endocrinology consultation, only vitamin D replacement therapy was started (Table 1).
DISCUSSION

We present a 17-year-old immobile patient who took antiseizure medication and fractured both femoral necks during an epileptic seizure. Spontaneous bilateral femoral neck fractures are extremely rare. All reported cases were secondary to high-energy trauma, epileptic seizures, electric shock, and bone metabolism disorders\cite{4,6,7}. Several cases of bilateral femoral neck fracture secondary to epileptic seizures have been reported\cite{8-10}. It is thought that the rigid shear force between the femoral shaft and neck, together with the sudden muscle contractions secondary to the seizure, cause the fractures\cite{11}. Our case suggested that the femoral neck fractures resulted from the strong tonic-clonic contractions that occurred despite the use of antiseizure medication. However, we think that the long-term use of valproic acid exacerbated the fractures by decreasing bone mineral density. Our patient’s immobility promoted fracture development due to the associated decrease in bone quality.

Bilateral femoral neck fractures treated by total hip replacement have been reported in elderly patients\cite{12,13}. Another study reported closed reduction and percutaneous screw fixation in a 30-year-old patient with bilateral femoral neck fractures after a hypoglycemic attack\cite{14}. A 24-year-old Turkish patient with bilateral femoral neck fractures and osteopenia on postoperative bone densitometry was treated with closed reduction and percutaneous cannulated screws\cite{5}.

Since our patient was immobile, used antiseizure drugs, and had sequelae of cerebral palsy, we deemed it appropriate to perform closed reduction with three percutaneous cannulated screws after considering the patient’s condition, as it is the least invasive rigid fixation and also protects the bone. The risk of avascular necrosis in femoral neck fractures is 12%-40% in Garden type 3-4 displaced fractures\cite{15}. Our patient was brought to our clinic 3 d after the fracture and treated quickly. Callus formation was seen 6 mo postoperatively and there was no avascular necrosis. With regular rehabilitation, there were no problems with the hip movements.

CONCLUSION

As antiseizure medication may decrease bone density, bone densitometry should be performed regularly in cases with long-term use of these drugs. Although the fixation method varies by patient age and activity level, bone-sparing surgery is preferred in young patients. Patients with epilepsy who have dislocated shoulders should also be evaluated for femoral neck fractures.

FOOTNOTES

Author contributions: Senocak E contributed to the writing and data analysis.

Informed consent statement: Informed written consent was obtained from the patient for the publication of this report and any accompanying images.

Conflict-of-interest statement: The author has no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Chen YL
L-Editor: Wang TQ
P-Editor: Chen YL
REFERENCES


Favorable response after radiation therapy for intraductal papillary mucinous neoplasms manifesting as acute recurrent pancreatitis: A case report

Ayaka Harigai, Kiyoshi Kume, Noriyoshi Takahashi, So Omata, Rei Umezawa, Keiichi Jingu, Atsushi Masamune

**Abstract**

**BACKGROUND**
There has been an increasing number of elderly patients with intraductal papillary mucinous neoplasm (IPMN), who are surgically intolerant and require less invasive treatment options, which are limited. In the present study, we report a case of IPMN presenting with acute recurrent pancreatitis (ARP), in which radiation therapy effectively prevented further attacks of ARP and reduced tumor volume.

**CASE SUMMARY**
An 83-year-old man was referred to our hospital with an asymptomatic incidental pancreatic cyst. Endoscopic ultrasound imaging and magnetic resonance cholangiopancreatography revealed a multiloculated tumor in the head of the pancreas, with dilated pancreatic ducts and mural nodules. The patient was diagnosed with mixed-type IPMN, and five years later, he developed ARP. Several endoscopic pancreatic ductal balloon dilatations failed to prevent further ARP attacks. Surgery was considered clinically inappropriate because of his old age and comorbidities. He was referred to our department for radiation therapy targeted at those lesions causing intraductal hypertension and radiation was administered at a dose of 50 Gy. An magnetic resonance imaging scan taken ten weeks after treatment revealed a decrease in tumor size and improvement of pancreatic duct dilatation. Fourteen months later, he remains symptom-free from ARP.

**CONCLUSION**
This case highlights the important role of radiation therapy in mitigating the signs...
and symptoms of ARP in patients with inoperable IPMN.

Key Words: Intraductal papillary mucinous neoplasm; Acute recurrent pancreatitis; Pancreas; Radiation therapy; Case report

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Core Tip: For intraductal papillary mucinous neoplasm (IPMN) patients with symptoms of acute recurrent pancreatitis (ARP), the only therapeutic option recommended by current guidelines is surgical intervention. However, a growing number of IPMN patients require minimally invasive treatment options because of old age, systemic conditions, or personal preference. Herein, we present a case of IPMN presenting with ARP, in which radiation therapy effectively prevented further attacks of ARP and reduced tumor volume. This case highlights the important role of radiation therapy in preventing further episodes of ARP in patients with IPMN who cannot undergo surgery.

INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a cystic lesion in which mucin-producing neoplastic epithelia proliferate abnormally. IPMN is benign, but is known to have malignant potential and requires regular surveillance; surgical resection is recommended for lesions at a high risk of malignancy. High-resolution imaging technology is being increasingly used to diagnose IPMN before it manifests any signs or symptoms[1]. Most patients with IPMN are asymptomatic until malignant transformation and are eventually diagnosed with intraductal papillary mucinous cancer, which has a poor prognosis. Therefore, current efforts are focused on identifying and treating IPMNs that are at a high risk of malignancy.

Recent studies have reported that some IPMNs present with acute pancreatitis (AP) or acute recurrent pancreatitis (ARP) associated with intraductal hypertension[2]. The prevention of repetitive attacks of ARP is preferred because ARP reduces the patients’ quality of life and may lead to irreversible chronic pancreatitis[3]. The latest guidelines state that patients with IPMN and accompanying AP may undergo surgical resection for symptomatic relief[4]. However, there has been inadequate discussion regarding other treatment options when surgery is not clinically appropriate. Here, we report a case of IPMN with ARP in which radiation therapy successfully prevented further attacks of ARP and reduced the tumor volume.

CASE PRESENTATION

Chief complaints

An 83-year-old man diagnosed with IPMN was referred to our radiation oncology department because of repetitive episodes of ARP resistant to endoscopic treatment.

History of present illness

The patient visited a physician to investigate an incidentally detected asymptomatic pancreatic cyst, and was subsequently referred to our hospital for suspected IPMN. Endoscopic ultrasound (EUS) imaging and magnetic resonance cholangiopancreatography (MRCP) revealed a 30 mm multiloculated tumor, located in the head of the pancreas; the main duct had a diameter of 10 mm and the mural nodules were 8 mm in height. The patient was diagnosed with mixed-type IPMN (Figure 1).

The patient was regularly monitored for four years using imaging for signs of malignancy. During regular outpatient surveillance, gradual dilation of the main pancreatic duct to 13 mm was observed, which met the “high-risk stigmata” criteria for surgical resection, as per IPMN management guidelines [4-6]. The patient’s old age and personal preference were indicative of conservative management with follow-up and not surgical intervention. Five years after the initial diagnosis, he developed mild AP twice, but recovered with supportive measures. However, the following year, he developed ARP once a
month for three consecutive months. Several attempts at endoscopic pancreatic ductal balloon dilatation failed to prevent the recurrence of AP, and pancreatic juice samples obtained by these endoscopic procedures did not show cytological malignancy. Although international IPMN guidelines suggest surgery for symptomatic relief in pancreatitis\[4\], the surgeons who consulted with this patient concluded that pancreaticoduodenectomy would not be clinically appropriate because of his old age and comorbidities. Because the episodes of ARP in this case were mainly attributed to intraductal hypertension caused by viscous mucin-rich pancreatic juice secreted from IPMN, the patient was referred to our department for radiation therapy to reduce mucin secretion and prevent further episodes of AP.

**History of past illness**

The patient had a medical history of right lacunar infarction with residual hemiparesis, prostate cancer, colorectal polyps, nephrotic syndrome, chronic pulmonary obstructive disease, and hemorrhoids.

**Personal and family history**

He had smoked 60 cigarettes per day for 55 years, from 22 to 77 years of age.

**Physical examination**

On presentation to our outpatient clinic, the patient had no abnormal pathological signs or symptoms, including jaundice.

**Laboratory examinations**

At our radiation oncology department, laboratory tests indicated that complete blood count, C-reactive protein, liver enzymes, and pancreatic enzymes, were within the normal range.

**Imaging examinations**

One month before initiating radiation therapy, MRCP revealed a 36.5 mm multiloculated tumor in the head of the pancreas and significant pancreatic main duct dilatation (17 mm in diameter). The common bile duct was not dilated (Figure 2).

**FINAL DIAGNOSIS**

The final diagnosis in the current case was IPMN leading to episodes of ARP, which was not indicated for surgery due to the patient’s age and comorbidities.

**TREATMENT**

The patient was treated with radiation therapy at a total dose of 50 Gy in 25 fractions for 5 wk. Radiation therapy was delivered using 10 MV photon beams from a linear accelerator equipped with a multileaf collimator. Volumetric modulated arc therapy was performed to reduce acute gastrointestinal toxicity (Figure 3). The gross target volume (GTV) was defined as the IPMN lesion, and the clinical target volume (CTV) was defined as equal to the GTV. The internal target volume for GTV was contoured with reference to the respiratory movement, using four-dimensional computed tomography. The planning target volume (PTV) was defined as the CTV plus a 5 mm margin. The prescribed dose was calculated to cover 95% of the PTV.
Harigai A et al. Radiotherapy for IPMN causing AP

Figure 2 Pancreatic magnetic resonance imaging scans of pre- and post-radiation therapy. A-C: T2-weighted imaging single scans and magnetic resonance cholangiopancreatography (MRCP) taken one month before radiation therapy; D-F: Magnetic resonance imaging scans and MRCP taken three months after radiation therapy. T2WI: T2-weighted imaging; MRCP: Magnetic resonance cholangiopancreatography.

Figure 3 Computed tomography image with dose distribution of radiation therapy. A: An axial image; B: A coronal image. White, red, inner-orange, outer-orange and yellow lines show 52.5 Gy, 50 Gy, 47.5 Gy, 45 Gy and 42.5 Gy, respectively.

OUTCOME AND FOLLOW-UP
During radiation therapy, the patient reported symptoms of acute radiation toxicity such as fatigue, nausea, radiation dermatitis, and diarrhea, all of which corresponded to grades 1 and 2 of the Common Terminology Criteria for Adverse Events[7]. The patient recovered completely within six weeks after radiation therapy. Magnetic resonance imaging performed ten weeks after the initiation of radiation therapy revealed a decrease in tumor size from 36 mm to 28 mm and an improvement in pancreatic duct dilatation (Figure 2). The patient had not experienced any symptoms indicating a recurrence of AP until his last follow-up, 14 mo after the administration of radiation therapy.

DISCUSSION
To the best of our knowledge, this report presents the first case in which radiation therapy was successfully administered to a patient with repetitive episodes of ARP caused by IPMN. The patient did not report any abdominal symptoms indicative of pancreatitis for at least one year after the completion of radiation therapy. Although chemoradiotherapy has recently been recognized as an adjuvant therapy, performed after surgical resection in patients with IPMN[8], little is known about the role of radiation therapy in unresected IPMN. Kameyama et al[9] reported the case of a patient with unresectable IPMNs with suspected involvement of the superior mesenteric artery, in which chemora-
Radiotherapy successfully shrunk the tumor prior to conversion surgery. However, there have been no reports of patients with IPMN receiving radiation therapy for symptomatic relief of ARP. Jang et al.[2] reported that among 488 patients with IPMN, 34 (7%) developed AP or ARP attributable solely to IPMN. Thus, considering our aging society, our patient is a representative case of ARP caused by IPMN, for which minimally invasive therapeutic measures are preferred. We expect that the number of similar cases will increase in the near future.

Therapeutic measures for ARP attributable to IPMN have not yet been established. Only a short explanatory note on symptomatic IPMN is found at the bottom of the IPMN management algorithm in the international guidelines of IPMN, stating, “pancreatitis may be an indication for surgery for relief of symptoms”[5]. However, regardless of the type of procedure, pancreatic surgery can lead to severe complications including postoperative pancreatic fistula (POPF). POPF, which causes leakage of pancreatic juice, intraperitoneal abscesses, and lethal hemorrhage from pseudoaneurysms, has an incidence of > 10%. Patients who develop ARP due to IPMN can also be treated endoscopically, which unfortunately failed in the present case. Another previously reported treatment option for pancreatic cysts is the injection of ethanol and paclitaxel into the cystic lesion.[10]. This EUS-guided technique is undoubtedly less invasive than surgery but could potentially lead to severe complications in patients with IPMN. Because IPMN cysts directly communicate with the main pancreatic duct, post-procedural AP may occur more frequently in IPMN than in other pancreatic cystic lesions[11].

Immediately after the patient was referred to our radiation oncology department, we developed this treatment strategy by hypothesizing that an appropriate dose of radiation therapy could have an effect on abnormal mucin secretion from IPMN. Although chemoradiotherapy might have a better tumor control[9], it was not selected considering the negative cytological malignancy of the pancreatic juice, age, and comorbidities of the patient. Research on adverse late effects of radiation therapy on the pancreas has shown that pancreatic exocrine insufficiency, which could result in malabsorption, occurs at 45 Gy[12]. Recently, there was a case report describing the application of chemoradiotherapy (50.4 Gy irradiation and gemcitabine) for invasive pancreatic IPMN[13]. We set the radiation dose for this patient based on previously reported experiences. We believe that this case will help establish radiation therapy as a novel nonsurgical treatment for patients with ARP caused by IPMN. Therefore, more such cases are essential to investigate the necessary and adequate radiation dose and to establish this treatment strategy.

**CONCLUSION**

This case showed the important role of radiation therapy in recurrent episodes of ARP in patients with IPMN, who cannot undergo surgical resection.

**ACKNOWLEDGEMENTS**

The authors thank the staff of the Department of Radiation Oncology at Tohoku University Hospital for their support in this study.

**FOOTNOTES**

**Author contributions:** Harigai A, Takahashi N and Umezawa R reviewed the literature; Kume K and Umezawa R followed this case on outpatient department; Omata S and Umezawa R contributed to radiation therapy treatment planning; Harigai A, Kume K, Umezawa R, Jingu K and Masamune A contributed to manuscript drafting; and all authors issued final approval for the version to be submitted.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES


Acute respiratory distress syndrome following multiple wasp stings treated with extracorporeal membrane oxygenation: A case report

Zheng-Yin Cai, Bao-Ping Xu, Wei-Hao Zhang, Huai-Wen Peng, Qing Xu, Huai-Bin Yu, Quan-Gen Chu, Shu-Sheng Zhou

Abstract

BACKGROUND

It is necessary for clinicians to be aware of a rare but possible acute respiratory distress syndrome (ARDS) complication caused by multiple wasp stings. Severe ARDS has a high mortality rate but no specific pharmacotherapies have been identified to date. This case study presents the first case of severe ARDS caused by multiple wasp stings, treated successfully with extracorporeal membrane oxygenation (ECMO). It also emphasizes the effectiveness of early ECMO treatment for severe ARDS with persistent hypoxemia.

CASE SUMMARY

A 24-year-old woman was admitted to the emergency department after being stung by more than 10 wasps within a 30-min period, with clinical symptoms of multiple rashes, dizziness, chest tightness, nausea, and vomiting. On the 2nd day of admission, the patient developed progressive dyspnea. The patient was diagnosed with ARDS based on clinical manifestations and lung computed tomography (CT) scan. Because of the progressive dyspnea, the intensive care unit physician performed endotracheal intubation and continued to provide ventilator support, but the patient’s respiratory distress worsened, as indicated by the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen. Veno-venous ECMO was initiated for 6 d. On day 7 of admission, ECMO was stopped. On the 11th day of admission, CT scan of the lungs revealed significant reduction of ground-glass opacities and consolidations. After about 2 wk, the patient recovered.
 completa from ARDS and was discharged to home. At the 2-mo follow-up, the patient was in good health with no recurrence of dyspnea nor chest tightness.

CONCLUSION
ARDS complication caused by multiple wasp stings may be fatal when mechanical ventilation becomes dangerous due to persistent hypoxemia and despite optimization of ARDS management. We propose that the early implementation of ECMO is a relatively effective treatment, although the evidence is relatively limited.

Key Words: Wasp; Bites and stings; Respiratory distress syndrome; Persistent hypoxemia; Extracorporeal membrane oxygenation; Case report

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INTRODUCTION
Although involvement of the respiratory system is a common clinical manifestation of multiple wasp stings, rapid progression to severe acute respiratory distress syndrome (ARDS) is rare. Severe ARDS has a high mortality rate; however, to date, no specific pharmacotherapies have been identified and treatment is focused on lung-protective ventilation[1]. Extracorporeal membrane oxygenation (ECMO) is a treatment in which blood is circulated outside the body to be oxygenated on a gas-permeable membrane. It has been shown to improve survival rates and outcomes in patients with severe ARDS in critical care settings[2,3], particularly in patients who have severe ARDS within the 1st week of mechanical ventilation and do not have multiple organ failure[4,5]. However, ECMO is also an invasive, costly and high-risk treatment, with complications such as thrombocytopenia and bleeding[6].

There is no evidence in the literature of the ECMO treatment of ARDS nor respiratory failure caused by wasp stings. This case study presents the first case of severe ARDS caused by multiple wasp stings, treated successfully with ECMO. It also emphasizes the effectiveness of early ECMO treatment of severe ARDS with persistent hypoxemia.

CASE PRESENTATION

Chief complaints
A 24-year-old woman was admitted to the emergency department (ED) after being stung by more than 10 wasps within a 30-min period.

History of present illness
After being stung, the patient had clinical symptoms of multiple rashes, dizziness, chest tightness, nausea, and vomiting. She was conscious and no other abnormalities were found.

History of past illness
The patient had no known or documented allergies.

Personal and family history
The patient’s personal and family history was unremarkable.
Physical examination
On clinical examination, the patient had a pulse of 120 beats/min, blood pressure of 84/56 mmHg (1 mmHg = 0.133 kPa), respiratory rate of 25 breaths/min, and pulse oximetry of 98% in room air. She had no cardiac murmurs or wet rales. Other than rash and erythema on her neck, chest and upper extremities, no other abnormalities were found on systemic examination.

Laboratory examinations
The patient's biological tests (including blood routine, markers of coagulation, liver and kidney functions, myocardial enzyme spectrum, and electrolytes) were normal.

Imaging examinations
The electrocardiogram revealed sinus tachycardia, without any signs of ischemia. Computed tomography (CT) scan of the lung revealed no abnormalities.

FINAL DIAGNOSIS
Anaphylactic shock caused by severe bee stings.

TREATMENT
The stingers were removed first, and the treatment then begun with adrenaline [0.5 mg intramuscular (IM)], methylprednisolone [80 mg intravenous (IV)], promethazine (25 mg IM), and omeprazole (40 mg IV). Three hours after admission, the patient's condition began to deteriorate and the chest tightness and pain worsened. Arterial blood gas analysis showed pH 7.36, partial pressure of oxygen (PaO₂) 50 mmHg (on 40% fraction inspired oxygen), partial pressure of carbon dioxide (PaCO₂) 40.2 mmHg, and bicarbonate 22.7 mmol/L. She was admitted to the intensive care unit (ICU), and noninvasive mechanical ventilation was started. IV adrenaline [0.5 mg/every 4 h (q4h)], promethazine (25 mg/d), and dexamethasone (10 mg/q12h) were administered, and continuous hydration infusions and other symptomatic treatment were also given.

On the second day of admission, the patient developed progressive dyspnea. CT scan of the lung (Figure 1A) revealed a small pleural effusion and bilateral lung multifocal ground-glass opacity. The ICU physician performed endotracheal intubation and continued to provide ventilator support. Subsequently, fiberoptic bronchoscopy examination revealed tracheal mucosal edema and congestion with foamy sputum in the main bronchial lumens but no obvious bleeding. Six hours after tracheal intubation, the patient’s respiratory distress worsened, with PaO₂/FiO₂ ratio of 39. Physicians decided to place the patient on veno-venous ECMO for 6 d. ECMO support was initiated with a blood flow of 3.0 L/min and a purge gas flow rate of 3 L/min. Ventilatory settings were adjusted to volume-controlled ventilation of 6 mL/kg ideal body weight, positive end-expiratory pressure of 8 cmH₂O, peak inspiratory pressure of 40 cmH₂O, respiratory rate of 20, and fraction of inspired oxygen of 100%. With minimal mechanical ventilation, the patient achieved stability, with a pulse rate of 84 beats per min and pulse blood oxygen saturation of 98%.

On the 7th day, ECMO was stopped, and the patient felt well and was clinically stable. CT scan of the lungs (Figure 1B and C) revealed large multiple patchy ground-glass opacities with consolidation, and a possible large pleural effusion in both lungs. As a result, the patient underwent closed thoracic drainage of hydrothorax. On the 11th day, CT scan of the lungs (Figure 1D) revealed significant reduction of ground-glass opacities and consolidations. However, the patient developed right pneumothorax with lung compression greater than 50%, necessitating treatment of the right lung with closed thoracic pneumothorax drainage.

OUTCOME AND FOLLOW-UP
On the 14th day, chest CT (Figure 1E) revealed that the pneumothorax had disappeared, and the patient was discharged to home. At the 2-mo follow-up visit, the patient was in good health, with no recurrence of dyspnea nor chest tightness.

