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Gut-brain axis: Focus on gut metabolites short-chain fatty acids

Cen Guo, Ya-Jing Huo, Yu Li, Yan Han, Da Zhou

Abstract

Emerging evidence supports that the gut microbiome, reconsidered as a new organ in the human body, can not only affect the local gut, but also communicate with the brain via multiple pathways related to neuroendocrine, immune, and neural pathways, thereby proposing the new concept of the microbiome-gut-brain (MGB) axis. Recently, the role of short-chain fatty acids (SCFAs), which are the main anaerobic fermented metabolites of the gut microbiota in the MGB axis, has garnered significant attention. SCFAs are involved in a broad range of central neurological diseases, including neurodegenerative diseases, cerebral vascular diseases, epilepsy, neuroimmune inflammatory diseases, and mood disorders. However, the underlying mechanism of SCFA-related distant organ crosstalk is yet to be elucidated. Herein, we summarize current knowledge regarding interactions between SCFAs and the MGB axis, as well as their protective effects against central neurological diseases.

Key Words: Gut-brain axis; Short-chain fatty acids; Neurological disease; Microbiome-gut-brain

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Core Tip: Recently, emerging evidence suggests that short-chain fatty acids (SCFAs) exert crucial functions on the brain. The levels of SCFAs can change in many neurological disorders such as Parkinson’s disease, Alzheimer’s disease, autism spectrum disorder, major depressive disorder, stroke, epilepsy, multiple sclerosis, and so on. Meanwhile, SCFAs might play a role in the pathogenesis of these diseases. In this review, we outline possible pathways of microbiota–gut–brain (MGB) axis, the interactions between SCFAs and MGB axis, as well as their relationships with different central neurological diseases, which helps to better understand the biological roles of SCFAs in neurological disorders via MGB axis and shed light on potential therapeutic approaches for these neurological disorders.

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INTRODUCTION

Microbes have existed on earth for hundreds of millions of years. However, it was not until 2000 that Lederberg first proposed the concept of “microbiota” and revealed its possible relationship with human diseases[1]. Henceforth, intestinal microbes, which have often been disregarded, but are currently regarded as a special organ of the human body, have become a research hotspot. It has been conservatively estimated that the gut contains more than 500 types of bacteria, over 10 trillion cells, i.e., 1.3 times more microbes than the human body, and constitute > 99% of the genes in our body[2-4]. It is fundamental to many physiological processes, including immunity, defense, digestion, and metabolism.

Over the past two decades, with the advancement of gene sequencing technology and the development of powerful bioinformatics analysis tools, researchers have gained a more comprehensive understanding of the role of intestinal flora in the development of human diseases. In addition, the scope of research has extended from digestive diseases to diseases of other systems such as the central nervous system (CNS). Recently, emerging evidence suggests a bidirectional interaction between intestinal microbiota and the brain. This crosstalk, known as the microbiota–gut–brain (MGB) axis, appears to be vital to many neurological diseases[5,6].

Short-chain fatty acids (SCFAs), primarily comprising acetate, propionate, and butyrate, are major microbial metabolites produced in the colony by the bacterial fermentation of specific dietary fibers, and they primarily serve as energy suppliers for colonocytes. Recently, many studies have supported the crucial function of SCFAs in the brain. Studies have shown that the levels of SCFAs change in many neurological diseases, including neurodegenerative diseases [Parkinson’s disease (PD), Alzheimer’s disease (AD), cerebral vascular diseases (stroke, transient ischemic attack, epilepsy), neuroimmune inflammatory diseases (multiple sclerosis, MS), neuromyelitis optical spectrum disorders (NMOSDs)], and mood disorders [autism spectrum disorder (ASD), major depressive disorder (MDD)], which all imply that SCFAs might be vital to MGB axis communication[7]. Herein, we outline possible pathways of the MGB axis and illustrate the interactions between SCFAs and the MGB axis, as well as their relationships in different CNS diseases.