DISCUSSION
In China’s vast hilly areas, wasp stings are one of the most common emergencies in the emergency departments of hospitals. They are also one of the environmental accidents that seriously threaten
human health. Some patients with wasp stings present with local hypersensitivity; however, a small number of patients develop multisystem involvement due to multiple stings[7]. The clinical manifestations of wasp stings differ, depending on the victim’s sensitivity to the venom and the number of stings received[8]. Symptoms associated with wasp sting range from simple papular urticaria and subcutaneous angioedema to skin necrosis, throat edema, severe anaphylaxis shock, and multiple organ dysfunction involving the kidney, heart, central nervous system, liver, respiratory system, and coagulopathy, all of which can be fatal[7,9]. It is critical to completely assess the patient’s condition, including the number of wasp stings, severity of the allergic reaction, any associated multiple system damage, and the need for cardiopulmonary resuscitation. Epinephrine is the medication of choice for the initial treatment of anaphylaxis following multiple wasp stings, and if administered promptly, can be lifesaving.

The pathogenesis of ARDS after wasp stings is poorly understood. Wasp venom is a well-known natural complex toxic mixture of polypeptides, enzymes, histamine, hyaluronic acid, and phospholipase A2[10]. Melittin, the main lethal component of wasp venom, affects membrane integrity[11]. In conjunction with melittin, the higher molecular weight enzyme phospholipase A2 acts as a cytolytic agent, causing tissue damage such as intravascular hemolysis, rhabdomyolysis, and acute lung injury[10]. Wasp venom can initiate a series of immune responses and even severe envenomation syndrome in the human body, resulting in the massive release of various cytokines and acute inflammatory storm[10]. These inflammatory factors can cause tissue and organ damage, including the respiratory system.
Wasp venom is a complex neuromuscular blocking agent, and its active substance can affect acetylcholine synthesis and release. It has a direct toxic effect on the membrane voltage of the striated muscle sodium ion channel, which can cause respiratory muscle paralysis and respiratory failure[11,13].

Despite some improvements, mortality from ARDS, particularly severe ARDS, remains a severe threat[1]. To date, no specific pharmacotherapies have been identified, and treatment is focused on lung-protective ventilation[1]. Physicians should strongly consider ventilation in a prone position when persistent hypoxemia cannot be relieved in ARDS patients with a PaO$_2$/FiO$_2$ ratio of < 150. It is also effective in patients with acute hypoxic respiratory failure without intubation[6]. Despite optimized standard therapies such as neuromuscular blockade with deep sedation and prone positioning for the previous 24 h, some patients continue to deteriorate clinically. ECMO is a treatment in which blood is circulated outside the body to be oxygenated on a gas-permeable membrane. It has been shown to improve survival rates and outcomes in patients with severe ARDS in critical care settings[2,3], particularly in patients who have severe ARDS within the 1st week of mechanical ventilation and do not have multiple organ failure[4,5].

There is no evidence in the literature of treatment of ARDS nor respiratory failure caused by wasp stings with ECMO. In the present case, despite receiving mechanical ventilation and other optimized standard therapies at an early stage, the patient’s respiratory status continued to rapidly deteriorate. ECMO treatment was started after she passed a comprehensive health assessment, and rapid improvement in the patient’s condition was observed. Thus, when mechanical ventilation becomes dangerous for patients with ARDS following multiple wasp stings due to persistent hypoxemia and despite optimization of ARDS management, we propose that the early implementation of ECMO is a relatively effective treatment, although the evidence is relatively limited[14,15].

CONCLUSION

Patients with multiple wasp stings need early assessment and treatment by emergency care physicians to reduce subsequent organ dysfunction, in order to shorten the disease course and improve the prognosis. Rapid progression to severe ARDS after wasp stings is rare, and severe ARDS has a high mortality rate. When mechanical ventilation becomes dangerous in patients with ARDS following multiple wasp stings due to persistent hypoxemia and despite optimization of ARDS management for the previous 24 h, we propose that the early implementation of ECMO is a relatively effective treatment, although the evidence is relatively limited.

FOOTNOTES

Author contributions: Cai ZY and Xu BP conceived and designed the study; Peng HW and Yu HB provided administrative support; Xu Q and Zhou SS provided the study materials or patient care/data; Zhang WH and Chu QG collected the data; Xu BP conducted the data analyses and interpretation; all authors contributed to the manuscript writing and gave final approval of the manuscript.

Informed consent statement: Informed and written consent was obtained from the patient to use his clinical information and data.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM
REFERENCES


Morphological and electrophysiological changes of retina after different light damage in three patients: Three case reports

Xi Zhang, Tao Luo, Yan-Rong Mou, Wei Jiang, Yan Wu, Heng Liu, Yi-Ming Ren, Pan Long, Fei Han

BACKGROUND

Light-induced retinal damage is a serious vision-threatening disease, resulting from unsuitable laser irradiation, high-power light and sustaining light exposure. Therefore, effectively evaluate the morphological and functional of retinal damage is urgently needed. Now, we mainly reported three patients suffered from typical light irradiations.

CASE SUMMARY

Patient 1 suffered from old laser pointer irradiation and followed with amblyopia treatment. Patient 2 suffered from acute high-energy light irradiation. Patient 3 suffered from sustaining optical fiber irradiation. Detailed morphological and functional examinations of the retina revealed that the lesions of the three patients had many similar characteristics, such as macular morphological changes, patent pattern visual monitoring amplitude or peak time abnormalities, multi-focus electroretinograms macular central amplitude density decreased.

CONCLUSION

In conclusion, light-induced retinopathy has many common features, which can help clinical medical staff to diagnose retinal photodamage diseases.

Key Words: Light-induced retinopathy; Diagnosis; Morphology; Electrophysiology; Case report

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Core Tip: In this case report, we reported three typical cases of retinal damage caused by light-related irradiations. Through the summary of their common characteristics, we can deepen the understanding of retinal diseases caused by light irradiation, and provide theoretical basis for the prevention, clinical diagnosis and treatment of such diseases.

URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11128.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11128

INTRODUCTION

No matter in the living environment or working environment, people must be exposed to a variety of light sources. Prolonged and continuous exposure or accidental exposure to strong light often causes serious damage to the eyes, some of which are even irreversible[1,2]. Generally speaking, there are two aspects of light damage in the human eye, including the damage of the refractive system (cornea, lens, etc.) and the photosensitive system (retina). For example, some studies have found that the electric light generated in the welding process can directly lead to corneal epithelial necrosis, resulting in acute electro-ophthalmia[3]. Some researchers also found that the incidence of cataract increases significantly after long-term ultraviolet irradiation[4,5]. Moreover, long-term blue light irradiation can directly damage the macula through photochemical effect[6].

Remarkably, retinal damage is often the most common, but also relatively serious in the process of light damage to the eye[7]. Recent studies found the case of a 13-year-old boy looking at a green diode laser with an average output of 154 MW reflected in a mirror. Fundus examination and auxiliary examination showed fracture macular thermal damage[8]. In addition, Turaka et al[9] reported a case of macular photodamage and made a mini-review. In the article, the authors cited a report from the Food and Drug Association, which stated that handheld laser Pointers emitting > 5 mW of power carry the risk of irreversible eye damage and skin burns. Alsulaiman SM reported the natural history and treatment outcomes of full-thickness macular holes caused by transient exposure to high-power handheld blue laser devices and concluded that transient exposure to high-power handheld laser devices can result in full-thickness macular holes[10].

In this case reports, we reported three typical cases of retinal damage caused by light-related irradiation. Through the summary of their common characteristics, we may deepen the understanding of retinal diseases caused by various light irradiation, and provide theoretical basis for the prevention, clinical diagnosis and treatment of such diseases.

CASE PRESENTATION

Chief complaints

Patient 1: A 13-year-old female student who was in amblyopia treatment process for one year. However, her vision acuity didn’t benefit from the treatment and her parents asked us to perform total ophthalmological examination to make a decision whether to continue the amblyopia treatment or not.

Patient 2: A 22-year-old male soldier whose right eye was instantaneous irradiated by high energy flashlight one month ago. He didn’t pay close attention to it at that time. Then, his right eye vision decreased 5 d later without photophobia, tears, eye pain and other symptoms. No remission was found after self-administration of eye drops (unknown details). Therefore, he went to our hospital for further treatment.

Patient 3: A 33-year-old male communications engineer was in a history of physical fitness. Half a year ago, his left eye vision decreased without obvious photophobia, tears and eye pain. Although he found symptoms, he did not receive treatment. Recently, he went to our hospital and complained his vision decreased significantly.

History of past illness

Patient 1: There was a history of laser pointer exposure.

Patient 2: His right eye was instantaneous irradiated by high energy flashlight one month ago.
Figure 1 Retinal morphologic examination. A: Fundoscopy revealed an irregular scar-like lesion in the macular of the right eye; B: Autofluorescence found a heterogeneous dark signal in the macular of the right eye; C: Fluorescein angiography revealed strong fluorescence leakage around the right eye macular; D: Optical coherence tomography (OCT) revealed a deficiency in the center of the fovea; E: OCT showed retinal pigment epithelium layer breakdown and macular thinning.

Patient 3: He had a long-term history of fiber-optic operation.

Physical examination

Patient 1: Then vision examination found the best corrected vision acuity (BCVA) was 1.0 in the right eye, and 0.4 in the left eye. In addition, the anterior segment was normal and the refractive medium was transparent in both eyes. Funduscopic and auto-fluorescence examination of left eye revealed a rough and uneven abnormality of macular (Figure 1A and B).

Patient 2: Specialist examination displayed that the patient’s BCVA was 0.3 in the right eye and 1.0 in the left eye. The anterior segment was normal and the refractive medium was transparent in both eyes.

Patient 3: Specialist examination found that the patient’s BCVA was 1.0 in the right eye and 0.6 in the left eye. The anterior segment was normal and the refractive medium was transparent in both eyes.
Figure 2 Electrophysiological examinations of retina. A: Patent pattern visual monitoring (PVEP) examination revealed that the amplitude of P100 of PVEP was reduced in the left eye (a1, a2 and a3 correspond to stimulation frequencies of 0.5 cpd, 1 cpd and 2 cpd, respectively); B: Multi-focus electroretinograms examination showed that the amplitude density of macular center was decreased in the left eye.

**Imaging examinations**

**Patient 1:** Angiography found a hyper-fluorescence feature and no fluorescent leakage at left eye macular (Figure 1C). Optical coherence tomography (OCT) showed that the macular had scar-like injury involving retinal pigment epithelium (Figure 1D and E). Meanwhile, the visual electrophysiological results indicated that the amplitude of P100 of pattern visual evoked potentials (PVEP) was reduced (Figure 2A), and full field electroretinogram (ffERG) was normal, and the amplitude density of multi-focus electroretinograms (mfERG) macular center decreased (Figure 2B).

**Patient 2:** Funduscopic and auto-fluorescence examination of right eye revealed a black shape punctuation abnormality surrounded with a ringlike margin lesion (Figure 3A-D). Angiography (FFA + ICGA) found a macular hyper-fluorescence leakage around a black shape punctuation at right eye (Figure 3E and F). OCT showed that the macular cystoid edema was significant, retinal pigment epithelium (RPE) layer of centra macular site was broken and choroidal neovascularization (CNV) was
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Zhang X et al. Characteristic of light-induced retinopathy

Figure 3 Retinal morphologic examinations. A-D: Funduscopic and auto-fluorescence examination revealed a black shape punctuation abnormality surrounded with a ringlike margin lesion in the right eye; E and F: Angiography (FFA + ICGA) found a macular hyper-fluorescence leakage around a black shape punctuation at right eye; G: Optical coherence tomography (OCT) revealed the macular fovea thickness increased; H: OCT showed the macular cystoid edema, retinal pigment epithelium layer breakdown and choroidal neovascularization in the right eye.

found in the right eye (Figure 3G and H). Meanwhile, the electrophysiological results showed that the amplitude of P100 of PVEP in right eye declined while the peak time was delayed (Figure 4A). FVEP and ffERG were normal, and the amplitude density of mfERG macular center was decreased (Figure 4B).

Patient 3: Funduscopic and auto-fluorescence examination of left eye revealed a blurred margin macular abnormality (Figure 5A and B). OCT discovered that the macular of left eye became more thinner, and the retinal pigment epithelium did not change significantly compared with right eye (Figure 5C). The visual electrophysiology indicated that the P100 amplitude of PVEP reduced in the left eye, while the function of ffERG cone cell system and the amplitude density of mfERG macular center decreased (Figure 6).

FINAL DIAGNOSIS

Patient 1
We made a diagnosis of old retinal injury induced by laser.

Patient 2
We made a diagnosis of acute retinal injury induced by strong-energy light irradiation.

Patient 3
We made a diagnosis of chronic retinal injury induced by sustaining light irradiation.

TREATMENT

Patient 1
We suggested to stop the treatment of amblyopia.

Patient 2
For patients with CNV, we made anti VEGF treatment, at present vision improved with right eye vision 0.5.

Patient 3
This patient need no further treatment and we suggest to make a safety goggles when working.
When retina is irradiated by light under normal physiological conditions, part of the photon energy is absorbed by the photoreceptor cells. Moreover, the rest of extra photons are absorbed by the retinal pigment epithelium or choroid to avoid heat accumulation\cite{11,12}. However, due to the direct effect of light energy, photoreceptor cells and RPE are also the most vulnerable tissues when the light irradiates abnormally\cite{13}. Moreover, animal study found müller glia cell activation participated in a laser-induced retinal degeneration and regeneration in zebrafish\cite{14}. During COVID-19 pandemic, researchers found retinas damages could be related with Neuropilin-1\cite{15}. At present, studies have indicated that various types of light stimulation, such as ultraviolet, blue light and laser could damage the retina through photochemical reaction, photothermal effect and photomechanical effect\cite{16-18}. As its biological effects can be accumulated, retinal injury can be caused by multiple irradiations, which can display the characteristic that the boundary of the damage area is clear in the early stage and fuzzy in the later stage\cite{19}.

**DISCUSSION**

Figure 4 Electrophysiological examinations of retina. A: Patent pattern visual monitoring (PVEP) examination showed that the amplitude of P100 of PVEP declined while the peak time was delayed in the right eye; B: Multi-fucus electroretinograms examination showed that the amplitude density of macular center was decreased in the right eye.
Figure 5 Retinal morphologic examinations. A and B: Fundoscopic and auto-fluorescence examination revealed a blurred margin macular abnormality of the left eye; C: Optical coherence tomography showed that the macular of left eye became thinner.
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Figure 6 Electrophysiological examinations of retina. Multi-focus electroretinograms examination showed that the amplitude density of macular center was decreased in the left eye.

In the cases, we observed three typical patients suffering from light-induced retinopathy.

In the first case, this young female patient received amblyopia treatment for one year and didn’t improve vision acuity. When retina related morphological and functional examinations were applied, we realized that this could be old laser-induced retina damage. Then the patients bring to mind that she was exposed to laser pen irradiation when played with classmates. Her left eye was found obvious pigmented scar in the macular region, which may be related to the proliferation and repair of peripheral RPE\(^\text{[20]}\). Angiography revealed that there were obvious round fluorescent defects at the corresponding lesion area of retina, which may be due to laser induced occlusion of retinal and choroidal vessels in macula, and then fluorescence perfusion defect. OCT showed that the outer nuclear layer of macular area was destroyed, resulting in the corresponding retinal layer continuity was disrupted. Consistent with the morphological results, electrophysiological results showed that the function of macula was significantly impaired, and the peripheral retina was not significantly abnormal.

In the second case, the soldier’s right eye vision acuity decreased after being exposed to instantaneous strong LED light. Because the high-energy visible light in the LED lamp is mainly blue light, fundus color and AF showed there was disorder of pigment in RPE of macular. The electrophysiological results indicated that there was no obvious abnormality in the peripheral retina of right eye, but the retinal function in the macular area was significantly damaged and the conduction function of optic nerve may be also affected to some extent.

In the third case, the patient is a middle-aged man who has been engaged in optical fiber work for a long time, mainly exposed to ultraviolet and blue light. Due to improper daily protective measures, visual acuity was obviously injured. Fundus examination showed that the patient’s macular in retina became thinner, which may be caused by the shortening of outer segment of photoreceptor or the detachment and disappearance of photoreceptor under long-term light stimulation resulting in thinning of the outer nuclear layer. In addition, RPE also showed atrophy and thinning after light injury. Similar to the previous two patients, this patient’s electrophysiological examination indicated that there is significant impairment of macular function.

Through the three cases, it can be found that the above three patients have a clear history of light damage. No matter what kind of light source equipment they experience, the macular of patients presents different forms of pathological lesion, especially in the outer nuclear layer where photoreceptor and RPE are located. In our cases, we found that retinopathy caused by light damage has similar morphological and functional characteristics. Specifically, the morphological changes were mainly pathological changes related to retinal pigment epithelium and photoreceptor, and the physiological function changes were largely associated with the decline of macular function. In terms of electrophysiological function, visual electrophysiology could easily assess majority light-induced macular injuries, including old cumulative asymptomatic damages, acute symptomatic damages and chronic
occupational exposure.

CONCLUSION
We identified children, military personnel and optical fiber communicators are likely to suffer from retinal damage caused by light. Commonly, children are often misdiagnosed as amblyopia. The degree of lesions is related to the energy and duration of light irradiation, and is often manifested as macular thinning, interruption of RPE continuity, CNV and other manifestations. The amplitude changes of PVEP are common in acute high-energy injuries, and fERG usually is normal. For long-term low energy sustained injury, PVEP amplitude is decreased and fERG cone system is decreased, too. No matter what kind of light damage, the amplitude density of mfERG in macular center is decreased.

ACKNOWLEDGEMENTS
We thank each author who contributed to this paper.

FOOTNOTES
Author contributions: Wu Y and Han F contributed to data collection and interpretation; Zhang X and Long P participated in writing the manuscript; Jiang W gave critical comment; Mou YR, Luo T, Liu H, and Ren YM participated in examining the patients and obtaining data; all authors read and approved the final manuscript.

Supported by the National Nature Science Foundation of China, No. 82001484.

Informed consent statement: Informed written consent was obtained from the patients for the publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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L-Editor: A
P-Editor: Zhang XD

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Perirectal epidermoid cyst in a patient with sacrococcygeal scoliosis and anal sinus: A case report

Zhou-Xin Ji, Song Yan, Xu-Can Gao, Li-Fen Lin, Qiang Li, Qi Yao, Dong Wang

Abstract

BACKGROUND

Perirectal epidermoid cysts are rare masses arising from the ectodermal germ cell layer of the hindgut and are predominantly found in middle-aged women. It is often difficult to make an accurate diagnosis of these cysts and it is equally challenging to distinguish it from other developmental cysts.

CASE SUMMARY

We report the case of an 18-year-old female patient with a perirectal mass who presented to the hospital with constipation. The patient experienced sacrococcygeal falls and burns on the left buttocks during growth. Three-dimensional computed tomography scans indicated abnormal sacral vertebrae with the sacral canal partially enlarged and opened. Pelvic magnetic resonance imaging showed a 55 mm × 40 mm × 35 mm unilocular cystic mass in the perirectal space and a solitary sinus in the left ischiorectal fossa. The cyst was completely resected posteriorly using the sacrococcygeal approach. The pathology was verified to be an epidermoid cyst. The patient remained recurrence-free after 6 mo of follow-up.

CONCLUSION

Successful treatment of perirectal epidermoid cysts depends on comprehensive evaluation. This is significant for the surgical approach and prognosis.

Key Words: Perirectal mass; Epidermoid cyst; Surgery; Anal sinus; Case report

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Core Tip: Perirectal cystic mass is a rare congenital developmental abnormality. An 18-year-old female was found with a perirectal mass due to defecation difficulties. She had suffered from sacrococcygeal falls and burns on the left buttocks during the growth experience. We performed a complete preoperative evaluation of this patient. Three-dimensional computed tomography scans showed that there was no damage to the sacral surface bone. Pelvic magnetic resonance imaging showed that the perirectal mass had a complete membrane without enhancement signs and no potential connection with the perianal sinus and sacral canal. Finally, the mass was completely removed through the sacrococcygeal approach and verified as an epidermoid cyst in histology. This case highlights the need to improve evaluation in the differential diagnosis of perirectal mass.

Citation: Ji ZX, Yan S, Gao XC, Lin LF, Li Q, Yao Q, Wang D. Perirectal epidermoid cyst in a patient with sacrococcygeal scoliosis and anal sinus: A case report. World J Clin Cases 2022; 10(30): 11139-11145

URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11139.htm

DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11139

INTRODUCTION

Epidermoid cysts are commonly found in different parts of the body; however, perirectal epidermoid cysts are extremely rare. Perirectal cysts are congenital abnormalities considered to originate from caudal embryonic vestiges\[1\]. Perirectal epidermoid cysts occur mostly in middle-aged women; however, they are rare in younger women\[2\]. An abnormal mass in the pelvic floor space is often incidentally discovered during routine examinations. Most patients with perirectal cysts do not exhibit clinical symptoms. However, some patients may present with non-specific symptoms resulting from the compression of adjacent tissues, including urinary retention, constipation and a palpable mass near the anus\[3\]. To help improve clinical diagnostic strategies and prevent misdiagnoses of the condition, we report a rare case of a perirectal epidermoid cyst occurring in a younger female.

CASE PRESENTATION

Chief complaints
An 18-year-old female patient presented to the clinic with a complaint of constipation.

History of present illness
The patient had difficulty in evacuating her bowels for 2 mo.

History of past illness
Three months after birth, the patient suffered from sacrococcygeal deformity due to an accidental fall and underwent an imaging examination at the local hospital without any therapy. At age five, her left buttock was scalded with boiling water.

Personal and family history
The patient had no family history of inflammatory bowel disease or hereditary tumors.

Physical examination
No abnormalities were found upon abdominal examination. Her buttocks were asymmetrical with irregular scar hyperplasia and shrinkage observed at the four o’clock position, which was approximately 3 cm away from the anal opening. Physical examination revealed a soft, mobile and poorly circumscribed mass without tenderness in the right perirectal region. The sacrum and coccyx were displaced to the right. Digital rectal examination revealed a bulge in the retrorectal area resulting in mild stenosis of the lumen (Figure 1).

Laboratory examinations
Laboratory test results were normal.

Imaging examinations
Colonoscopy revealed a slight stenosis of the area between the rectum and anal canal without erosion, ulceration or tumor formation. Three-dimensional (3D) computed tomography (CT) revealed abnormal sacral vertebrae with the sacral canal partially enlarged and opened. No destruction of the local sacral
bone was observed (Figure 2). Magnetic resonance imaging (MRI) revealed a 55 mm × 40 mm × 35 mm well-circumscribed unicameral cystic mass in the pelvis that adhered to the left rectal wall posteriorly to the sacrum resulting in a right anterior displacement of the rectum. The vaginal wall was compressed and wrinkled (Figure 3). Enhanced strips in the scan extended from the levator ani muscle to the skin of the left buttock (Figure 4). Based on the MRI findings, preoperative diagnoses included a presacral epidermoid cyst, anal sinus and sacrococcygeal scoliosis.

**FINAL DIAGNOSIS**

The cystic mass was identified to be an epidermoid cyst.

**TREATMENT**

The cystic mass did not affect the patient’s spine and the sinus in her left buttock showed no signs of infection. Complete surgical excision was performed using the posterior transsacrococcygeal approach. The patient was placed in the jackknife position after spinal anesthesia. A longitudinal median incision was made over the mass of the body surface on the left side of the coccyx. The skin, subcutaneous tissue, fat layer and levator ani muscle were cut layer by layer to reveal the space of pelvic floor. The cystic mass was firmly attached to the puborectalis and left posterior wall of the lower rectum. Using both blunt and sharp dissection to carefully dissect the surrounding anatomical structures, the cyst was completely excised. The cyst measured 55 mm × 40 mm × 35 mm and was filled with a soybean curd residue-like material. The rectum was confirmed to be intact by using an intraoperative anoscope. The space of the pelvic floor was stitched into layers with a drainage tube left in situ. Histologically, the cystic cavity was covered with squamous epithelium and composed of gray and white cheese-like layered keratinocytes mixed with exfoliated broken epidermal cells, keratin and cholesterol.

After surgery, the patient was hospitalized for purgative and preventive antibacterial treatment. We changed the dressing after defecation twice daily. The patient was discharged 2 wk after the surgery with a drain and the stitches were removed.

**OUTCOME AND FOLLOW-UP**

Six months after surgery, the patient remained recurrence-free.

**DISCUSSION**

The presacral space is a triangular space between the posterior sacrum and anterior rectum that is bounded by the peritoneal reflection superiorly and levator ani muscles inferiorly[4]. Developmental cystic masses arising from the presacral space include several kinds of tumors including dermoid cysts, epidermoid cysts, chordomas, adrenal rest tumors, anterior sacral meningoceles, cystic hamartomas, tailgut and rectal duplication cysts[5]. Epidermoid cysts in the presacral space are uncommon with an incidence of 1 in 40000-63000 hospital admissions and 60% of perirectal epidermoid cysts are congenital...
Perirectal epidermoid cysts are typically slow-growing; approximately 26%-50% of patients are asymptomatic and they are usually incidentally discovered during imaging[7]. Compression of pelvic structures by an enlarging cyst may present with urinary complaints, constipation, perianal pain or a palpable mass in the preoccipital region. When there is an infection, these masses may result in perianal discharge, fistulous opening and bleeding in the rectum. Although epidermoid cysts are common developmental cysts[6].
skin lesions, they rarely develop into squamous cell carcinomas. Malignant tumors arising from epidermoid cysts are reported to appear at a rate of 0.011%-2.2%. The exact pathogenesis of epidermoid cysts becoming malignant tumors remains unclear. However, the disease progression may be attributed to chronic inflammatory responses to repeated cyst ruptures and a subtotal resection of the cyst wall.

Elevated levels of AFP or HCG may be indicative of germ cell tumors. Colonoscopy may reveal extrinsic rectal compression and exclude intestinal space-occupying lesions. Transrectal ultrasonography may be useful for assessing the location and extent of small cystic masses and their connection with the anal sphincter. CT examination clearly showed bone destruction by malignant presacral masses. MRI is superior to CT in differentiating between any bone, spinal canal or meningeal involvement and its relationship with surrounding soft tissues and organs to determine the appropriate surgical plan. Although infections, hemorrhages or calcifications in these lesions may alter the signal intensity, subtle changes in the signal intensity favor epidermoid cysts. However, these findings are not specific. Except for suspicious cancerous lesions, preoperative biopsy should not be performed to prevent tumor dissemination, abscess, fecal fistula or meningitis.

Choosing a surgical plan for presacral tumors largely depends on the tumor’s location, size and relationship with surrounding tissues and organs. Common surgical approaches are transsacroccygeal, transabdominal, transspincter and combined transabdominal and transsacral approaches. If the mass is small (≤ 10 cm), located at the caudal level (below S4) and does not invade surrounding structures, the sacral approach is usually adopted. When the mass is located at a high spinal level (above S3), the transabdominal approach is a better option. When the mass is large, its location near surrounding organs such as the ureter and iliac vessels is unclear and it is difficult to employ a single approach; thus, the combined abdominal sacroccygeal approach can be selected. The sphincter approach is an option for patients with small, low-lying lesions. Gynecologists choose the transvaginal approach because it provides a sufficient field of vision, shorter operative time and lower blood loss in low-lying retrorectal lesions.

The differential diagnoses of perirectal cystic lesions include tailgut cysts, cystic teratomas, chordomas and anterior sacral meningoceles. In female patients, a high (in terms of location) perirectal mass is misdiagnosed as ovarian cystadenoma. The unique feature of this case is that a perirectal mass with perianal sinus and sacroccygeal malformation was found in a young female patient. To accurately determine the extent of the mass lesion and rule out other pathologies, the patient underwent several imaging examinations. MRI revealed a solitary abscess in the left ischiorectal fossa which had no sinus interacting with the presacral mass. Given the patient’s history of scalding, sterile necrotic tissue may have accumulated in the perianal sinus. Three-dimensional CT scans revealed an abnormal sacral vertebra with the sacral canal partially enlarged and opened; however, there was no damage to the sacral surface bone. The wall of the cyst was remote from the sacral canal, the opened sacral canal was at the S3 Level and the cyst was below S4. Evidence of an anterior sacral meningocele is insufficient. Although extremely rare, benign cysts can also progress into malignant tumors. This case highlights the importance of pre-operative imaging and evaluation to identify the nature of the presacral mass which is crucial for surgery and prognosis.

Laparoscopic surgery is an option because of its minimal invasiveness, low risk of complications and complete tumor removal. Considering that the patient was a young female who had not given birth, surgery was performed using the transsacroccygeal approach to avoid damaging the pelvic organ. During surgery, we cut the cystic mass to reduce its volume for a larger operative space. In cases of suspected malignant tumors, it should be carefully stripped along the capsule to prevent rupture and metastasis. In this regard, the importance of preoperative differential diagnosis is emphasized.

CONCLUSION

Distinguishing an epidermoid cyst from other perirectal cystic masses is a significant diagnostic challenge. The clinical manifestations of presacral masses vary and once found, colonoscopy, sacroccygeal CT and pelvic MRI findings should be further evaluated. Using the tumor’s location, size and relationship with the surrounding organs, an appropriate surgical plan should be selected.

ACKNOWLEDGEMENTS

We would like to thank Dr. He De, a chief physician from General Surgery, The Second Affiliated Hospital of Shenzhen University, Shenzhen, China.
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FOOTNOTES

Author contributions: Yao Q was the first to treat patients in the clinic, Yan S and Ji ZX were involved in managing the patients and assisting in the operation; Wang D was the main surgeon; Ji ZX prepared the manuscript and drafted it; Lin LF and Li Q prepared the images; Wang D revised the manuscript and is the corresponding author; All authors contributed to the article and approved the submitted version.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors have no conflict of interest, financial or otherwise.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Synchronous gastric cancer complicated with chronic myeloid leukemia (multiple primary cancers): A case report

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Abstract

BACKGROUND
With the advancement of medical technology and improvement in living standards, the incidence of multiple primary cancers has gradually increased. In particular, tumors of the digestive system account for a large proportion of multiple primary cancers. The diagnosis and treatment of chronic myeloid leukemia, particularly with synchronous gastric cancer, at the first consultation is relatively rare.

CASE SUMMARY
Herein, we present the case of a middle-aged man who was referred to the Department of Hematology owing to an elevated white blood cell count. After the examination, he was diagnosed with chronic myeloid leukemia and was administered imatinib. Three months after the initial diagnosis, he visited our hospital again for abdominal pain, and further examination revealed gastric malignancy. After discussion with a multidisciplinary team, S-1 (Tegafur, Gimeracil, and Oteracil Potassium Capsules) combined with oxaliplatin—SOX regimen—was initiated. Later, the patient’s condition rapidly progressed. He developed colonic obstruction and underwent an ostomy; however, he died less than 6 months after the initial diagnosis.

CONCLUSION
Multiple primary cancers are influenced by environmental and genetic factors; a standardized multidisciplinary discussion plays a key role in treatment.

Key Words: Multiple primary cancers; Gastric cancer; Leukemia; Leukemia inhibitory factor; Case report
Core Tip: Digestive system tumors consist of a large proportion of multiple primary cancers. In this study, we present the case of a patient with gastric cancer and concomitant chronic myeloid leukemia. To better diagnose and treat such patients, we reviewed the literature available on leukemia complicated by gastric cancer-related multiple primary cancers and analyzed its disease mechanisms, clinical symptoms, and treatment alternatives. This study will be a useful reference for the diagnosis and treatment of patients with such conditions.

Citation: Zhao YX, Yang Z, Ma LB, Dang JY, Wang HY. Synchronous gastric cancer complicated with chronic myeloid leukemia (multiple primary cancers): A case report. World J Clin Cases 2022; 10(30): 11146-11154
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11146.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11146

INTRODUCTION

Among malignant tumors, gastric cancer has the highest morbidity and mortality. Patients with early gastric cancer often exhibit no overt symptoms, whereas those with advanced gastric cancer may present with abdominal distention, discomfort, nausea, vomiting, hematemesis, and melena. In contrast, leukemia is a malignant clonal disease of hematopoietic stem cells. The primary clinical manifestations of leukemia include anemia, abnormal coagulation, fever, susceptibility to infection, hepatosplenomegaly, lymphadenopathy, and ostealgia[1]. The administration of chemotherapy drugs, such as imatinib, has resulted in a better prognosis and improved quality of life in patients with leukemia and gastric cancer[2].

Cases of patients with multiple primary cancers involving gastric cancer combined with leukemia are extremely rare, and diagnosis and treatment of this condition is difficult. Wang reported the case of an older patient with acute leukemia complicated by gastric cancer who presented with abdominal pain but eventually died of multiple organ failure 1 mo after consultation[3]. This patient was initially diagnosed with chronic myeloid leukemia and then with gastric cancer 1 mo later.

Diagnosis of such patients is extremely difficult, and we reviewed the literature that could be relevant in the diagnosis and treatment of such patients.

CASE PRESENTATION

Chief complaints
The patient was a 43-year-old male farmer who was admitted to the hospital owing to the diagnosis of chronic myeloid leukemia for 3 mo and a 1-mo history of intermittent vomiting.

History of present illness
The patient showed an elevated white blood cell count during the national grassroots public welfare physical examination at a local hospital 3 mo before admission. He did not report fever, chills, low-grade fever, night sweats, dizziness, headache, or rash. Next, he was referred to a higher-level hospital for a more thorough blood examination, which revealed the following results: red blood cell count, 3.57 × 10^{12}/L; white blood cell count, 150.27 × 10^{9}/L; promyelocyte percentage, 15%; mature lymphocyte percentage, 60%; and mature monocyte percentage, 15%. Later, inpatient examination revealed the following results: white blood cell count, 136.59 × 10^{9}/L, red blood cell count, 3.82 × 10^{12}/L; neutrophil percentage, 90.7%; and neutrophil count, 123.98 × 10^{9}/L. T and B lymphocyte immune function test revealed the following findings: cluster of differentiation (CD)3+, 31.2%; CD3+ and CD4+, 15.7%; CD3+ and CD8+, 12.0%; CD4+/CD8+, 1.31%; and CD3− and CD19+, 4.5%. The bone marrow cytology test revealed the following findings: (1) Myeloid hyperplasia was observed to a significant extent with 93.5% myeloid cells and 6.5% erythroid cells; (2) The granule:red ratio was 14.38:1; (3) The myeloid system was abnormally hyperplastic, particularly with middle and late myelocytes; eosinophils, basophils, and mitotic cells were also observed; (4) The extent of erythroid hyperplasia was relatively low (5) A decreased proportion of lymphocytes was observed; and (6) Seven megakaryocytes, which were granular giant cells, were observed within 1 wk.

Identifying middle and late myelocytes on blood films was easy. The size of the red blood cells did not change, the bone marrow smear filling was acceptable, and platelets were scattered and clustered. At this stage, chronic myeloid leukemia was considered. The leukemia immunophenotyping test...
revealed the following results: A blast cell area accounting for approximately 0.6% of nuclear cells was observed; increased proportion of granulocytes by approximately 90.7% was noted; fully expressed cMPO, CD13, CD33, and CD64 along with partially expressed CD16, CD15, CD11b, CD10, and CD4 were observed, and the remaining were negative. An early myeloid development pattern was observed, with most development observed in the middle stage; therefore, mature granulocyte proliferative disease (chronic phase chronic myeloid leukemia) was considered. The level of P170 (CD243) was 0.2%. The digital quantitative analysis test detected the BCR-ABL-p210 fusion gene. Chest computed tomography (CT) scan revealed the following results: (1) Micronodules were observed in the posterior segment of the left upper lobe apex, which could be old lesions; and (2) The local bone of the left fifth anterior rib was rough and dense, which could be an old fracture. Color Doppler showed slight tricuspid valve and aortic regurgitation but normal left ventricular systolic and diastolic function.

At this point, the diagnosis of chronic myeloid leukemia was clear (Figure 1), and symptomatic treatment (alkalization, hydration, and plasma cells) was provided. After the white blood cell count reduced to a safe level, he was treated with imatinib mesylate and discharged. One month after discharge, the patient developed pain in the left lower extremity, which was not reported in the consultation. Later, he developed nausea, which was relieved after vomiting a small amount of gastric content. This was accompanied by a productive cough with white sticky sputum, but he did not show fever, chills, abdominal pain, or diarrhea. His body weight decreased by 7.5 kg over 3 mo.

**History of past illness**
The patient was a healthy individual without diabetes, hypertension, or other underlying diseases.

**Personal and family history**
The patient had no contributory family history.

**Physical examination**
Physical examination showed slight abdominal tenderness, with no rebound tenderness and tension.

**Laboratory examinations**
For further diagnosis and treatment, we performed a series of laboratory and imaging examinations. The results of the blood routine and biochemical tests were normal. The four tests for hematopoiesis showed a slight decrease in vitamin B12 and ferritin levels.

**Imaging examinations**
CT examination of the chest and abdomen showed an increase in the thickness of the wall of the gastric antrum and pylorus. It revealed a blurred surrounding fat space and the presence of multiple enlarged lymph nodes in the cardia, hepatic hilum, greater omentum, and retroperitoneum (Figure 2). A whole body bone scan revealed abnormal bone metabolism in the bilateral scapula, rib, and iliac bone; thus, multiple bone metastases were considered (Figure 3). Meanwhile, gastroscopy showed the presence of a large amount of retained material in the gastric cavity; yellowish mucus; and huge ulcers in the lower part of the gastric body, gastric angle, and gastric antrum. Although the pylorus was deformed, the lens body could pass through it. These findings were suggestive of gastric cancer (Borrmann type IV) with bile reflux 2 and reflux esophagitis grade C (Figure 4).

**Pathology**
Pathological analysis revealed a small number of atypical cells in the gastric antrum. Immunohistochemical results were as follows: CKL(2+), CD56(−), ki67 (40%), CD68 (focal 1+), her-2(1+), MPO(−), CD117(−), CD15 (focal 1+), and CD34 (vascular+). Considering the results of morphological and immunohistochemical analyses (Figure 5), poorly differentiated adenocarcinoma was diagnosed.

**FINAL DIAGNOSIS**
Based on the patient’s medical history, clinical characteristics, and diagnostic results, the final diagnosis was advanced gastric cancer, abdominal lymph node metastasis, bone metastasis, and chronic myeloid leukemia.

**TREATMENT**
Owing to the distinct condition of the patient, we opted to conduct a multidisciplinary discussion on this case. It was decided that imatinib (400 mg, once daily) administration was to be continued for chronic myeloid leukemia and SOX regimen to be started for gastric cancer with bone metastasis. Antiemetics and acid-suppressing drugs were used as adjuvant therapy.
Figure 1 The patient’s karyotype is 46, XY, t (9;22) (q34;q11). A: The typical translocation between the chromosomes 9 and 22 was found in all 20 metaphase cells analyzed; B-D: Bone marrow smear shows an extremely active cellular proliferation, myeloid cells that are dominated by myelocytes and metamyelocytes, and easily observable/high rate of eosinophils and basophils.

Figure 2 Computed tomography images show gastric cancer. A: Computed tomography (CT) in venous phase show edematous and thickened gastric wall; B: CT in the arterial phase, the gastric wall was thickened and significantly enhanced.

OUTCOME AND FOLLOW-UP

The patient had severe nausea and vomiting during the second cycle of chemotherapy, which was attributed to incomplete intestinal obstruction (Figure 6). However, the obstruction was not relieved after conservative treatment, and exploratory laparotomy and ileostomy were performed.

Following laparotomy, we found severe adhesion of the gastric antrum and colonic hepatic flexure. Portions of the small intestine, ascending colon, and transverse colon showed considerable dilatation. Multiple white, hard nodules were observed in the small mesentery. Considering the preoperative examination results, we decided to perform terminal ileal double-lumen fistula. An area of 1 cm around the right McBurney’s point was considered the stoma. The skin and subcutaneous tissue were incised layer-by-layer, and the terminal double ileum was led out through the ileocecal region, 15 cm away from the ileocecal opening. A double-lumen stoma was performed, and the stoma was sutured layer-by-layer for reinforcement.
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Figure 3 Emission computed tomography images show abnormal bone metabolism in the bilateral scapulae, ribs, and ilium; multiple bone metastases were considered.

Figure 4 Gastroscopic images show gastric cancer (Bowman type IV). A: A large amount of retained material in the gastric cavity and huge ulcers in the lower part of the gastric body, angle, and antrum; B: The ulcers base is uneven, brittle, and easy to bleed. Local peristalsis has disappeared.

During the operation, several hard nodules were harvested for subsequent biopsy, which revealed metastatic adenocarcinoma (Figure 7). After discharge, the patient unfortunately passed away in December 2021 (less than 6 mo since the first consultation).

DISCUSSION

The continuous progress in medicine and improvement in living standards have extended the lifespan of humans. In addition, the detection rate of multiple primary cancers has gradually increased[4].

Duplicate carcinoma was first reported by Billroth in 1879. Also referred to as multiple primary malignant tumors, duplicate carcinoma involves the simultaneous or successive occurrence of two or more different pathological tissue types in the same organ or tissue or in different organs or tissues in different parts of the same individual. Briefly, it is the presence of two or more primary malignancies. According to the time of appearance of the second malignant tumor, multiple primary cancers can be categorized into synchronous multiple primary cancers (interval of < 6 mo) and metachronous multiple primary cancers (interval ≥ 6 mo). The diagnostic criteria for multiple primary cancers are as follows: (1) Each tumor is malignant; (2) Each tumor occurs in different parts and exists independent of each other; (3) Each tumor has unique morphological characteristics and its own metastatic pathway; and (4) Tumors showing recurrence and metastasis are excluded[5].

There are several pathogenic mechanisms underlying multiple primary cancers, and the most studied mechanisms are those underlying the carcinogenic effects of radiotherapy and chemotherapy, environmental factors, genetic factors, and gene interactions. A previous study reported the case of a woman who underwent total gastrectomy for advanced gastric cancer and received regular postoperative TS-1
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Figure 5 Pathological examination after gastroscopic biopsy reveals the presence of a small number of atypical cells. A-C: Hematoxylin-eosin staining of biopsy specimens indicate poorly differentiated adenocarcinoma (A, 40 ×; B, 40 ×; C, 100 ×); D-F: Immunohistochemical staining shows that the specimens are positive for CKL (D, 200 ×), and Ki-65 (E, 200 ×) and negative for Her-2 (F, 200 ×).

Another older male patient underwent gastric cancer surgery and was diagnosed with chronic myeloid leukemia 2 years after TS-1 chemotherapy[7]. Furthermore, chronic myeloid leukemia has been reported after chemotherapy using drugs other than TS-1[8]. Moreover, postoperative follow-up studies have shown that patients with breast cancer who received radiotherapy and chemotherapy after surgery have a substantially higher chance of developing multiple primary cancers[9]. Furthermore, environmental factors, such as long-term exposure to chemical and radioactive substances, may be associated with the occurrence of multiple primary cancers[10]. The incidence and prognosis of multiple primary cancers vary among different ethnic groups, which might be because of the effects of genetic factors[11]. A retrospective analysis of cervical cancer and endometrial cancer showed that radiation therapy, smoking, and human papillomavirus infection were significantly associated with the risk of multiple primary cancers[12]. Moreover, frequent exposure to radioactive substances, especially I\textsubscript{131} therapy, increased the risk of second primary cancer after thyroid cancer surgery. Because of the limited number of cases of multiple primary cancers and the lack of research at present, the mechanism underlying gene interaction in the occurrence of multiple primary cancers remains unelucidated.

The patient in this case was a middle-aged man from a rural area who had no bad living habits. He had an acute onset and rapid disease progression, which may be attributed to multiple factors. First, his nutritional status was poor, with reduced immune surveillance capacity. Second, there may be a genetic interaction between the first primary cancer leukemia and gastric cancer. In particular, leukemia inhibitory factor and myeloid leukemia-1 are differentially expressed in the tissues of patients with chemotherapy; she was eventually diagnosed with secondary chronic myeloid leukemia after 3 years[6]. Another older male patient underwent gastric cancer surgery and was diagnosed with chronic myeloid leukemia 2 years after TS-1 chemotherapy[7]. Furthermore, chronic myeloid leukemia has been reported after chemotherapy using drugs other than TS-1[8]. Moreover, postoperative follow-up studies have shown that patients with breast cancer who received radiotherapy and chemotherapy after surgery have a substantially higher chance of developing multiple primary cancers[9]. Furthermore, environmental factors, such as long-term exposure to chemical and radioactive substances, may be associated with the occurrence of multiple primary cancers[10]. The incidence and prognosis of multiple primary cancers vary among different ethnic groups, which might be because of the effects of genetic factors[11].
leukemia and gastric cancer, and both play key roles in disease development. However, further studies on the interaction mechanism are warranted[13-16]. Third, during the treatment for leukemia with imatinib, the patient showed severe adverse gastrointestinal reactions, which necessitated short-term drug suspension (4 d) treatment, thereby resulting in the rapid progress of gastric cancer.

In patients with leukemia and gastric cancer, the clinical symptoms associated with leukemia and gastric cancer can either appear simultaneously or successively. The diagnosis is primarily based on blood routine, bone marrow biopsy, imaging, gastroscopy, and pathological analyses. In terms of treatment, acute leukemia is preferentially treated when it is associated with gastric cancer. When gastric cancer is complicated by bleeding, obstruction, and other emergencies, prioritizing the treatment of gastric cancer is essential. However, the effect of imatinib in the development of chronic myeloid leukemia secondary to gastric cancer chemotherapy should be noted. In cases of gastric cancer complicated by leukemia, a multidisciplinary discussion on several fields, including radiology, pathology, gastroenterology, hematology, radiotherapy, and general surgery, is ideal for formulating the best treatment plan for the patient[17,18].

Metachronous duplication carcinoma has a significantly better survival time and prognosis compared with synchronous duplication carcinoma owing to early detection of the second primary cancer of metachronous duplication carcinoma[19]. Existing studies have reported that early diagnosis and treatment can substantially improve the survival and prognosis of patients with multiple primary cancers.

This patient had abdominal discomfort at the initial diagnosis and underwent abdominal B-ultrasound examination; however, gastric cancer was not detected. Advanced gastric cancer was detected on CT conducted after 1 mo of abdominal pain and discomfort. In such patients, routine chest and abdominal plain CT examinations at the initial diagnosis can be useful in the timely detection of multiple primary cancers. In addition, for further diagnosis and treatment of such patients, particular gastric cancer types—such as hepatoid adenocarcinoma of the stomach, lymphoepithelioma-like gastric carcinoma, and hereditary diffuse gastric cancer (HDGC)—cannot be ignored. Tumor markers, gastrin, C14 urea breath testing, CHD1 detection, and colonoscopy are useful in the diagnosis and treatment of
these patients[20-22].

**CONCLUSION**

Despite the rapid progress in medical technology, more studies should be conducted for the timely diagnosis and treatment of patients with gastric cancer complicated by chronic myeloid leukemia. There is an urgent need to strengthen the understanding of recurrent cancer. For patients with high-risk factors for multiple primary cancers, conducting more comprehensive examinations, formulating an appropriate diagnosis, and ensuring adequate treatment and follow-up are critical. Appropriate guidelines regarding the diagnosis and treatment of recurrent cancer are required in addition to multidisciplinary discussions to formulate optimal treatment plans for patients with multiple primary cancers. Simultaneous gastric cancer with chronic myeloid leukemia has a worse prognosis and shorter survival time than its metachronous counterpart. The pathogenesis of gastric cancer complicated by chronic myeloid leukemia should be further studied because of the current challenges in the diagnosis and treatment of patients with malignant tumors.

**ACKNOWLEDGEMENTS**

We wish to thank all the medical workers involved in the diagnosis and treatment of this patient, especially the multidisciplinary team of the First Hospital of Lanzhou University for their guidance in the diagnosis and treatment.

**FOOTNOTES**

**Author contributions:** Zhao YX, Yang Z, and Dang JY performed the experiments and image acquisition; Zhao YX, Yang Z, Ma LB, and Wang HY designed the study and wrote the manuscript; Zhao YX, Yang Z, and Ma LB edited the manuscript.

**Supported by** Natural Science Foundation of Gansu Province, China, No. 17JR5RA272; Research Fund project of The First Hospital of Lanzhou University, No. Idyyyn2021-120, No. Idyyyn2020-98, and No. Idyyyn2021-30.

**Informed consent statement:** This study was approved by the Ethics Committee of the First Hospital of Lanzhou University. The patient was not required to provide informed consent, as the analysis used anonymized clinical data, obtained after obtaining written consent to treatment.

**Conflict-of-interest statement:** All authors have no conflicts of interest to declare.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016) and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**L-Editor:** A

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Giant struma ovarii with pseudo-Meigs’s syndrome and raised cancer antigen-125 levels: A case report

Yan Liu, Gao-Yan Tang, Lu Liu, Hui-Min Sun, Hai-Yan Zhu

Abstract

BACKGROUND
Struma ovarii is a type of monodermal mature teratoma composed entirely or mainly of thyroid tissue, accounting for 1% to 3% of all ovarian teratomas and 0.3% to 1.0% of all ovarian tumors. Of which, struma ovarii with ascites and pleural effusion, called pseudo-Meigs’s syndrome and raised cancer antigen-125 levels (CA 125) is even rarer.

CASE SUMMARY
This paper reports the diagnosis and treatment of a patient of struma ovarii with pseudo-Meigs’s syndrome, presenting with the clinical features of ovarian carcinoma: Complex pelvic mass, gross ascites, right pleural effusion and markedly elevated serum CA 125 levels. During the operation, a cystic-solid mass about 20 cm × 10 cm × 5 cm in the right adnexa and a solid mass with the size of 3 cm × 2 cm × 0.1 cm in the left ovary were observed. She underwent right adnexectomy and resection of the left ovarian mass and histopathology revealed a mature left-sided ovarian teratoma and struma ovarii of right adnexal mass. During 1-year follow-up, the patient recovered well, tumor markers and other indicators returned to normal.

CONCLUSION
The diagnosis and treatment process of this case suggests that the clinical symptoms of struma ovarii with pseudo-Meigs’s syndrome are lack specificity, which is easily misdiagnosed. Clinicians should improve the understanding of this disease, enhance the awareness of early screening, and improve the level of diagnosis and treatment.
Key Words: Struma ovarii; pseudo-Meigs’s syndrome; Ascites; Pleural effusion; Cancer antigen-125; Case report

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Core Tip: Struma ovarii with pseudo-Meigs’s syndrome and elevated serum cancer antigen-125 is easily preoperatively misdiagnosed as ovarian cancer, leading to unnecessary extended surgery. In this case, the patient of giant struma ovarii with pseudo-Meigs’s syndrome underwent conservative surgery in the form of a right salpingo-oophorectomy, as there was no evidence of malignancy according to the preoperative biopsy and intraoperative frozen analysis. Besides, this patient was premenopausal and to our knowledge, she is the youngest with this disease.


URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11155.htm

DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11155

INTRODUCTION

Struma ovarii, a special type of ovarian teratoma, is a highly differentiated monodermal teratoma that arises from ovarian primordial germ cells and is defined as mature teratoma composed of a minimum of 50% of thyroid tissue by World Health Organisation, accounting for 1% to 3% of all ovarian teratomas and 0.3% to 1.0% of all ovarian tumors [1,2]. Meigs’s syndrome represents a solid benign ovarian neoplasm, such as fibroma, granulosa cell tumor or thecoma with hydrothorax and ascites which are completely resolved spontaneously after surgical removal of the tumour [3]. When ascites and hydrothorax are associated with other ovarian tumors, it is defined as pseudo-Meigs’s syndrome [4]. Struma ovarii is rare, but struma ovarii with pseudo-Meigs’s syndrome is even rarer and it is easily misdiagnosed in clinical practice [5]. In order to deepen clinicians’ understanding of this disease, here, we present a case of benign struma ovarii associated with pseudo-Meigs’s syndrome and elevated cancer antigen-125 (CA 125).

CASE PRESENTATION

Chief complaints
A 37-year-old, Chinese woman, premenopausal, presented to gynecologic clinic with a complaint of abdominal bulge for 4 mo.

History of present illness
Symptoms started 4 mo before presentation with abdominal bulge, without abdominal pain.

History of past illness
She had a history of breast fibroma surgery 6 years ago.

Personal and family history
The patient denied any family history of malignant tumours.

Physical examination
Physical examination revealed obvious abdominal distension, positive mobility voiced sounds, positive fluid wave tremor and weak bowel sounds. Besides, the vital signs were as follows: Body temperature, 37.2 °C; blood pressure, 122/83 mmHg; pulse, 102 beats per min; respiratory rate, 18 breaths per min. Furthermore, the right breast had old surgical scars. Gynecological examination: an irregular mass, with a diameter of 12 cm, was found on the right ovary; left ovary and uterus had no obvious abnormalities.

Laboratory examinations
Tumor marker carbohydrate antigen 199 was not elevated (33.87 U/mL, reference, 0-37), but CA 125 was 1492.23 U/mL (reference, 0-35). Besides, thyroid function tests were within normal limits: free triiodothyronine, 6.24 pmol/L (reference, 3.5-6.5); free thyroxine, 19.63 pmol/L (reference, 11.5-22.7);
thyroid-stimulating hormone, 1.44 μIU/mL, (reference, 0.55-4.78). No abnormality was found in routine blood analyses.

**Imaging examinations**

Ultrasoundography showed a 12.8 cm × 8.0 cm right adnexal mass containing solid and cystic components with abundant vascularization and 2.8 cm × 2.1 cm solid left adnexal mass. Besides, there was a large amount of free peritoneal fluid and thickened greater omentum (Figure 1). Computed tomography (CT) scan of the chest, abdomen, and pelvis revealed right lung atelectasis with a large right pleural effusion, gross ascites, and a large complex cystic pelvic mass (Figure 2). Overall, the radiological findings were suspicious of ovarian cancer.

**FINAL DIAGNOSIS**

Cytological examination of pleural fluid and ascites indicated only reactive mesothelial cells with a few lymphocytes, histiocytes and neutrophils with no malignant cells identified. Then pathological histology of percutaneous biopsy of the pelvic mass showed hyperplastic fibrous tissue and mature thyroid follicles, without cellular and structural atypia, which was suspicious of struma ovarii combined with immunohistochemistry (Figure 3). Combined with the analysis of pathological histology and immunohistochemistry of the biopsies, the preoperative diagnosis was highly suspicious of struma ovarii.

The final histopathology revealed a mature left-sided ovarian teratoma and struma ovarii of right adnexal mass (Figure 4).
Figure 3 Hematoxylin-eosin staining and immunohistochemistry of percutaneous biopsy of the pelvic mass. A: Hematoxylin-eosin staining showed multiple benign colloid-filled thyroid follicles (× 200); B-D: Immunohistochemistry (IHC) examination revealed that pelvic mass was positive for thyrogbulin (× 200), thyroid transcription factor-1 (× 200) and Cytokeratin-7 (× 200), respectively; E-L: IHC examination revealed that pelvic mass was negative for Cytokeratin-20 (× 200), caudal-related homeobox transcription factor 2 (× 200), Estrogen receptor (× 200), calretinin (× 200), P53 (× 200), P16 (× 200), Wilms tumor-1 (× 200) and Ki-67 (× 200), respectively.

Figure 4 Histopathological analysis of the resected specimen. A: Hematoxylin-eosin stained left ovary showing teratoma (× 200); B: Microscopic appearance of the right ovary showing variable-sized thyroid follicles (× 200).

**TREATMENT**

The patient was arranged for an exploratory laparotomy for diagnostic and therapeutic purposes on October 22, 2020. During the operation, 3000 mL of straw-colored ascites was drained. A large solid neoplasm (20 cm × 10 cm × 5 cm) originating from the right ovary was twisted clockwise for half a turn together with the right fallopian tube and part of the intestinal canal was adherent to the mass. Besides,
the left ovary was slightly atrophic, containing a cystic mass, with the size of 3 cm × 2 cm × 0.1 cm. Intraoperative examination of all abdominal and pelvic organs did not show any additional lesions. The patient subsequently underwent right salpingo-oophorectomy and resection of the left ovarian mass and intestinal adhesiolysis and the excised specimens were sent for frozen analysis to rule out malignancy.

OUTCOME AND FOLLOW-UP

The patient recovered uneventfully and pleural effusion disappeared 5 days after surgery. Besides, CA 125 returned to normal range level (27.26 U/mL) 1 month after surgery. The patient was followed up for 1 year after operation and there were no signs of obvious abnormality.

DISCUSSION

Struma ovarii, as a highly specific mature teratoma, is mostly benign, with malignant transformation only occurring in 0.5%-10% of cases[1,6]. Struma ovarii can occur in female patients of any age, but perimenopause is the peak period of the disease, and it is usually asymptomatic, whereas patients with large struma ovarii may show abdominal distention, as in our case[7]. Because there are no obvious specificities in ultrasound, CT or magnetic resonance imaging (MRI) for struma ovarii, it is difficult to differentiate from ovarian cancer on imaging, especially for struma ovarii accompanied by ascites and pleural effusion, called pseudo-Meigs’ syndrome and elevated CA 125, which can mimic ovarian malignancy. Fujiwara et al[8] reported positron emission tomography/CT combined with thyroid scintigraphy may be useful to define the diagnosis in struma ovarii with pseudo-Meigs’ syndrome. Up to now, accurate preoperative diagnosis for struma ovarii by conventional imaging alone remains challenging and postoperative pathology is still required to confirm the diagnosis.

In the literature, 13 cases have been published on struma ovarii combined with pseudo-Meigs’ syndrome and elevated CA 125, we describe another case of struma ovarii combined with pseudo-Meigs’ syndrome and elevated CA 125[5,8-18]. Of all the cases, most of the patients were in their fifth or sixth decade when diagnosed with struma ovarii and almost 78.6% (11/14) of cases were postmenopausal women. Then, the most common presenting symptom was abdominal distension and the tumour sizes ranged between 5-23 cm in the large dimension, with an average size of 12 cm. Besides, most cases were preoperatively misdiagnosed as ovarian cancer and were treated by hysterectomy and bilateral salpingo-oophorectomy[5,8-17] and only two patients (including this case) underwent conservative surgery[18]. The ascites and hydrothorax disappeared completely and CA 125 levels returned to normal following surgery and all the cases had good prognosis. There are some unique features in our patient. Firstly, she was premenopausal, and to our knowledge, she is the youngest with this disease. Secondly, considering young age of our patient in order to avoid postoperative hormonal substitution, she underwent conservative surgery in the form of a right salpingo-oophorectomy as there was no evidence of malignancy according to analysis of percutaneous biopsy of the pelvic mass and frozen examination.

CONCLUSION

In summary, we confirm that struma ovarii is difficult to characterize on conventional imaging modalities and such patients should be diagnosed based on imaging features combined with pathology. In addition, more precise preoperative diagnosis should be performed to avoid unnecessary extended surgery.

ACKNOWLEDGEMENTS

We would like to thank our patient for participating in this study.

FOOTNOTES

Author contributions: Tang GY wrote the first draft of the manuscript; Liu Y and Liu L were responsible for treatment of the patient; Sun HM provided images of hematoxylin-eosin and immunohistochemistry; Zhu HY revised the manuscript; all authors have read and approved the final manuscript.
Supported by the Shandong Medical and Health Technology Development Project, No. 202102080115.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: All authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Country/Territory of origin: China


S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

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Longest survival with primary intracranial malignant melanoma: A case report and literature review

Tang-Fai Wong, Yin-Sheng Chen, Xiang-Heng Zhang, Wan-Ming Hu, Xiao-Shi Zhang, Yan-Chun Lv, Dong-Cun Huang, Mei-Ling Deng, Zhong-Ping Chen

Abstract

BACKGROUND
Primary intracranial malignant melanoma (PIMM) is rare, and its prognosis is very poor. It is not clear what systematic treatment strategy can achieve long-term survival. This case study attempted to identify the optimal strategy for long-term survival outcomes by reviewing the PIMM patient with the longest survival following comprehensive treatment and by reviewing the related literature.
CASE SUMMARY
The patient is a 47-year-old Chinese man who suffered from dizziness and gait disturbance. He underwent surgery for right cerebellum melanoma and was subsequently diagnosed by pathology in June 2000. After the surgery, the patient received three cycles of chemotherapy but relapsed locally within 4 mo. Following the second surgery for total tumor resection, the patient received an injection of Newcastle disease virus-modified tumor vaccine, interferon, and β-elemene treatment. The patient was tumor-free with a normal life for 21 years before the onset of the recurrence of melanoma without any symptoms in July 2021. A third gross-total resection with adjuvant radiotherapy and temozolomide therapy was performed. Brain magnetic resonance imaging showed no residual tumor or recurrence 3 mo after the 3rd operation, and the patient recovered well without neurological dysfunction until the last follow-up in June 2022, which was 22 years following the initial treatment.

CONCLUSION
It is important for patients with PIMM to receive comprehensive treatment to enable the application of the most appropriate treatment strategies. Long-term survival is not impossible in patients with these malignancies.

Key Words: Primary intracranial malignant melanoma; Immunotherapy; Newcastle disease virus-modified tumor vaccine; β-elemene; Long-term survival; Case report

INTRODUCTION
Malignant melanoma (MM) is the most dangerous type of skin cancer. Melanoma accounts for approximately 10% of all patients who develop brain metastases. Approximately one-third of patients with newly diagnosed metastatic melanoma are estimated to have brain metastases[1]. Primary central nervous system (CNS) melanoma accounts for approximately 1% of all melanomas[2,3]. The diagnosis is very challenging. Three criteria have been proposed to diagnose primary CNS melanoma: (1) No melanoma on the skin or eyeball; (2) No surgery history of skin or eyeball melanoma; and (3) No metastatic melanoma in internal organs. Currently, it is believed that the source of primary CNS malignant melanoma may be the melanocytes of the pia mater. From a molecular point of view, the collision of the key structures of these cells leads to focal neurological symptoms, which in turn leads to the formation of malignant melanoma. This disease usually occurs in people under the age of 50, and there is no obvious sex difference. Generally, the disease course is short, and the survival period is usually several months to several years. The survival period is not significantly related to a patient's age. The diagnosis is usually confirmed by pathological biopsy of specimens obtained by surgery. The histopathology has the following characteristics: Tumor cells are of different sizes, most of which are larger than normal cells; the cells are polygonal in shape; the nuclei are round; the nucleoli are obvious; and most of them have obvious nuclear divisions. The cells are consistent with the appearance of malignant melanoma in other parts. In terms of immunohistochemistry, immunohistochemical markers specific to malignant melanoma include HMB45, S100, and SOX10. The positive rate is usually greater than 90%, which is a reliable basis for diagnosis[4]. In terms of treatment, surgical resection is the main treatment for CNS malignant melanoma. Removal of the tumor can prolong survival to a certain extent, but the overall prognosis is very poor. Due to the presence of the blood-brain barrier, chemotherapy
usually does not take effect. Radiotherapy can delay tumor recurrence, but it does not significantly help prolong the survival of patients. Therefore, it can be used but with little significance. Immunotherapy is only effective for metastatic malignant melanoma[5]. It has been reported recently that bevacizumab has a certain effect on patients with malignant melanoma brain metastases[6]. However, more treatment methods for primary CNS malignant melanoma still need to be developed.

**CASE PRESENTATION**

**Chief complaints**
A 47-year-old man visited our hospital for regular brain magnetic resonance imaging (MRI) follow-up after surgery to treat primary intracranial malignant melanoma (PIMM) 21 years ago.

**History of present illness**
All symptoms were denied, and clinical examination findings were negative. The regular brain MRI in July 2021 showed a mixed iso-/hyperdense mass in the right cerebellopontine angle (CPA) measuring 34 mm × 21 mm with a clear margin, so the recurrence of the melanoma was regarded as highly possible again. No melanoma was found on the skin or eyeball. Surgical treatment with gross-total resection (GTR) was arranged on August 12, 2021, which was the third operation.

**History of past illness**
In June 2000, the patient suffered from dizziness and gait disturbance. Brain MRI revealed a lesion in the right cerebellum, and surgical treatment was applied. Melanoma was diagnosed by histopathology examination. The patient received three cycles of adjuvant chemotherapy with dacarbazine 400 mg (d1-5), vindesine 4 mg (d1, d5), cisplatin 30 mg (d1-5), and interferon 3 µm subcutaneously 3 times a week. However, the tumor relapsed locally 4 mo after the operation (Figure 1). The patient received a second surgical treatment in October 2000. Histopathology examination revealed melanoma (Figure 1). After the two operations, it was considered that melanoma was not sensitive to radiotherapy and chemotherapy. To prolong his survival period and improve his quality of life, our team used the experimental treatment of Newcastle disease virus (NDV)-modified tumor vaccine through subcutaneous injection twice[6]. Additionally, the patient received interferon (3 µm subcutaneously 2 times a week) and β-elemene (500 mg QD for 14 d each month) for the first 6 mo, followed by maintenance treatment of interferon and β-elemene every 3 to 4 mo, resulting in a total treatment course of 43 mo up to November 2004. He had undergone regular follow-up, and his condition had been healthy, including tumor-free survival during these 21 years.

**Personal and family history**
The patient had no specific personal or family history.

**Physical examination**
The patient had no neurological symptoms. No melanoma was found on the skin or eyeball.

**Laboratory examinations**
No specific findings of routine blood tests, blood biochemistry, or immune indices were noted.

**Imaging examinations**
The regular brain MRI in July 2021 showed a mixed iso-/hyperdense mass in the right cerebellopontine angle (CPA) measuring 34 mm × 21 mm with a clear margin (Figure 2), so the recurrence of the melanoma was regarded as highly possible again.

**REVIEW OF CASES AND LITERATURE**
We searched the PIMM in English and Chinese language papers using the search engine of PubMed and Medline-based with keywords of primary intracranial melanoma or primary cerebral melanoma and surgery or radiotherapy or chemotherapy or immunotherapy. All studies published during the period from 1993 to 2021 were collected. Metastases of CNS melanocytic neoplasm and intracranial meningeal melanocytoma were ruled out. In addition, metastatic melanoma without a known primary tumor was also ruled out, as patients who did not undergo workup with positron emission tomography (PET) or whole-body computed tomography (CT) were not enrolled in this study. Sampson et al[1] reported that the overall median survival of patients without treatment for MM was 3 to 4 mo, the 1-year survival rate was 9% to 19%, and only rare patients had prolonged survival. After MM was treated with stereotactic radiosurgery followed by either immunotherapy or targeted therapy, the median overall survival (OS)
was 11 mo, and the 1- and 2-year OS rates were 49.5% and 27.4%, respectively, according to Gaudy-Marqueste et al[7], which dramatically improved survival in MM. Baena et al[8] and Arai et al[9] summarized 130 patients with PIMM over the past 30 years. They reported that the mean age of PIMM patients was 45.8 years. No significant sex difference was found. Intracranial hypertension and focal neurologic deficits were commonly observed. The mean OS after gross total resection (> 22 mo) was significantly better than that after surgeries leaving behind residual tumor (12 mo). While there was no significant difference in the survival period between patients with and without adjuvant therapies, leptomeningeal enhancement diagnosed on the initial MRI was the worst prognostic factor. Nakagawa et al[10] reported a patient with PIMM who survived for 9 years and 6 mo after three surgeries to remove the tumor and after receiving adjuvant chemoimmunoradiotherapy in 1989. Önal et al[11] reported a long-term OS of 17 years in a patient who underwent gross total resection of PIMM and received adjuvant chemotherapy with methyl-CCNU in 2006. Li et al[12] established an OS rate of 62.8% at 6 mo and over 5 years at 17.2%, with an estimated median survival time (EMST) of 12 mo. The EMST was better in patients with a solitary-type lesion (13 mo) than in those with a diffuse-type lesion (5 mo). In their review of all patients, those receiving gross total resection with adjuvant radiation therapy and/or chemotherapy had significantly higher 1- and 5-year OS rates, which were 73% and 40.1%, respectively, and a longer EMST (53 mo) than patients who underwent gross total resection alone (20.5 mo) or radiation and/or chemotherapy without resection (13.0 mo). In our case, a 47-year-old male patient was initially diagnosed with PIMM and survived for 22 years after comprehensive treatment, including surgical removal of the tumor three times, adjuvant chemoimmunoradiotherapy, and β-elemene, an extract from the natural plant turmeric with antitumor activity. This is the longest OS case ever reported in the English and Chinese literature according to a search of the PubMed and MEDLINE databases.

**MULTIDISCIPLINARY EXPERT CONSULTATION**

Not applicable.
Figure 2 Magnetic resonance imaging at second recurrence. A-C: Brain magnetic resonance imaging (MRI) T1-weighted postcontrast image (A) axial, (B) transverse, (C) sagittal, which shows irregular soft tissue with heterogeneous hyperintense signals and subtle contrast enhancement in the right cerebellopontine angle cistern and annular cistern (arrow); D and E: Axial MRI T2-weighted images show isointensity, while axial MRI T1-weighted image (E) shows a hypointense mass with an unclear boundary with the right tentorium and brain stem compression (July 10, 2021, before the 3rd operation).

**FINAL DIAGNOSIS**

The patient was diagnosed with recurrent right CPA PIMM.

**TREATMENT**

During the third operation, it was observed that the tentorial margin had obviously turned black, and a dark black mass was seen under the petrosal vein. The tumor was solid, soft, tender, black, and rich blood supplied to attach to the dura mater, sparing the parenchyma of the cortex. The facial nerve was pushed outward and upward, and the trochlear and trigeminal nerves were pressed forward and downward. The tumor had a complete and smooth capsule, with a dark coal-like appearance and a black sesame paste-like content (Figure 3). The histopathology examination revealed melanoma (Figures 4A-C) positive for HMB45, Melan A, S-100, SOX-10, and p16. The Ki-67 index was 8% (+) (Figure 4D).

Chromosomal locations of positive genes were detected by fluorescence in situ hybridization (FISH) in MM: RREB1-6p25/6p11.1-q11.1 (Figure 6 and Table 1). Further examinations included CT scans of the chest, abdomen, and pelvic region as well as PET scans of the whole brain and body, which were all negative. The patient was discharged from the hospital 10 d after GTR with no complications and went on for adjuvant radiotherapy (IMRT, GTV 45 Gy/9 f, CTV 27 Gy/9 f) and chemotherapy with temozolomide as a 5-d oral schedule every 4 wk (administered at 150 mg/m²/d for the first cycle, then 200 mg/m²/d for forward cycles).

**OUTCOME AND FOLLOW-UP**

Brain MRI showed that no residual tumor or recurrence was found in the right CPA 3 mo after the 3rd operation (Figure 5). Up to the last follow-up on June 17, 2022, the patient recovered well with no recurrence or related sequelae. His condition was fine without neurological dysfunction, and he resumed his normal life.
Table 1 Malignant melanoma FISH detection

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosomal location</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCND1 signal count/count nuclei</td>
<td>6q23</td>
<td>Negative</td>
</tr>
<tr>
<td>MYB signal count/count nuclei</td>
<td>6q25</td>
<td>Negative</td>
</tr>
<tr>
<td>RREB1 abnormal cell count/counted cells</td>
<td>6p25/6p11.1-q11.1</td>
<td>Positive</td>
</tr>
<tr>
<td>MYB missing cells/counted cells</td>
<td>6p23/6p11.1-q11.1</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Filter set: DAPI, TRITC, FITC, GOLD. Abnormal signal interpretation standard: CCND1 signal count/count nuclei ≥ 2.5; MYB signal count/count nuclei ≥ 2.5; MYB missing cells/counted cells ≥ 31%; RREB1 abnormal cell count/counted cells ≥ 63%.

DISCUSSION

The incidence is 0.005/100000 for melanoma. There is a slight female predisposition, with a female-to-male ratio of 1.5:1. The age range of patients with primary nodular melanoma is 15 to 71 years, averaging 43 years. Intracranial melanoma is classified as primary or metastatic, and PIMM accounts for 1% of all melanomas[13]. Primary melanoma derives from leptomeningeal melanocytes. Pedersen et al [14] established the first model of melanoma driven by the oncogenic NRAS gene and reported two cases of children with melanoma of the CNS that presented mutations in the NRAS gene. The CNS melanoma is associated with mutations in the GNAQ and GNA11 genes; however, mutations in the NRAS gene are rare in adults[15].

The symptoms and signs are secondary to either the local effects on the CNS parenchyma or hydrocephalus. The rapid progression with increasing intracranial pressure may suggest malignant transformation, which results in irritability, vomiting, lethargy, seizures, and so on. The diagnosis of melanocytic lesions relies on histopathological examination. Most benign and malignant melanocytic lesions display melanin pigment distributed within tumor cells, tumor stroma, and the cytoplasm of tumoral macrophages. Rare melanocytomas and fortuitous primary melanomas do not show melanin pigment, consistent with amelanotic melanoma. Histopathological and immunohistochemical examinations are highly sensitive for amelanotic melanoma.

Isiklar et al[16] classified the MRI manifestations into four groups: (1) The melanotic group, with hyperintensity on T1 and hypointensity on T2; (2) The amelanotic group, with iso-/hypointensity on T1 and iso-/hyperintensity on T2; (3) The mixed group, suiting neither of the two criteria; and (4) The hemorrhagic group, with characteristics of intra/peritumoral hemorrhage. There are hematopoietic neoplasms, cystic changes, and necrosis. One of them was suspected to be amelanotic melanoma. In our present case, T1-weighted hyperintense and T2-weighted isointensity signals consistent with the melanotic group were noted (Figure 3). The immunohistochemical analysis showed positive staining for HMB-45, S100, and vimentin. These results are important in the differential diagnosis of melanoma, particularly the positive staining for HMB-45 which is a specific biomarker for melanoma. Actually, the case in the present study also echoes such findings. These new findings reveal that RREB1 functions as both a transcriptional repressor and transcriptional activator for the transcriptional regulation of target genes. RREB1 is believed to function as a diagnostic biomarker or new drug target for melanoma detection.
Figure 4 Immunohistochemical and histopathological analysis of confirmed recurrent melanoma at the 3rd operation. A-D: Immunohistochemical staining of tumor cells showed positivity for (A) HMB-45, (B) S-100, (C) SOX-10, and (D) Ki67 (8%) (A1, B1, C1, and D1: × 200; A2, B2, C2, and D2: × 400); E: Hematoxylin-eosin staining showed that the tumor cells were diffusely distributed in flakes, with abundant cytoplasm, pigment granules in some cells, round or oval nuclei, nucleoli, and mitotic figures (3 cells/10 high power fields) (E1: × 100; E2: × 400).

Figure 5 Magnetic resonance imaging at last follow-up. A-C: Brain magnetic resonance imaging (MRI) T1-weighted postcontrast image (A) axial, (B) sagittal, (C) transverse; D: Axial MRI T2-weighted image show that no residual tumor or recurrence was found in the right cerebellopontine angle 3 mo after the operation.

Three criteria have been proposed to diagnose primary CNS melanoma: (1) The skin or eyeballs are negative for melanoma; (2) The skin or eyeballs have no history of melanoma resection; and (3) The internal organs are negative for melanoma metastasis. Our presented case had histopathology confirmed MM in the CPA. Whole-body examination ruled out the existence of melanoma outside of the CNS.

MM, which is highly aggressive and chemoradioresistant, has a poor prognosis and easily metastasizes. The prognosis of PIMM lesions appears to be better than that of metastatic examples. It is clear that total resection of tumors should be the key point for treatment[9,10]. For our case of PIMM, gross total resection was achieved; furthermore, excessive removal of invaded adjacent meninges in the 2nd surgery could be one of the important factors resulting in his long-term survival. Immunotherapy has developed rapidly for MM treatment[17]. The prognosis for patients with melanoma brain metastasis (MBM) has also improved, coinciding with the approval of PD-1 immune checkpoint inhibitors and combined BRAF/MEK targeting therapy[18]. However, controversy remains for MM in the CNS; at least, there is little clinical evidence showing efficacy for PIMM[19]. With respect to the
experience of our case, the patient survived for more than 21 years after the comprehensive treatment. Although this patient suffered a relapse after the first surgery, he continued to survive in the following 21 years or more after the second surgery in conjunction with ensuing adjuvant treatment. It remains questionable which of the following could yield effects apart from surgery: Radiotherapy, chemotherapy, and immunotherapy. Based on our analysis, gross total resection should be the key leading to curative effects, while postoperative adjuvant treatments are also important, as used in this case. Franak et al. [20] reported in 1998 that the survival rate of AJCC (American Joint Committee on Cancer) stage III malignant melanoma patients was 59% 15 years after NDV oncolysate therapy. NDV has been evaluated as an anticancer agent because this virus has been shown to have direct toxic effects on tumor cells as well as indirect effects that appear to be mediated through stimulation of the host immune system [21, 22]. In the case of our patient, we applied NDV-modified tumor vaccine combined with interferon treatment, which could make some contribution; however, this patient received comparatively long-term β-elemene treatment. β-Elemene is a sesquiterpene compound extracted from the herb Curcuma Rhizoma and is used to treat several types of cancer including brain cancers such as gliomas [23]. Studies have shown that β-elemene can inhibit cell proliferation, arrest the cell cycle, and induce cell apoptosis. β-Elemene also regulates the expression of several key molecules that are involved in tumor angiogenesis and metastasis [24]. Furthermore, β-elemene has been shown to have regulatory effects on the immune response; for example, β-elemene transforms the polarization of macrophages from M2 to M1, which is considered to be an antitumor phenotype to kill tumor cells directly and stimulate antitumor T cells [25]. Therefore, it is reasonable to speculate that β-elemene treatment should also have helped this patient in combination with NDV-modified tumor vaccine immunotherapy.

**CONCLUSION**

PIMM is quite rare, and its prognosis is poor. However, comprehensive treatment, including surgical resection followed by appropriate adjuvant treatment strategies, may prolong patient survival. We hope that the PIMM case reported in this paper, which describes a patient whose life was extended by 22 years, can provide useful information for the reference of medical practitioners and patients alike, thereby boosting their confidence in adopting the treatment reported therein.

**FOOTNOTES**

**Author contributions:** Chen YS, Hu WM, Lv YC, Huang DC, and Deng ML designed and performed the research content; Wong TF, Zhang XH, and Chen ZP wrote the paper; all authors wrote, read, and approved the final manuscript.

**Informed consent statement:** Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

**Conflict-of-interest statement:** All authors declare no direct conflict of interest for this work.

**CARE Checklist (2016) statement:** All authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by
Longest survival with PIMM

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Spontaneous remission of hepatic myelopathy in a patient with alcoholic cirrhosis: A case report

Chun-Yan Chang, Chen Liu, Fang-Fang Duan, Hang Zhai, Shan-Shan Song, Song Yang

**Abstract**

**BACKGROUND**
Hepatic myelopathy (HM) is a rare neurological complication of advanced cirrhosis. Prognosis of patients with HM is generally poor without timely liver transplantation or interventional therapy. Self-resolving HM in patients with alcoholic cirrhosis has never been reported.

**CASE SUMMARY**
A 53-year-old man with alcoholic cirrhosis and recurrent overt hepatic encephalopathy for 1 year was admitted for lower extremity weakness, slow movement, and stumbling gait. The patient was diagnosed with HM after excluding other causes of spastic paraparesis. The patient refused liver transplantation. However, the patient kept total abstinence and received a multidisciplinary treatment for complications of decompensated cirrhosis. The symptoms of HM resolved gradually after 2 years of treatment. All complications of alcoholic cirrhosis resolved after 4 years of follow-up.

**CONCLUSION**
The case demonstrates that HM can resolve in patients without liver transplantation after total abstinence and systemic management of complications.

**Key Words:** Alcoholic cirrhosis; Hepatic myelopathy; Hepatic encephalopathy; Spastic paraparesis; Therapeutics; Case report
Core Tip: Hepatic myelopathy (HM) is a rare neurological complication of advanced cirrhosis. Prompt liver transplantation or interventional therapy may reverse the symptoms of HM. Self-resolving HM in patients with alcoholic cirrhosis has never been reported. Our report presents that self-resolving HM in a patient with alcoholic cirrhosis is possible without any liver transplantation and interventional therapy after promptly controlling the etiology and systemic management of complications. This case provides new insight into the self-remission of patients with HM.

INTRODUCTION

Hepatic myelopathy (HM) is a rare neurological complication of advanced cirrhosis. The clinical manifestations of HM are progressive spasmic paralysis of the limbs and do not involve sensory or sphincter motor symptoms, commonly in patients with recurrent hepatic encephalopathy (HE) [1]. Other causes of spastic paraparesis and partial transverse myelopathy should be ruled out before establishing the diagnosis [2]. Although the first case of HM was reported 30 years ago, the prognosis profiles of patients with HM, especially the rare cases, remain obscure [3]. Limited data have demonstrated that prompt liver transplantation or interventional therapy may reverse the symptoms of HM [4]. In 2017, di Biase et al. [5] has reported the first case of self-resolving HM in patients with hepatitis C virus (HCV)-related cirrhosis after HCV treatment. Since then, no case of self-resolving HM was reported. To the best of our knowledge, no case of self-resolving HM for alcoholic cirrhosis has been reported. Herein, we report the first case of self-resolving HM from our large cohort of patients with alcoholic cirrhosis [6]. We also reviewed the treatment of patients with HM.

CASE PRESENTATION

Chief complaints

A 53-year-old man with alcoholic cirrhosis was admitted to Beijing Ditan Hospital of Capital Medical University for lower extremity weakness, slow movement, and stumbling gait that required walking assistance with a crutch in January 2015.

History of present illness

The patient was diagnosed with decompensated alcoholic cirrhosis with ascites in September 2011. In December 2011, he was admitted to the hospital due to gastroesophageal variceal bleeding and received splenectomy combined with a gastroesophageal devascularization surgery. In April 2013, he was hospitalized for comorbid acute hepatitis B and suffered from recurrent overt HE since then. Since January 2015, the patient gradually developed weakness in both lower limbs, slow movement, and hobbling gait.

History of past illness

The patient had no relevant medical history.

Personal and family history

The patient had a history of heavy drinking for 25 years, with an average alcohol intake of 200 g per day.

Physical examination

Abdominal examination suggested hepatomegaly and positive shifting dullness. Neurological system examinations demonstrated slurring speech, normal cranial nerves, increased muscle tension and grade 4/5 power of lower limbs, exaggerated deep tendon reflexes, and no sensory deficit or sphincter involvement.

Laboratory examinations

Serial results of liver function and whole blood count are presented in Table 1. Blood ammonia concentration fluctuated between 50 and 87 μmol/L during the occurrence of overt HE. In January 2015,
hospitalization, hepatitis B surface antigen, and anti-HCV tests were negative. Additionally, human immunodeficiency virus (HIV), Syphilis, Epstein-Barr virus (EBV), and cytomegalovirus tests were negative. Serum vitamin B-12 level was normal. Cerebrospinal fluid analysis was normal.

**Imaging examinations**

Contrast abdominal computed tomography revealed liver cirrhosis, esophageal and gastric varices, gastro-left renal shunt, and portal vein thrombosis (Figure 1). Magnetic resonance imaging (MRI) of the brain indicated hyperintensities in the bilateral globus pallidus (Figure 2). Moreover, whole spinal MRI and lumbosacral MRI were performed and revealed normal results. The electromyogram showed normal nerve conduction velocity in the bilateral tibial nerves. Somatosensory evoked potentials of the lower limbs were normal. Motor evoked potential was abnormal in both lower limbs.

**FINAL DIAGNOSIS**

Multidisciplinary expert consultation was performed; this included experts in hepatology, neurology, infectious diseases, and radiology, to find for the cause of the spastic paraparesis. The cranial and spinal MRI showed no intracranial or spinal space occupation. Normal serum vitamin B-12 levels allowed subacute combined degeneration of the spinal cord to be ruled out. Primary lateral sclerosis was not considered since spastic paraparesis in this patient get spontaneously resolved and does not involve the upper limbs. Spinal multiple sclerosis was excluded based on the normal spinal MRI and lack of sensory deficit or sphincteric involvement. Myelopathy related to HIV, EBV or other pathogens infections was ruled out based on the normal infection biomarkers and normal cerebrospinal fluid status. Moreover, hereditary spastic paraplegia, Wilson's disease, radiation myelopathy, vascular spinal cord disease, and other causes of spastic paraparesis were ruled out due to the lack of specific neurological features and lack of characteristic distinguishing abnormalities on neuroimaging. The patient was diagnosed with HM after exclusion of any other potential causes of spastic paraparesis.

**TREATMENT**

The patient rejected liver transplantation for financial reasons. The patient chose abstinence and took furosemide, spironolactone, lactulose, L-ornithine-L-aspartate for ascites and HE. The patient was followed up every 3-6 mo.

**OUTCOME AND FOLLOW-UP**

The patient chose abstinence and symptomatic treatment. During follow-up, he had less ascites and overt HE attacks. Since 2018, he had reported gradual improvement of his lower limb weakness and hobbling gait. In August 2019, the patient reported that he could walk without the assistance of a crutch. The liver function test revealed normal alanine transaminase, aspartate transaminase and albumin levels. Abdominal ultrasound revealed no signs of ascites and disappearance of the portal vein thrombosis. The patient was regularly followed up until October 2021, and has since demonstrated normal liver function and regular limb movement.

| Table 1 Serial results of liver function test and whole blood cell count |
|----------------------------------|----------------|----------------|----------------|----------------|----------------|
| ALT (U/L)                       | 25             | 28             | 42             | 25             |
| AST (U/L)                       | 42             | 26             | 36.1           | 41.3           |
| ALB (g/L)                       | 30.0           | 32.0           | 36.1           | 32             |
| TBIL (μmol/L)                   | 53.1           | 15.7           | 19.3           | 47.0           |
| Hb (g/L)                        | 108            | 82             | 139.0          | 153            |
| WBC (10⁹/L)                     | 6.4            | 8.5            | 9.4            | 8.8            |
| PLT (10⁹/L)                     | 71             | 159            | 79             | 100            |

ALT: Albumin; AST: Alanine transaminase; ALB: Albumin; AST: Aspartate transaminase; Hb: Hemoglobin; PLT: Platelet; TBIL: Total bilirubin; WBC: White blood cell.
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Figure 1 Contrast abdominal computed tomography revealed cirrhosis, esophageal and gastric fundus varicose veins, fundus-left renal shunt, and portal vein thrombosis. A: Arrow shows portal vein thrombosis; B: Arrow shows esophagogastric varices.

Figure 2 The cranial magnetic resonance imaging revealed increased T1W symmetric signal in the bilateral globus pallidus.

DISCUSSION

HM is a rare complication of cirrhosis, which is common in patients with portosystemic shunts and recurrent HE. Its main clinical manifestation is progressive spastic paraparesis. Diagnosis of HM needs to exclude other causes for spastic paraparesis, which include amyotrophic lateral sclerosis, hereditary and toxic myelopathy, multiple sclerosis, paraneoplastic syndromes, radiation myelopathy, infectious causes of myelopathy, and vascular spinal cord disease[7]. Regarding this patient, he had a history of cirrhosis and recurrent HE attacks. Contrast abdominal computed tomography showed portosystemic shunting. In addition, MRI of the brain indicated cirrhosis and HE. The diagnosis of HM was established after exclusion other potential causes of spastic paraparesis by multidisciplinary expert consultation.

Early spinal cord injury in HM is characterized by symmetrical demyelination of corticospinal tracts due to nitrogenous toxins such as ammonia. The demyelination is reversible with prompt management of the underlying liver disease and/or portosystemic shunts. As the disease progresses, axonal loss occurs, which may be irreversible[8,9].

Troisi et al[10] reported the first case of a patient with HM in whom myelopathy improved after liver transplantation. Since then, an increasing number of studies have demonstrated that liver transplantation might reverse HM[1,4,11-15], although some studies have reported otherwise[16,17]. When comparing patients in whom HM was reversed after liver transplantation and patients whose HM was not reversed, it is generally recognized that the likelihood of HM reversal may be higher when liver transplantation is performed within 18 mo after the onset of symptomatic HM[4]. This theory was further verified by Koul et al’s report, in which two children with acute HM after hepatitis A infection recovered completely after receiving donor liver transplantation[14].

For HM secondary to transjugular intrahepatic portosystemic shunt (TIPS) or surgical splenorenal shunt, reports have revealed that prompt shunt occlusion or shunt limitation may reverse HM[18-21]. Some studies have reported that shunt limitation, not shunt occlusion, is useful for reversing early-onset
HM after TIPS[20,21]. Shunt limiting is preferred, as total shunt occlusion might have a higher risk of adverse events related to the rapid increase of portal hypertension. Moreover, Philips et al[22] reported partial splenic artery embolization (PSAE) for a patient with HM. Neurological function improved rapidly and constantly after PSAE. The authors concluded that PSAE may improve liver function, decrease PHT, and lower portosystemic shunting in this way to ameliorate neurological symptoms. Intestinal microbiota is closely related to HE, and some studies have reported that fecal microbiota transplantations (FMT) might improve HE[23]. Based on this, Sun et al[24] reported a case of HM in a patient who received FMT, and neurological function improved after three repetitions of FMT. More studies have revealed that repairing gut microbiota may decrease portal hypertension and repair the blood-brain barrier[25,26]. Further, there is increasing data to demonstrate the usefulness of FMT for improving HE[27,28]. Considering the shared pathogenesis of HM and HE, FMT for HM seems promising and is worth further investigation.

In 2017, di Biase et al[5] reported an interesting case of self-resolving HM. This patient with HCV-related cirrhosis was treated with sofosbuvir plus ribavirin. HM improved 6 mo after HCV treatment. The case demonstrates that self-resolving HM might be possible after relief of the underlying liver disease. As in our case, HM was relieved with total abstinence, and liver function was restored. Additionally, the 6-year follow-up demonstrated sustained re-compensation of liver cirrhosis in this case.

CONCLUSION
As the first reported case of self-resolving HM in a patient with alcoholic cirrhosis, the case demonstrates that self-remission of HM is possible even without liver transplantation after total abstinence and systemic management of complications.

FOOTNOTES
Author contributions: Chang CY designed and contributed to the manuscript draft; Liu C and Duan FF analyzed and interpreted the imaging data; Zhai H and Song SS collected the patient’s clinical data; Yang S reviewed this paper and approved the final version of this manuscript.

Supported by: Chinese foundation for hepatitis prevention and control, Tianqing liver disease research fund subject, No. TQGB20210050; and Beijing Municipal Administration of Hospitals Incubating Program, No. PX2022071.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Wang JJ

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Cauda equina syndrome caused by the application of DuraSeal™ in a microlaminectomy surgery: A case report

Kuei-Lin Yeh, Szu-Hsien Wu, Chiou-Shann Fuh, Yi-Hung Huang, Chu-Song Chen, Shing-Sheng Wu

Abstract

**BACKGROUND**

The management of dural tears is important. While a massive dura can be repaired with absorbable suture lines, cerebrospinal fluid leakage can be attenuated by dural sealant when an unintended tiny durotomy occurs intraoperatively. DuraSeal is often used because it can expand to seal tears. This case emphasizes the need for caution when DuraSeal is used as high expansion can cause complications following microlaminectomy.

**CASE SUMMARY**

A 77-year-old woman presented with L2/3 and L3/4 lateral recess stenosis. She underwent microlaminectomy, foraminal decompression, and disk height restoration using an IntraSPINE® device. A tiny incident durotomy occurred intraoperatively and was sealed using DuraSeal™. However, decreased muscle power, urinary incontinence, and absence of anal reflexes were observed postoperatively. Emergent magnetic resonance imaging revealed fluid collection causing thecal sac indentation and central canal compression. Surgical exploration revealed that the gel-like DuraSeal had entrapped the hematoma and, consequently, compressed the thecal sac and nerve roots. While we removed all DuraSeal™ and exposed the nerve root, the patient’s neurological function did not...
recover postoperatively.

CONCLUSION
DuraSeal expansion must not be underestimated. Changes in neurological status require investigation for cauda equina syndrome due to expansion.

Key Words: Cauda equina syndrome; DuraSeal; Microlaminectomy; Spinal stenosis; Case report

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Core Tip: The number of laminectomies is increasing, and incidental durotomy sometimes occurs intraoperatively. One of the approaches to manage dural tears was using sealants such as DuraSeal™. We present the case of a 77-year-old patient who suffered from incidental durotomy with treatment of using DuraSeal™ when undergoing spine surgery. Postoperative cauda equina syndrome was noted. Surgical exploration revealed thecal sac and nerve roots compression by entrapped hematoma. Our case highlights the potential catastrophic consequences of over-expansion of dural sealant, and demonstrates that cauda equina syndrome should be considered if neurological symptoms develop following application of DuraSeal™.

INTRODUCTION
As life expectancy increases worldwide, degenerative diseases of the lumbosacral spine are becoming more common[1]. Debilitating conditions are currently the major causes of morbidity, disability, and lost productivity[2,3]. The current treatment of choice for spine degeneration is laminectomy for nerve root decompression. In laminectomy, managing intraoperative cerebrospinal fluid (CSF) leakage is important because it increases the risk of sequelae such as meningitis or abscesses, as well as the late development of pseudomeningocele[4,5].

When incidental durotomy occurs intraoperatively and causes CSF leakage, primary dural closure is not always feasible or may not be watertight[6,7]. An alternative solution is the use of a polyethylene glycol hydrogel dural sealant, DuraSeal™. This sealant comprises PEG ester and trilysine amine solutions. When these two solutions are mixed, a reaction occurs and covers the ruptured dura. The mixed solution expands and forms a watertight layer, providing sufficient time for the dura to adequately heal following this application. However, this expansion may also be associated with the development of cauda equina syndrome (CES). Here, we report a case of CES occurring following dural closure and consequent compromised neurological function due to DuraSeal™ expansion in the spinal canal.

The study was approved by the Institutional Review Board of Shin-Kong Wu Ho-Su Memorial Hospital (202020708R).

CASE PRESENTATION
Chief complaints
A 77-year-old woman with an underlying condition of hypertension for over 15 years who had undergone bilateral cataract surgery 10 years ago presented to the orthopedic outpatient department of our institute with progressive radicular pain, chronic lumbalgia, and right thigh pain. She complained of neurological claudication that had lasted for over five years.

History of present illness
The patient presented to the orthopedic outpatient department of our institute with progressive radicular pain, chronic lumbalgia, and right thigh pain. She complained of neurological claudication that had lasted for over five years.
**History of past illness**
She had hypertension for over 15 years, and had undergone bilateral cataract surgery 10 years ago.

**Personal and family history**
Her family history was unremarkable.

**Physical examination**
Conservative treatments, such as physiotherapy, administration of muscle relaxants, shockwave treatment, and oral medications including non-steroidal anti-inflammatory drugs, local anesthetic, and steroid injection over the past year had not alleviated the symptoms. Magnetic resonance imaging (MRI) was performed to evaluate disease severity in our hospital.

**Laboratory examinations**
She did not receive laboratory examinations which related to her spine lesions.

**Imaging examinations**
T2-weighted MRI (Figure 1) revealed collapsed disc height at the L2-3 and L3-4 Levels and a bulging disk compressing the thecal sac and right neural foramen, causing bilateral lateral recess stenosis and neuroforaminal narrowing, especially on the right side, abutting the L3 and L4 nerve roots.

**FINAL DIAGNOSIS**
Based on these imaging findings, lumbar stenosis at the L2/3 and L3/4 Levels was diagnosed, accompanied by neurological symptoms.

**TREATMENT**
Surgical treatment was suggested and the severity of the disease, risks of surgery, and alternative treatments were discussed with the patient. Microlaminectomy and ossified ligamentum flavum removal followed by foraminotomy were planned; therefore, the traversing and exiting neural structures were free of compression. After adequate microlaminectomy, IntraSPINE®, an interlaminar dynamic spacer, was implanted between the L2-3 and L3-4 Levels of the interlaminar space to restore the disc height.

Microlaminectomy for foraminal decompression was performed at the L2/3 and L3/4 Levels. During microlaminectomy, a tiny unintended durotomy occurred, and CSF leakage was observed during decompressive microlaminectomy via an extradural spinal approach. To seal the CSF leakage, we covered the dural defect with oxidized regenerated cellulose, Surgicel, followed by DuraSeal™ (around 2 cc) and a final layer of dry Gelfoam (Pharmacia & Upjohn) before securing hemostasis. This step has been widely used in our past surgical experience in cases of incidental durotomy. After completing lumbar decompression, sealing the dura tear, and implanting the IntraSPINE®, a hemovac was used for blood drainage and the wound was closed.

The patient had no neurological discomfort one day after surgery; however, the following day, bilateral lower-extremity numbness and weakness occurred. The Medical Research Council (MRC) scale of muscle power decreased from 5 to 2 (5: Normal muscle power, 2: Active movement with gravity eliminated) on the distal muscles in the bilateral lower extremities and deteriorated gradually. We attempted to remove urine from the Foley tube, but urinary retention was observed. The residual urine volume was > 200 cc. In addition, the bulbocavernous and anal reflexes were absent. The neurological dysfunction might not have been related to the intraoperative decompression and disk height restoration using an IntraSPINE® device because the symptoms did not appear immediately but rather 2 days after the surgery. Based on these observations, CES was suspected.

An emergent T2-weighted phase MRI examination revealed regional fluid collection at the surgical bed, protruding anteriorly at the junction of L2 and L3 to L4 Levels. This fluid caused thecal sac indentation and narrowing of the central canal (Figure 2). Therefore, emergent exploration and decompression of the thecal sac were performed. Intraoperatively, a large amount of gel-like DuraSeal™ had formed a layer around the thecal sac and entrapped the extradural hematoma, resulting in spinal cord compression. We removed all DuraSeal™, exposing the bilateral L3 and L4 nerve roots, and ensured that no DuraSeal™ material was compressing the nerve roots (Figure 3).
OUTCOME AND FOLLOW-UP

Unfortunately, although the patient was undergoing rehabilitation and physical therapy was initiated, muscle power and urinary and stool incontinence persisted for four months postoperatively. Her American Spinal Injury Association score was A.

DISCUSSION

Intraoperative incident durotomy is one of the most common complications of spinal surgery, especially revision surgery. This adverse event is always related to CSF leakage from the subarachnoid space via dural defects[9]. The incidence of incident durotomy ranges from 0.1% to 15.9%, depending on the difficulty of spinal surgery[9,10]. Despite the fairly low incidence, the risks and associated costs of these adverse incidents cannot be ignored[11]. Longer admission lengths, higher postoperative infection rates, and lower postoperative satisfaction were also noted in these patient groups.

If the CSF leakage is not sealed, further complications can develop, including nausea, vomiting, vertigo, tinnitus, postural headache, meningitis, and fistula formation[12]. The methods to control CSF leakage include direct dural repair. This can be achieved using an absorbable suture line or by grafting fat, muscle, or fascia to the tear[13,14]. However, direct repair may not be an ideal or feasible solution depending on the position of the tear[15]. DuraSeal™ provides a useful alternative treatment for dural tears because the material can expand to reduce CSF leakage[16]. Furthermore, the non-toxicity, bioabsorbability, and accessibility of this material have led to its widespread use[17]. DuraSeal™ can swell by up to 50%, reaching peak expansion within 3-14 d, and persisting for approximately four weeks[18].

Our study is not the first to report neurological complications associated with DuraSeal™ use. The first reported case was that of a 13-year-old girl who underwent cervical decompression and fusion for Chiari malformation in 2007[19]. In 2009, a case of postoperative cauda equina compression syndrome caused by the use of DuraSeal™ before spinal decompression surgery was reported[15]. Similarly, DuraSeal™-related CES was reported after total laminectomy and transforaminal lumbar interbody fusion in 2012[16]. All these cases involved nerve compression due to DuraSeal™ expansion.

Currently, microlaminectomy is preferred over traditional laminectomy for decompression to reduce the breakdown of bony structures and blood loss, as well as the length of hospital stay and healthcare costs[20]. However, microlaminectomy reduces the extradural space more than total laminectomy, with
Figure 2 Postoperative T2-weighted magnetic resonance imaging. A-C: Sagittal views; D-F: Axial views. Regional fluid collection at the surgical bed, protruding anteriorly at the junction of L2 and L3 toward the L4 Level are visible. The fluid has caused an indentation of the thecal sac and narrowing of the central canal.

Figure 3 Removal of the gel-like DuraSeal™. The gel-like DuraSeal™ is compressing the thecal sac and narrowing the central canal.

a consequent increase in the possible mass effects. Applying an expandable agent such as DuraSeal™ dramatically increases the risk of CES compared to total laminectomy alone because the small extradural space provides limited space for DuraSeal™ expansion. Furthermore, it is difficult to predict the nature of the expanding material in the epidural space, with potentially serious consequences.

It is important to achieve adequate hemostasis before dural closure. DuraSeal™ is a self-polymerizing agent that can rapidly produce a watertight hydrogel layer over the dural surface. If hemostasis is not under control before applying DuraSeal™, the hematoma can be entrapped, contributing to the development of complications[6].

There have been several reports of neurological complications following the intraspinal application of absorbable gelatin sponges, such as Gelfoam, or oxidized cellulose products, such as Surgicel, a loosely woven fabric of cellulose[21,22]. In 2015, a CES case was reported to have been caused by the
application of Surgicel after lumbar microdiscectomy and foraminal decompression\cite{23,24}. Thus, except for DuraSeal\textsuperscript{TM}, excess intraspinal sealants should be removed when hemostasis is achieved\cite{25}.

CONCLUSION

The present case highlighted that the potential postoperative expansion of DuraSeal\textsuperscript{TM} should never be underestimated when this product is used in locations sensitive to compression, such as microlaminectomy. The publication of this case will raise awareness of the possibility of DuraSeal\textsuperscript{TM} expansion and the concomitant, potentially irreversible, postoperative complications.

FOOTNOTES

Author contributions: Yeh KL, Wu SH, Fuh CS, Wu SS, and Huang YH contribute to conceptualization; Yeh KL, Chen CS, Fuh CS, and Wu SS contribute to methodology; Yeh KL, Wu SH, Chen CS, and Huang YH contribute to validation; Yeh KL, Huang YH, Wu SS, and Fuh CS contribute to investigation; Wu SH, Chen CS, Fuh CS, and Wu SS contribute to data curation; Yeh KL, Wu SH, Fuh CS, Huang YH, and Wu SS contribute to writing-original draft preparation; Yeh KL, Wu SH, Fuh CS, Huang YH, and Wu SS contribute to writing-review and editing; Wu SS and Yeh KL contribute to supervision; all authors have read and agreed to the published version of the manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

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Bioceramics utilization for the repair of internal resorption of the root: A case report

Abdullah Mahmoud Riyahi

**Abstract**

**BACKGROUND**

The objective of this work is displaying a successful treatment for an internal resorption case under operating microscope using bioceramic material.

**CASE SUMMARY**

Periapical radiograph showed radiolucent lesion representing large internal resorption of the root. The respective defect was obturated using endosquence bioceramic material follow up at the month 18 after treatment revealed no abnormal finings clinically and radiographically.

**CONCLUSION**

New generations bioceramics have many advantages that internal root resorption cases can benefit from. The use of operating microscope helps to apply obturating materials with precision. However, long term study on a large sample is required in future studies.

**Key Words:** Resorption; Root; Treatment; Internal; Bioceramics; Endodontics; Case report

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INTRODUCTION

Internal resorption of the root is an inflammatory process that starts inside the pulp and results in dentin loss and potential cementum invasion \(^1\). Internal resorption can lead to perforation of the root if it progresses. Vital tissues apical to the resorptive area are required for the process of internal resorption to be active \(^2\). In its classical representation radiographically, the resorptive defect can be seen as round radiolucency with symmetrical enlargement of the canal space\(^3\). Internal resorption represents one of the treatment challenges in endodontics; therefore, many previous studies have been conducted on this subject, including case reports\(^4-7\).

Endodontic treatment success relies on sufficient root canal system instrumentation, disinfection and obturation\(^8\). In general, bioceramics have demonstrated favorable physicochemical properties. Moreover, new generation bioceramics have improved on some of existing drawbacks of previous materials\(^9\). Promising results can be expected from the bioceramics due the antibacterial and anti-biofilm characteristics in addition to the biocompatible nature of the material\(^10\). This study aims to demonstrate a comprehensive management solution for internal root resorption with the use of a bioceramic material based as an obturation material for the resorptive defect.

CASE PRESENTATION

Chief complaints

A 51-year-old female who was referred for evaluation of tooth 21 presented with a chief complaint of discomfort associated with an upper front tooth.

History of present illness

Some discomfort associated with upper front teeth.

History of past illness

The patient has history of multiple dental caries which was treated with restorations and crowns.

Personal and family history

The patient has no relevant medical history.

Physical examination

Upon clinical assessment, tooth 21 responded negatively to both cold and electrical pulp tests. In addition, no mobility or deep probing were detected. However, the tooth was tender to percussion and bite upon testing. A periapical radiograph of the tooth in question is shown in **Figure 1A**. Radiographic examination showed what appeared to be a large internal resorptive defect related to tooth 21. The endodontic diagnosis was necrotic pulp with symptomatic apical periodontitis. The patient wanted to try to save the tooth if possible. Planned treatment was nonsurgical endodontics and final restoration if the tooth was found to be restorable.

In addition, the clinical examination of tooth 11 showed no response to vitality testing. Although slight tenderness to percussion was reported, the tooth responded normally to palpation. The tooth also had no deep probing or mobility. Radiographic evaluation showed that tooth 11 underwent previous endodontic treatment with a fill short of the apex.

Laboratory examinations

There is no laboratory examinations.

Imaging examinations

Periapical radiographs were obtained for teeth in question.
Riyahi AM. Bioceramics utilization for treating internal resorption

**Figure 1 Imaging.** A: Preoperative preapical radiograph showing tooth 21 with large resorption; B: Clinical image showing bioceramic material placed in area of resorption; C: Radiograph was taken after endodontic treatment is completed and final restorations placed; D: Month 18 follow up radiograph showed no abnormalities related to teeth 11 and 21.

**FINAL DIAGNOSIS**

The diagnosis was previously treated tooth, with symptomatic apical periodontitis. Planned treatment included endodontic retreatment and final restoration.

**TREATMENT**

**First visit**

To provide local anesthesia, 1.8 mL cartridge of xylocaine 2% with epinephrine 1:80000 was administered as buccal infiltration to tooth 21. After rubber dam isolation, the access cavity was prepared under an operating microscope. The working length was found to be 19 mm. Hand files were used to create the glide path. K3 (Sybron Endo, Orange, CA) Rotary Files were used to prepare the root canal at a speed of 300 rpm. Irrigation was carefully performed using 5.25% sodium hypochlorite. The canal was dried using paper points and obturated with gutta-percha and AH plus sealer (Dentsply International Inc., York, PA, United States) using the vertical compaction obturation technique. The resorptive defect was obturated with EndoSequence® BC RRM-Fast Set Putty (Brasseler United States, Savannah, GA) using pluggers of different sizes under an operating microscope (Figure 1B). The provisional crown was cemented, and occlusion was checked.
Second visit
After one week, the patient had no complaints related to tooth 21. The tooth responded negatively to both percussion and palpation. Rubber dam isolation was obtained, and the access cavity was prepared for tooth 11. The previously placed obturation material was removed from the canal. A ProTaper Universal (Tulsa Dental, Tulsa, OK) rotary retreatment system was used for this purpose. Subsequently, instrumentation was completed using K3 rotary files and irrigation using sodium hypochlorite. The canal was obturated using gutta-percha and AH Plus sealer. The access cavity was temporized using Cavit (3M ESPE, St. Paul, MN, United States), followed by glass ionomer restoration. The provisional crown was cemented, and occlusion was checked. The patient was referred for the final restoration of both teeth 11 and 21. A periapical radiograph was obtained after the crowns cemented by the restorative dentist, as shown in Figure 1C.

OUTCOME AND FOLLOW-UP
The patient was seen at the month 18 after treatment for evaluation. The patient had no complaints. Clinical examination showed no abnormal findings. Teeth 11 and 21 responded normally to percussion and palpation with no mobility detected. Periapical Radiographs showed no abnormalities as seen in Figure 1D.

DISCUSSION
Internal resorption of the root poses an endodontics treatment challenge for various reasons. The irregular nature of the resorptive lesion and the possible perforation externally of the root surface are among the factors of difficulty in these situations[11]. However, salvaging a functional tooth remains one of the main objectives of endodontic treatment. The utilization of new materials with favorable properties can be beneficial in these cases.

Various studies have examined the characteristics of bioceramics and the potential advantages of these materials[12,13]. Bioceramics are bio-inert, biocompatible, and non-toxic[14]. In addition, a previous study found similar sealing capability when evaluating Endosequence Bioceramic Root Repair Material Putty and Mineral Trioxide Aggregate[15]. A new generation of bioceramics have been reported to be clinical used for treatment of internal resorption that cause perforations. In a previous study[16], bioceramic sealer was utilized for management of perforating internal resorption in chamber/coronal canal region.

Microscope-improved visualization is one of the advantages of using magnification[17]. Using the operating microscope throughout the course of treatment in this case was helpful in visualizing and precisely applying the material to the resorptive defect. Obtaining cone beam computed tomography (CBCT) is valuable in identifying the perforation in the internal root resorption[18]. In this case, CBCT image preoperatively could be beneficial for determining the size and the extension of the resorptive lesion prior treatment. Furthermore, the use of bioceramic sealer instead of the resin based sealer could be advantageous in such case.

A combination of correct diagnosis and proper management is important for the success of root canal treatment. The use of an operating microscope, bioceramics, and coronal seal after endodontic treatment can be important for treating internal root resorption. However, future studies with representative samples are required to evaluate long-term outcomes.

CONCLUSION
Internal resorption represents one of many endodontic treatment challenges. The use of a new generation of bioceramics in such cases has potential benefits that can add to overall treatment success. Further studies are required to evaluate the outcomes.

FOOTNOTES
Author contributions: The author wrote and revised the manuscript.

Informed consent statement: Informed consent for treatment was obtained.

Conflict-of-interest statement: The author declares that he has no conflict of interests.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was
prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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Fibrous hamartoma of infancy with bone destruction of the tibia: A case report

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BACKGROUND
Fibrous hamartoma of infancy (FHI) is a rare disease of infancy with unknown etiology. The disease mainly involves soft tissue, has no specific clinical manifestations, and is difficult to diagnose. At present, the diagnosis is mainly confirmed by histopathological examination, and the main treatment is surgical resection of the pathological tissue, which is prone to recurrence.

CASE SUMMARY
A five-month-old female patient was admitted to our hospital with swelling in the right calf. Two biopsies were performed in our hospital and another hospital, respectively, confirming the diagnosis as fibrous hamartoma. After exclusion of surgical contraindications, resection was performed with clear margins of 1 cm. Radiographic examination showed tumor recurrence more than four months after the operation, and surgery was performed again to extend the resection margins to 1.5 cm. The patient is recovering well, and after a follow-up of 36 mo, shows no signs of recurrence.

CONCLUSION
Our case report demonstrates that FHI should be considered in the differential diagnosis for a lower extremity mass with bone destruction. For FHI with bone destruction and unclear boundaries, excision margins of 1.5 cm could be superior to margins of 1 cm.

Key Words: Infant; Tibia; Fibrous hamartoma; Bone destruction; Case report

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Core Tip: Fibrous hamartoma of infancy (FHI) is a rare disease of infancy with unknown etiology. The disease mainly involves soft tissue, has no specific clinical manifestations, and is difficult to diagnose. At present, the diagnosis is mainly confirmed by histopathological examination, and the main treatment is surgical resection of the pathological tissue, which is prone to recurrence. Our case report demonstrates that FHI should be considered as part of the differential diagnosis for a lower extremity mass with bone destruction. For FHI with bone destruction and unclear boundaries, excision margins of 1.5 cm are superior to margins of 1 cm.

INTRODUCTION

Fibrous hamartoma of infancy (FHI) is a rare disease of infancy and childhood. It is a benign tumor with no obvious tendency for deterioration. Most of these tumors develop by the age of two years, often occurring in the axilla, back and other parts of the trunk, and rarely occurring in the tibia. Generally, accumulating subcutaneous soft tissue and accompanying bone destruction is extremely rare [1-4]. The diagnosis of FHI is mainly confirmed by histopathological examination. Herein, a case of FHI with bone destruction of the tibia is reported.

CASE PRESENTATION

Chief complaints
A five-month-old female patient was found to have swelling of her right calf three months prior to admission.

History of present illness
A five-month-old female patient was found to have swelling of her right calf three months prior to admission. X-ray examination in another hospital showed a tumor of the right tibia. Magnetic resonance imaging (MRI) examination suggested a space occupying lesions in the upper segment of the right tibia, which were mostly considered to be eosinophilic granulomas. Puncture biopsy in the other hospital revealed a small amount of fibrous hyperplastic tissue without obvious tumor cells.

History of past illness
The child was in good health and had no special disease.

Personal and family history
There was no similar case in the patient's family.

Physical examination
Physical examination revealed slight swelling in the anterior aspect of the middle part of the right leg, puncture scar with good local healing, normal tissue local skin temperature, no redness and ulceration of the skin, no local tenderness, and no obvious abnormality.

Laboratory examinations
Microscopically, the tumor tissue was staggered in bundles and the cells were fusiform, and the immunohistochemical results included Ki67 (index approximately 5), Desmin (-), S100 (-), smooth
muscle actin (SMA) (scattered +), and CD34 (blood vessel +).

**Imaging examinations**
Radiographic examination in our hospital showed an area of bone destruction in the middle part of the right tibia with uneven internal density, unclear boundaries, slightly expansive, approximately 2.7 cm × 1.6 cm in size, and an anterior cortical bone defect (Figure 1). Computed tomography (CT) examination showed an eccentric, expansive soft tissue density shadow in the middle and upper segments of the right tibia, corresponding bone resorption and destruction, and local cortical bone defect of approximately 2.7 cm × 1.6 cm (Figure 2).

**FINAL DIAGNOSIS**
After puncture biopsy, naked eye examination showed a significant amount of gray-white broken tissue with a volume of 1.5 cm × 1 cm × 0.5 cm. Microscopically, the tumor tissue was staggered in bundles and the cells were fusiform (Figure 3A). Immunohistochemical analysis revealed Ki67 (index approximately 5), Desmin (-), S100 (-), Smooth Muscle Actin (SMA scattered +), and CD34 (blood vessel +) (Figure 3B-D). Pathological diagnosis was consistent with FHI.

**TREATMENT**
During the first surgical resection under radiographic guidance, a 4.5 cm incision was made at the middle part of the right tibia, which had the maximal swelling, through the puncture biopsy site and traversing the skin, subcutaneous tissue, and fascia. The anterior periosteum of the middle part of the tibia was subsequently explored and cut, revealing destruction and a defect of the anterolateral cortex of the tibia. The bone marrow cavity was filled with granulation tissue and showed fiber-like changes. We abided by the principles of tumor-free resection during the operation. The anterior side of the tibia showed cortical damage of approximately 0.2 cm × 2 cm. The proximal and distal ends of the medullary cavity were closed, and the diseased tissue in the medullary cavity was completely scraped off with a curette followed by the removal of the diseased tissue with 1 cm clear margins. Kirschner wire was inserted through the proximal and distal ends of the medullary cavity and the tumor cavity was repeatedly soaked with distilled water for more than 10 min. Thereafter, the tumor walls were cauterized with an electric knife, wiped three times with anhydrous alcohol, and generously washed with 0.9% saline and diluted iodophor. An appropriate amount of allogeneic bone was implanted in the bone defect, and no obvious active bleeding was observed. A drainage tube was placed, the periosteum was sutured, and wound closure was completed in layers. Postoperative pathological examination revealed that the tumor tissue showed bundle-shaped staggered arrangement and fusiform cells, in which immature bone trabecular components were seen (Figure 4). The pathological diagnosis was a benign fibrous osseous lesion, which was consistent with the results of the previous biopsy, confirming the diagnosis of FHI.

Four months after the initial operation, Radiographic examination showed an increase in the lesion area of the middle and upper segments of the right tibia, and recurrence was suspected (Figure 5). Based on this and the patient's history, clinical signs, and auxiliary examination, reoperation was performed. The scar of the original incision on the right leg was used as a landmark and the current incision was extended to the proximal and distal ends of the tibia along the original incision, lengthening it to approximately 6 cm, and again traversing the skin, subcutaneous tissue, and fascia, which revealed destruction and a defect of the bone cortex of the anterior tibia. The distal bone graft showed adequate healing, but a considerable amount of granulation tissue had to be removed, after which the diseased tissue was resected with clear margins of 1.5 cm. The remaining procedures of the operation were similar to those of the first operation.

**OUTCOME AND FOLLOW-UP**
After a follow-up of 36 mo, at present, the patient has no obvious abnormality, as reported by the parents during consecutive telephonic follow-up calls. Postoperative pathological examination showed hyperplastic spindle cells with a small amount of bone tissue (Figure 6), and the pathological diagnosis was consistent with FHI.
DISCUSSION

FHI is a rare superficial benign soft tissue tumor of infants with unclear boundaries. Its pathogenesis and biological characteristics are still unclear. The disease usually occurs in children less than two years of age, of which approximately 23% are born with it, and male to female incidence ratio is approximately 2.4\[5\]. FHI mostly occurs in the axilla, followed by the upper arm, thigh, back, groin, buttocks, and external genitalia\[4-6\]. The clinical manifestations include a subcutaneous mass of relatively small volume, but it may occasionally be larger. It is mostly a solitary lesion but may present as multiple lesions, and the number may differ considerably among cases. Occasionally, it may be adherent to the underlying fascia, but invasion of muscle is rare, with destruction of bone being even more rare. Unlike other benign tumors, FHI often shows unclear boundaries. The diagnosis can be made by ultrasonography, CT, MRI, and pathological examination. Ultrasonography findings of FHI mostly include a "snake-like" uneven and increased echogenic mass with unclear boundaries and uneven contour. Color Doppler flow imaging shows no or scattered spotty blood flow signals in the lesion\[7\], but ultrasonography cannot confirm the diagnosis. CT shows a mixed density mass of fat, soft tissue, and blood vessels, with unclear boundaries, no obvious capsule, and inhomogeneous enhancement\[8\]. CT examination has limited specificity and can only play an auxiliary role in the diagnosis of FHI. MRI mostly shows mixed signal masses rich in fat, with an interspersed band of beam-like fibrous connective tissue shadow in adipose tissue. Signals of fat and fibrous tissue are characteristic, and the signal of fat inhibition sequence image is high. Enhancement scan shows no enhancement\[9\]. MRI is of great importance in the diagnosis of FHI due to no radiation exposure, arbitrary axial and multi-parameter imaging characteristics, high tissue resolution, and good hemodynamic analytic ability, and can effectively differentiate benign and malignant lesions with diffusion-weighted imaging\[10\]. At present, the definitive diagnosis of FHI is by histopathological examination. The tissue composition of FHI is complex and diverse, and is mainly divided into three types: (1) Fibroblasts; (2) primitive mesenchymal cells; and (3) mature adipose tissue. The treatment of FHI is mainly surgical resection, and complete resection with disease free margins is very important to prevent postoperative recurrence.
Figure 3 Histopathological examination. A: Spindle fibroblasts and myofibroblasts arranged in bundles between collagen fibers, spindle or wave nuclei (hematoxylin and eosin stain ×100); B: Immunohistochemical Ki67 (index approximately 5%) (×100); C: Immunohistochemical smooth muscle actin positive (×100); D: Immunohistochemical CD34 positive (×100).

Figure 4 Histopathological examination. The nuclei are hyperchromatic, star-shaped, ovoid, and wavy, and dense bundles of staggered fibroblasts, among immature bone trabeculae, are seen (×100).

Our patient was five months of age, which with the range of onset age in most reported cases of FHI. The location of the disease was the anterolateral part of the middle part of the right tibia. At present, there are few detailed reports on FHI of the tibia[1-3,11,12]. In this patient, the anterolateral cortex of the middle part of the right tibia was destroyed. Detailed reports on bone destruction in FHI are very scarce [1-3,12]. In the presence of a lower limb mass and bone destruction, the possibility of FHI should be considered after considering the patient’s symptoms and imaging examinations. The child underwent two puncture biopsies before the resection procedure. For preoperative diagnosis of the disease, we should consider whether it was necessary to perform a repeat biopsy. Based on evaluation of clinical presentation and preoperative imaging examinations, clinicians can determine whether the disease is benign or malignant. If it is considered as benign, surgical treatment can be performed immediately, and postoperative pathological examination can avoid multiple biopsies and surgeries, relieve pain and...
psychological pressure, relieve economic pressure, and avoid tumor implantation metastasis. The patient’s tumor recurred four months after surgery, and the possible reasons were as follows: FHI was not resected with adequate clear margins, resulting in failure of complete resection during surgery, and repeat biopsies were performed before surgery, destroying the intact capsule of the tumor and resulting in proliferation and seeding of tumor cells to other sites.

Although FHI is a benign tumor, it is infiltrative. Tumor cells can easily enter the adjacent tissue space and infiltrate and destroy the surrounding tissue. To prevent tumor recurrence, intraoperative resection should be expanded. If complete resection is not possible, approximately 15%-16% of patients may have relapse. Therefore, it is recommended to achieve clear surgical margins of at least 1 cm, with the resection depth reaching the level of adjacent normal tissues. In this case, although the tumor was resected with clear margins of 1 cm during the first operation, the tumor recurred after surgery. A second operation was performed to resect the tumor with clear margins of 1.5 cm. No obvious abnormality was found during the follow-up period of 36 mo after the second surgery. Thus, the resection scope for FHI complicated by bone destruction may not be the same as that for FHI alone. Currently, there is no unified standard for scope of FHI surgical resection with or without bone destruction. For FHI with ill-defined boundaries and bone destruction, pathological fractures can be avoided by extension of excision.

FHI is a rare benign tumor and diagnosis is often difficult. FHI should be considered in the presence of a lower limb mass with bone destruction. For FHI with bone destruction, resection with clear margins of 1.5 cm may have a better therapeutic effect and a lower recurrence rate. However, individual case studies cannot effectively determine the efficacy of the resection range of ill-defined FHI with bone destruction; therefore, future research should focus on exploring this topic.
CONCLUSION

Our case report demonstrates that FHI should be considered in the differential diagnosis for a lower extremity mass with bone destruction. For FHI with bone destruction and unclear boundaries, excision margins of 1.5 cm may be superior to margins of 1 cm.

FOOTNOTES

Author contributions: Qiao YJ, Yang WB, Chang YF and Zhang HQ find the special case; Qiao YJ, Yang WB, Yu XY and Zhou SH performed the research; Qiao YJ, Yang WB, Yang YY and Zhang LD followed up; All authors have read and approve the final manuscript.

Supported by Youth Science and Technology Foundation of Gansu Province, No. 20JR5RA588; Youth Science and Technology Foundation of Gansu Province, No. 21JR7RA014; Key RESEARCH and Development Program of Gansu Province, No. 21YF5FA154.

Informed consent statement: I declare that the participant provided informed consent prior to study inclusion.

Conflict-of-interest statement: All authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

Accidental esophageal intubation via a large type C congenital tracheoesophageal fistula: A case report

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Specialty type: Anesthesiology
Provenance and peer review: Unsolicited article; Externally peer reviewed.
Peer-review model: Single blind

BACKGROUND
Tracheoesophageal fistula (TEF) is a congenital anomaly characterized by interruptions in esophageal continuity with or without fistulous communication to the trachea. Anesthetic management during TEF repair is challenging because of the difficulty of perioperative airway management. It is important to determine the appropriate position of the endotracheal tube (ETT) for proper ventilation and to prevent excessive gastric dilatation. Therefore, the tip of the ETT should be placed immediately below the fistula and above the carina.

CASE SUMMARY
A full-term, one-day-old, 2.4 kg, 50 cm male neonate was diagnosed with TEF type C. During induction, an ETT was inserted using video laryngoscope and advanced deeply to ensure that the tip passed over the fistula, according to known strategies. The passage of the ETT through the vocal cords was confirmed via video laryngoscope. However, after inflating the ETT cuff, breath sounds were not heard on bilateral lung auscultation. Instead, gastric sounds were heard. Considering that a large fistula (approximately 6.60 mm × 4.54 mm) located 10.2 mm above the carina was confirmed on preoperative tracheal computed tomography, the possibility of unintentional esophageal intubation was highly suspected. Therefore, we decided to uncuff and withdraw the ETT carefully for repositioning, while monitoring auscultation and end-tidal CO₂ simultaneously. At a certain point (9.5 cm from the lip), clear breath sounds and proper end-tidal CO₂ readings were suddenly achieved, and adequate ventilation was possible.

CONCLUSION
Preanesthetic anatomical evaluation with imaging studies in TEF is necessary to minimize complications related to airway management.

Key Words: Tracheoesophageal fistula; Imaging study; Anatomy; Intubation; Airway
Hwang SM et al. Esophageal intubation via a large TEF

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**Core Tip:** Anesthetic management in tracheoesophageal fistula (TEF) repair is challenging for anesthesiologists because of the difficulty in airway management. Unexpected events during airway management can occur, resulting in catastrophic outcomes, such as desaturation, hypoxic damage, and even death. In our case, esophageal intubation was unintentionally performed because of the large fistula. We predicted the possibility of this event based on the preceding tracheal computed tomography, which helped us to obtain a better clinical outcome. Evaluating the anatomy of each patient with TEF using imaging studies before induction is essential to minimize complications and facilitate prompt management as necessary.

**INTRODUCTION**

A tracheoesophageal fistula (TEF) is a group of congenital anomalies characterized by interruptions in esophageal continuity with or without fistulous communication with the trachea. It has an incidence of one in 2500–3000 live births. There are five types of congenital TEF based on the Gross and Vogt classification. The most common type of congenital TEF is esophageal atresia with a distal TEF, namely, Gross type C/Vogt type IIIb (86%)\[1\]. Congenital TEF has been associated with other anomalies. Up to 10% of neonates with congenital TEF have VATER or VACTERL (vertebral defects, anorectal malformations, cardiac defects, TEF, renal anomalies, radial dysplasia, and limb defects)\[2,3\].

After birth, neonates with TEF experience recurrent coughing, gagging, choking, reflux, cyanosis during feeding, and excessive salivation. Failure to pass a nasogastric tube is usually the first sign checked at the clinic. On plain chest and abdominal radiographs, the tip of the catheter can appear curled up at the chest or upper neck level. Gas in the stomach and intestines can be found in some cases, suggesting distal TEF\[4\].

Surgical repair of the defect is the definitive treatment for congenital TEF. It is usually performed within 24–72 h in neonates. Delayed surgical repair can render the neonates more susceptible to pneumonitis due to aspiration of saliva, accumulated in the upper pouch, or gastric acid reflux through the TEF\[5\].

Successful airway management is essential for anesthetic management. However, it can be challenging in patients with TEF because of anatomical abnormalities of the airway. During airway management of TEF, unexpected events can cause catastrophic outcomes, such as desaturation, hypoxic damage, and death\[6-8\]. Adequate positioning of the endotracheal tube (ETT) below the fistula and above the carina is important for proper ventilation and prevention of excessive gastric dilatation. This is achieved by advancing the ETT at the level of the carina. Alternatively, it can be inserted into the main bronchus and then slowly withdrawn until equal air entry is confirmed on lung auscultation\[9\]. However, various types and sizes of TEF make the intubation process more complicated. This study presents a case of unintentional esophageal intubation in a patient with a large TEF.

**CASE PRESENTATION**

**Chief complaints**

A full-term, one-day-old, 2.4 kg, 50 cm male neonate was scheduled for surgical correction of a type C TEF.

**History of present illness**

The clinical diagnosis was confirmed via an imaging study, which revealed a connection between the lower esophageal segment and the trachea (Figures 1 and 2).

**History of past illness**

The patient had a patent ductus arteriosus (PDA) measuring 2–3 mm and an atrial septal defect (ASD)
Personal and family history
The patient had no relevant family history.

Physical examination
Before anesthetic management in the operating room, the patient was breathing spontaneously on room air, and lung sounds were clear bilaterally on auscultation. There were no symptoms indicative of respiratory abnormalities, and cardiac physical examination revealed unremarkable findings.

Laboratory examinations
Results from preoperative blood tests, including full blood count, liver function test, kidney function test, and electrolyte test results, were within the normal ranges.

Imaging examinations
Echocardiography performed on day one after birth revealed a PDA measuring 2–3 mm and an ostium secundum ASD measuring 3–4 mm with a left-to-right shunt and without dilatation or hypertrophy of the atria and ventricles. No regurgitation and stenosis of the four heart valves was noted, and the
coronary artery system and ventricular function were normal. Before starting anesthetic management, the tracheal computed tomography (CT) images were evaluated. A large fistula (approximately 6.60 × 4.54 mm) was observed 10.2 mm above the carina (Figure 2).

### FINAL DIAGNOSIS

The patient was diagnosed with a type C TEF. For its surgical correction, general anesthesia was induced under standard monitoring (electrocardiography, pulse oximeter oxygen saturation, and blood pressure) using 8% sevoflurane in oxygen without a muscle relaxant. A cuffed ETT with an inner diameter of 3.5 mm (Hi-Contour Oral/Nasal Tracheal Tube Cuffed, Shiley™) was inserted between the vocal cords using video laryngoscope with a #0 Miller blade. The ETT was gradually advanced up to 12 cm as measured from the lip to ensure that the ETT passes over the fistula. However, after inflating the ETT cuff, end-tidal CO2 readings could not be obtained. On bilateral lung auscultation, breath sounds were not heard bilaterally. Instead, gastric sounds were heard. The patient’s oxygen saturation, measured by pulse oximetry, gradually decreased to 60%. In our case, a large fistula was suspected to be the cause of unintentional esophageal intubation.

### TREATMENT

Although we confirmed the vocal cords using a video laryngoscope, we decided to remove the ETT immediately after the first intubation attempt. After the ETT was removed, mask ventilation with 100% oxygen was initiated to support spontaneous breathing. Oxygen saturation rapidly recovered to 100%. External pressure was gently applied to the abdomen during mask ventilation to minimize gastric dilatation. In the second attempt, a new cuffed ETT of the same size was inserted using video laryngoscopy with a #0 Miller blade. The ETT was advanced 11 cm from the lip. However, even though we confirmed the vocal cords with a video laryngoscope for the second time, no breath sounds were heard, but gastric sounds were checked again on auscultation. Instead of removing the ETT, the ETT was deflated and slowly withdrawn until 8 cm from the lip. Auscultation of both the lungs and stomach was performed during this process. Subsequently, the ETT was adjusted to 9.5 cm from the lip. Clear breath sounds were heard in both lungs with an adequate end-tidal CO2 readings, and no gastric sounds or dilation were noted. After confirming proper ventilation, a neuromuscular block agent was administered.

### OUTCOME AND FOLLOW-UP

Surgical repair was performed with the patient in the left decubitus position. The position of the ETT was confirmed by chest and stomach auscultation after the positional change. Intraoperatively, a large Gross type C (Vogt IIIb) fistula was observed, and surgery was successfully performed. Oxygen saturation was maintained at 99%–100% during anesthesia. Endotracheal intubation was maintained postoperatively for additional care and the patient was transferred to the neonatal intensive care unit. The gastrografin test performed one week postoperatively did not reveal any leakage. Subsequently, the patient was successfully extubated and oral feeding was initiated. The patient had no other complications.

### DISCUSSION

Placing the ETT in an appropriate position is crucial for successful airway management of TEF. Over the decades, several strategies for ETT placement in TEF have been studied[8,10-14]. The traditional technique for positioning ETT in TEF patients required that the tip of the ETT be initially located in the right main bronchus through the carina, and gradually withdrawn to the point at which bilateral lung sounds can be appreciated[10]. The ETT placement was then confirmed by either auscultation or bronchoscopic evaluation.

The video laryngoscope we used could increase the success rate of intubation by confirming the vocal cords. However, it could not inspect the subglottic space. Therefore, we believe that both flexible and rigid bronchoscopes can play an important role in confirming the proper position of an ETT in TEF. Additionally, the bronchoscope provides the benefit when a Fogarty balloon catheter is used. This alternative strategy is designed to block the fistula and ventilate isolately[8,11]. However, our center did not have a Fogarty balloon catheter and a bronchoscope with an external diameter small enough to pass through the pediatric ETT. Therefore, we used the traditional technique for intubating our patient.
Moreover, the cuff of the ETT may play an important role during the intubation process for a TEF. Compared to an uncuffed ETT, a cuffed ETT may provide better ventilation by blocking the fistula when the tip of the ETT is placed distal to it. If ETT without Murphy’s eye is used, positioning the cuffed ETT bevel facing forward is also helpful in blocking the fistula.[12,13]

When desaturation episode occurred during the first intubation attempt, we decided to remove the ETT and initiate mask ventilation immediately. It was challenging to determine the main cause of inadequate ventilation and desaturation immediately. Considering that the functional residual capacity tends to be lower in newborns, desaturation can arise faster and result in complications, such as hypoxic damage, or even death. Therefore, immediate mask ventilation was crucial for ensuring adequate ventilation. During this process of securing the airway, maintaining spontaneous breathing is also important. Without spontaneous breathing, continual mask ventilation is required to restore oxygen saturation, and in cases of TEF, gastric distention through the fistula can worsen. The avoidance of neuromuscular blocking agents can help reduce gastric distention and regurgitation[13,14].

In airway management, the sooner the cause of intubation failure and inadequate ventilation is identified, the faster it can be managed. As we confirmed the passage of the ETT through the vocal cords using a video laryngoscope, bronchospasm was first considered. However, there was no wheezing, and only gastric sounds were heard, thus, indicating esophageal intubation. Then, the large size of the fistula was suspected to be the main cause. It was approximately 6.60 mm × 4.54 mm as we preoperatively checked, and seemed big enough that the 3.5 mm cuffed ETT (Outer diameter 4.9 mm) to pass through it. In the second attempt, when the same situation arose, we immediately adjusted the ETT to ensure its proper position. This immediate management was possible because of pre-evaluation of the imaging studies.

Familiarity with the airway anatomy is essential in every anesthetic case. This is even more important in cases at risk of difficult intubation, such as TEF. Holzki et al[15] reported bronchoscopic findings in 113 neonates with TEF. The fistula was located > 1 cm above the carina in 67%, < 1 cm above the carina in 22%, and below the carina in 11% of patients. Based on type C TEF illustrations in general, the trachea and esophagus are connected perpendicularly[1,13,16]. Therefore, the possibility of esophageal intubation through the fistula appears low. However, Lehavi et al[16] reported a case in which the trachea and esophagus were not connected perpendicularly, but rather, at an obtuse angle. When performing the preanesthetic anatomical evaluation with imaging studies, we focused only on the size and position of the fistula and did not pay much attention to the angle between the trachea and the esophagus. However, fistula size and position were not the only factor that affected the possibility of esophageal intubation. When the tracheal CT was reviewed again postoperatively, the angle between the trachea and fistula was found to be an obtuse angle, at approximately 146° (Figure 2A). We assumed that this obtuse angle played an important role in correlating with the large fistula size. Therefore, as in our case, the possibility of esophageal intubation through the fistula increases when the patient has both a large size and an obtuse angle.

Additionally, preoperative tracheal CT can help predict the appropriate depth of the ETT, which can vary depending on the position of the fistula. In our case, the tracheal CT assessment revealed an ETT depth of 9.8 cm (Figure 2A). Although a measurement bias may exist, it is only within a few millimeters, and it turned out to be a similar value of 9.5 cm in result. Initially, in the traditional strategy, the ETT should be inserted deeply, beyond the fistula. Therefore, the ETT goes deeper than the predicted depth. However, the predicted depth obtained on CT can be helpful when trying to adjust the ETT to an appropriate position.

When evaluating imaging studies including tracheal CT, it is important to obtain information on not only the type of TEF but also the size, position, and angle. In our case, the fistula was large (6.60 mm × 4.54 mm) and located 10.2 mm above the carina and at an obtuse angle of 146° (Figure 2). We believe that preoperative awareness of anatomical conditions makes it possible to assess adverse situations earlier.

Therefore, evaluation of the anatomy of TEF patient using imaging studies is recommended prior to anesthetic management to minimize the possibility of intubation failure and other damaging consequences. In addition to the type and position of the fistula, its size and angle formed by the esophagus and trachea should be considered. In particular, the sagittal view of tracheal CT is essential for determining the angle between the trachea and the fistula. Based on this, anesthesiologists can detect the cause of intubation failure more promptly and minimize complications.

CONCLUSION

Understanding the anatomic condition using imaging studies is essential for appropriate airway management of TEF. In our case, the possibility of esophageal intubation via a large fistula in a patient with type C congenital TEF was detected on preoperative tracheal CT. The tracheal CT played an important role to obtain information about the type, size, position, and angle of TEF. Preanesthetic anatomical evaluation using imaging studies, such as tracheal CT, is essential for the airway management and the prevention of catastrophic events.
FOOTNOTES

Author contributions: Hwang SM contributed to manuscript writing and editing; Kim MJ and Kim SR contributed to data collection; Kim SY contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient’s parents for the publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

CASE REPORT

Ventral hernia after high-intensity focused ultrasound ablation for uterine fibroids treatment: A case report

Jung-Woo Park, Hwa Yeon Choi

Abstract

BACKGROUND
High-intensity focused ultrasound (HIFU) ablation is a minimally invasive approach in gynecology that is used to manage uterine fibroids. Although this procedure is safe and effective, adverse outcomes are becoming a major problem.

CASE SUMMARY
We present a case of ventral hernia that occurred as a rare and delayed complication of HIFU ablation for uterine fibroids treatment. The patient came to the hospital with abdominal bloating that occurred 6 mo after ultrasound-guided HIFU ablation for managing uterine fibroids. The ventral hernia, which occurred due to atrophied muscle layers following the procedure, was confirmed by imaging studies and intraoperative findings. She required a hernia repair with mesh and hysterectomy for definitive treatment of uterine fibroid.

CONCLUSION
High-intensity ultrasound ablation should be performed only on appropriate candidates. Patients should be educated about potential complications of the procedure and the possibility of subsequent treatment. Post-procedural long-term follow-up for detecting delayed adverse effects is important.

Key Words: Uterine fibroids; High-intensity focused ultrasound ablation; Conservative treatment; Ventral hernia; Complication; Case report

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Core Tip: We report a case of ventral hernia induced by ultrasound-guided high-intensity focused ultrasound (HIFU) ablation for the management of uterine fibroids. The case highlights the importance of long-term follow-up for delayed and rare complications after HIFU ablation.

Citation: Park JW, Choi HY. Ventral hernia after high-intensity focused ultrasound ablation for uterine fibroids treatment: A case report. World J Clin Cases 2022; 10(30): 11204-11209
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11204.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11204

INTRODUCTION
High-intensity focused ultrasound (HIFU) is a nonsurgical therapeutic technique for uterine fibroids. It is a desirable option for patients who want to save the uterus, regardless of fertility preservation. Recent studies reported favorable clinical outcomes in HIFU compared to conventional surgery and other non-invasive treatments[1-3]. However, despite the proven safety and efficacy of HIFU, adverse responses remain a concern. Here, we present the case of a patient who presented with delayed abdominal bloating after ultrasound-guided HIFU (USgHIFU) ablation.

CASE PRESENTATION

Chief complaints
A 43-year-old woman presented to the outpatient clinic with abdominal bloating, which had started 6 mo prior.

History of present illness
She had undergone USgHIFU for treatment of uterine fibroids at a private hospital 1 year prior to presentation.

History of past illness
The patient had a uterine fibroid with a maximal diameter of 8 cm. She underwent USgHIFU ablation to reduce the size of the uterine fibroid, which decreased to 6.2 cm after the procedure. She did not have any history of trauma or weight change. She had no history of previous surgical procedures or relevant illnesses.

Personal and family history
The patient denied having any relevant personal or familial history.

Physical examination
Her body mass index was 23.8 kg/m². Her abdominal exam was significant for distension without tenderness and a 10 cm palpable mass in the lower left quadrant. She had no fever. The cervical examination presented no remarkable findings, such as vaginal discharge or odor.

Laboratory examinations
Findings of laboratory examinations in blood and urine were unremarkable.

Imaging examinations
Transvaginal sonography revealed a 7-cm-sized uterine fibroid and a fascial defect in the left lower abdomen. Subsequent magnetic resonance imaging scans revealed that the uterine fibroid and the defect measuring 11 cm × 10 cm in the left rectus abdominis muscle were located at the USgHIFU treatment site (Figure 1A and B).

FURTHER DIAGNOSTIC WORK-UP
A diagnostic laparoscopy was performed, and subserosal fibroid and ventral hernia were identified in the operating room (Figures 2 and 3). The defect of the left rectus abdominis muscle measured 13 cm × 12 cm.
Figure 1 Pelvic magnetic resonance imaging shows thin skin and a fascial defect (yellow arrows) at the anterior pelvic wall. The right rectus abdominis muscle is intact, but the left rectus abdominis muscle is atrophied. The subserosal uterine fibroid (white arrowheads) was located at the anterior of the uterus (white arrow). A: Axial T2-weighted image; B: Sagittal T2-weighted image.

Figure 2 7-cm-sized protruding subserosal uterine fibroid is located in the anterior of the uterus.

Figure 3 The defect (yellow arrows) in the left rectus abdominis muscle was identified.

**FINAL DIAGNOSIS**

Considering intraoperative findings, the final diagnosis was a ventral hernia induced by USgHIFU.

**TREATMENT**

We performed a total laparoscopic hysterectomy with bilateral salpingectomy for curative treatment of
the uterine fibroid at the patient’s request. Concurrently, ventral herniorrhaphy was performed with a 20 cm × 15 cm sized composite mesh. Pathological examination confirmed the diagnosis of leiomyoma with red degeneration. The patient was discharged in good condition on postoperative day 5.

OUTCOME AND FOLLOW-UP

All the symptoms, including abdominal bloating and palpable mass, improved after the surgery. Follow-up was performed for 3 years in an outpatient setting, and no further complications were identified.

DISCUSSION

Uterine fibroid is one of the most common gynecologic diseases in reproductive women, with prevalence varying widely from 4.5% to 68.6% depending on countries and diagnostic methods[4]. The treatment goal is to improve fibroid-related symptoms, such as abnormal uterine bleeding, dysmenorrhea, and bulk symptoms, considering the patient’s health status and need for fertility preservation [5]. Management options include medical, interventional, and surgical therapies[3-8]. Traditionally, hysterectomy is an effective and definitive surgical treatment for uterine fibroid[6]. As the patient’s desire to retain the uterus increases regardless of fertility preservation, myomectomy and interventional treatments, which include myolysis, uterine artery embolization, and HIFU, tend to increase in all age groups, even in perimenopausal women[7].

HIFU ablation is a novel therapeutic modality that induces coagulative necrosis of the uterine fibroid and treats it. It has been widely used since the 2000s and has gained acceptance as an effective noninvasive treatment[8-10]. A recent study reported long-term outcomes of up to 8 years of HIFU treatment for symptomatic fibroids[11]. Patients who underwent HIFU ablation showed higher symptom relief rates, lower symptom recurrence rates, and fewer complications compared to those who underwent uterine-sparing surgeries[11].

Although the safety and efficacy of HIFU have been demonstrated, adverse outcomes remain a concern. Complications of HIFU ablation vary from mild to severe. The commonly experienced minor complaints include lower abdominal pain and vaginal discharge, which subside in most patients within one week[12-13]. However, major adverse effects are uncommon with incidences of 0.14% to 0.38%, including skin burns, leg pain, sciatic nerve injury, and bowel injury[12-13]. Given the advancements of HIFU since its introduction, the major complications have seemingly decreased[10]. However, unexpected and serious problems, such as vertebral osteomyelitis and incarcerated internal hernia, have been reported[14-15].

In our case, the abdominal muscles were atrophied following HIFU ablation, resulting in late ventral hernia, which is a rare and critical complication requiring surgical repair. An acquired ventral hernia is common after surgery but rare after a non-invasive procedure. It may be caused by inaccurate targeting and use of excessive power during USgHIFU. However, immediate detection of inappropriate power settings that cause thermal damage in USgHIFU is challenging, as it is difficult to monitor real-time temperature[9]. Yin et al[16] reported several susceptibility factors for thermal damage to the wall structure, including thick abdominal wall, presence of abdominal scar, and excessive total energy for ablation. Thermal injury following HIFU ablation can occur in any abdominal structure, but extensive destruction of the muscle layers is uncommon.

In addition to critical side effects, the possibility of requiring subsequent therapy is an inherent limitation of HIFU ablation as an interventional treatment for uterine fibroid. Choe et al[17] analyzed the characteristics of patients who underwent additional surgery after HIFU ablation to treat uterine fibroids[16]. Patients with uterine fibroids measuring greater than 10 cm and in multiple numbers, as well as persistent symptoms after HIFU ablation, have a higher risk of post-procedural operation[17]. In a recent study, the risk factors for reintervention, including secondary HIFU ablation and conventional surgeries, were reported as young age, large-sized uterine fibroid, and submucosal uterine fibroid[18]. In 72.2% of the patients, the reintervention occurred mainly between 2-4 years after the procedure[18]. Therefore, this period is critical for judging the patient’s progress during the follow-up period, particularly for patients who have risk factors for reintervention.

CONCLUSION

Enjoying the advantages of new treatments should not prevent efforts to achieve better outcomes. Therefore, HIFU ablation must only be performed on carefully selected patients. Although HIFU ablation is considered an optimal, conservative therapy, physicians should discuss the possible need for subsequent intervention with their patients. Patients must be educated and encouraged to report
complaints after HIFU therapy to detect unexpected complications. A long-term follow-up may be required to monitor for delayed adverse outcomes and decide on appropriate additional treatment.

FOOTNOTES

Author contributions: Choi HY contributed to the data collection and the manuscript writing; Park JW treated the patient and contributed to the conceptualization and supervision of the entire work; all authors have read and approved the final manuscript.

Informed consent statement: A written informed consent was obtained from the patient for publication of this case report.

Conflict-of-interest statement: The authors have nothing to disclose.

CARE Checklist (2016) statement: All authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wang DM
L-Editor: A
P-Editor: Wang DM

REFERENCES


C-Reactive protein role in assessing COVID-19 deceased geriatrics and survivors of severe and critical illness

Wassan Nori

**Abstract**

Numerous risk variables, including age, medical co-morbidities, and deranged inflammatory response, lead to higher mortality in a senior population with coronavirus disease 2019. C-reactive protein (CRP), an acute phase inflammatory protein secreted by the liver, was tested in the elderly, showing a diagnostic and prognostic role. However, recent research has shed light on new applications for CRP in geriatrics. It was used as a follow-up marker and as a therapeutic target. Early and accurate identification of patients’ risks may mitigate the devastation of the invading virus in older cases and permit the implementation of a quick treatment plan for those most likely to deteriorate.

**Key Words:** COVID-19; Geriatrics; Deceased; Severe infection; C-reactive protein; Age

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**Core Tip:** Elderly patients suffer higher morbidity and mortality rates. The elderly are a high-risk group due to their deranged immune responses, associated medical illnesses, and poor responses to supportive treatment. C-Reactive protein (CRP) is an inflammatory marker used in the investigation panel of coronavirus disease 2019. CRP distinguished severe infections and predicted deleterious outcomes. Increased levels were reported in the deceased, critically ill, and elderly with respiratory failure underlying exaggerated inflammatory response and overactive cytokines production. Recent studies have discussed a therapeutic avenue for the elderly. CRP may help guide clinical decisions and patient follow-up, ultimately improving outcomes.
Citation: Nori W. C-Reactive protein role in assessing COVID-19 deceased geriatrics and survivors of severe and critical illness. World J Clin Cases 2022; 10(30): 11210-11213
URL: https://www.wjgnet.com/2307-8960/full/v10/i30/11210.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i30.11210

TO THE EDITOR

With interest, we read Wang et al’s study published in World J Clin Cases 2022, which discussed differences in lab biomarkers and patient risk factors linked to fatal outcomes in elderly patients following the acquisition of coronavirus disease 2019 (COVID-19)[1]. Advanced life expectancy and improved medical services have increased the number of geriatrics in the community, who represent a critical vulnerable group for COVID-19[2].

Geriatric vulnerability to severe COVID-19 can be attributed to aging, which renders immunity in more than one way. Aging increases inflammatory responses to pathogens and reduces the efficacy of suppressing infections. A positive correlation was confirmed between older ages and increased mortality rates (MR); sixty-year-old patients had mortality rates of 4.5% vs 1.4% for patients under sixty years[3,4]. Recinella et al[3] study declared a one-and-a-half-fold increase in MR for every five years of a patient’s age. In addition, many geriatrics suffer from chronic illnesses such as diabetes and hypertension, making them more likely to have severe COVID-19[5]. Finally, many COVID-19 treatment approaches have been less effective in older patients[7]. Understanding indicators for ominous COVID-19 in the elderly is vital for an optimum and quick treatment strategy.

C-reactive protein (CRP) is a hepatic protein produced in response to inflammation. It defends the body against injury or infection by activating the immune system. CRP serum levels were linked to respiratory functions and were used to predict respiratory failure. It was widely used in the COVID-19 investigation panels[8].

CRP showed a meaningful high level in COVID-19 cases; a more significant rise was reported in severe forms of the infection, which served as a marker of severe infection[9]. In cases with a rapidly progressive course, cases that suffered from significant lung damage; and cases that ended in patient death, a CRP > 100 mg/L was reported; thus, CRP was used as a prognostic marker to predict aggravating of current infection and worse prognosis[9].

The Wang et al[1] study demonstrated a strong significant correlation between CRP in the sera of geriatric patients ($r = 0.67; P = 0.023$) and the fatality rates among cases, which was consistent with previous studies[3,10].

Inflammatory cytokine overproduction contributes to higher levels of CRP among severe COVID-19 cases. Overactive cytokines can damage lung tissue, increasing CRP levels even more[9].

What is new about CRP in geriatrics is that its levels were used to follow recovered patients post-COVID-19. Interestingly, higher CRP values were associated with higher scores in High-Resolution Computed Tomography, which implies the benefit of CRP as a follow-up biomarker in tracking complete recovery in older patients[11].

Many agreed that serum CRP increased dramatically in the progressing COVID-19 infection, and its concentration is positively associated with poor outcomes[8,9]. Esposito et al[12] used selective CRP apheresis to quickly and effectively reduce CRP among cases with severe COVID-19 complicated with respiratory failure and 100 mg/L. The mean age of those cases was 62 years old, and all had medical co-morbidities. Those patients had multiple sessions of apheresis based on the severity of their CRP levels. The mortality rates were 14 percent, and the rest had a reduced CRP that exceeded 83 percent of the initial reading with a negligible side effect.

A comparable improvement was noticed in the radiological exam flowing apheresis, and the cases were discharged well. Esposito et al[12] recommended targeting CRP as a therapeutic approach in severe COVID-19 cases.

CRP is a rapid, low-cost, reproducible inflammatory biomarker that has been proven valuable in other vulnerable groups[8,9,13], including pregnant women and newborns, with good diagnostic potential in categorizing patients’ risk added to its prognostic value[14,15].

CONCLUSION

CRP assessed infection severity, predicted progressive course, and mortality rates in the geriatric group. Furthermore, it served as a follow-up biomarker in the recovery period and showed optimistic results for severe cases, which opened the door to more therapeutic avenues in practice.
ACKNOWLEDGEMENTS

To our beloved university, Mustansiriyah, for continuous support.

FOOTNOTES

Author contributions: Nori W designed research and reviewed data; wrote and revised the letter; the author has read and agreed on the final version of the manuscript.

Conflict-of-interest statement: All the author declares; that we have no conflict of interest.

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