MGB AXIS AND SCFAs

An increasing number of studies indicated that multiple direct and indirect pathways involving immune, neural, and humoral signaling exist, through which the gut microbiota can modulate the MGB axis and vice versa. Downward, the CNS can modulate the release of satiety peptides, affect the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system, and body immune system, thereby ultimately altering the state of intestinal epithelial cells and change the intestinal function. Conversely, the gut microbiota may affect the brain upward via the following mechanisms[4]: (1) The neural pathway: Some gut microbes can produce neuroactive metabolites (e.g., SCFAs) and neurotransmitters (e.g., GABA), and over 90% of 5-hydroxytryptamine (5-HT) is synthesized by enterochromaffin cells (EC). These microbial productions can be released into the blood circulation, pass through the blood-brain barrier (BBB), or activate other pathways, ultimately affecting neural function. The enteric nervous system (ENS) can directly communicate with the spinal cord and brain through the vagus nerve; (2) Endocrine pathway: The gut microbiota can regulate the HPA axis participating in stress responses. In addition, EC cells can synthesize hormones (e.g., peptide YY) that are involved in the modulation of eating, affecting either the hypothalamic centers of appetite control or indirectly affecting the vagal-brainstem-hypothalamic pathway; and (3) Immune pathway: The gastrointestinal tract has the
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densest concentration of immune cells and can release cytokines and chemokines that can infiltrate the blood and lymphatic systems, or affect neural messages carried by the vagal and spinal afferent neurons to the brain. Furthermore, gut microbiota can affect neuroinflammation via bacterial metabolite-mediated mechanisms, likely via SCFAs.

SCFAs are small organic monocarboxylic acids with a chain length of carbon atoms of less than six, of which more than 95% of them are acetate, propionate, and butyrate. The majority of SCFAs, reaching up to 50 to 200 mmol/L in the large intestine, are produced by the microbiota through the anaerobic fermentation of indigestible dietary fibers or resistant starch. Only a small proportion of SCFAs is acquired by the consumption of fermented foods[5,8]. The content of SCFAs in human feces is approximately 60 g/kg for acetic acid, 10-20 g/kg for propionic acid[9], and 3.5-32.6 g/kg for butyric acid[10], with a ratio of 60:20:20[11]. The exact levels of SCFAs vary among different individuals depending on the composition of the microbiota and the amount of complex carbohydrates in the diet. SCFAs, particularly butyrate, are absorbed by the colonic epithelium via monocarboxylate transporters (MCTs) and provide energy for the colon. SCFAs can cross the BBB, possibly owing to the abundant expression of MCTs in intracranial endothelial cells[12]. The remaining SCFAs are primarily utilized by hepatocytes, resulting in only a small fraction of SCFAs released in circulation, with concentrations of 1-15 μM for propionate and butyrate, and 100-200 μM for acetate in circulation[11].

In addition to their local protective effects on the gut, including enhancing gut motility and gut barrier integrity, SCFAs exhibit promising performance in the MGB axis. It has been reported that SCFAs function in the brain via two major cellular mechanisms. One is to bind to and activate G protein-coupled receptors, of which GPR43 and GPR41, which were later renamed as free fatty acid receptor 2 (FFAR2) and FFAR3, respectively, are the most investigated mechanisms. They are broadly expressed in the gastrointestinal mucosa and immune system[13]. FFAR3 has been shown to be highly expressed in brain tissue and the BBB[14], based on the finding that all three major SCFAs exist in the cerebrospinal fluid, although their concentrations were relatively low[15]. Another mechanism is to induce histone deacetylase (HDAC) inhibitory effects, with butyrate being the most potent inhibitor of class I and IIa HDACs[16]. Research has shown that the effects of SCFAs on HDACs are dose dependent. It is widely accepted that HDACs are involved in brain development and various neuropsychiatric diseases. Furthermore, SCFAs can interact with the brain through the three major MGB axis pathways mentioned above. SCFAs can interact with the neural pathway by reinforcing BBB integrity[17], affecting levels of neurotrophic factors[18], promoting serotonin biosynthesis[19], or directly activating vagal afferent[20]. Furthermore, SCFAs can promote the endocrine pathway by modulating the secretion of peptide YY[21]. Additionally, SCFAs can interfere with the immune pathway by directly affecting immune cells and immune modulators to maintain homeostasis. SCFAs can regulate the differentiation, recruitment, and activation of systemic inflammatory cells, including neutrophils, dendritic cells, macrophages, monocytes, and T cells[22,23], thereby affecting systemic inflammation as well as the microglial structure, maturation, and activation involved in neuroinflammation[24,25].

In summary, SCFAs might directly or indirectly communicate along the MGB axis by activating GPRs or inhibiting HDACs. They can enter the bloodstream, activate the vagus pathway, facilitate the secretion of other hormones or neurotransmitters, interfere with the immune response, and finally participate in neuropathologies.

SCFAs AND NEURODEGENERATIVE DISEASES

AD is the most typical form of dementia among member of the older population. Recently, emerging evidence has shown that the gut microbiota participates in the pathophysiology of AD and exhibits a different composition in AD patients[26,27]. In 2019, an oral drug that affects reconditioned gut microbiota received its first approval in China for the treatment of mild to moderate AD to improve cognitive function. In this context, the roles of SCFAs in AD have garnered significant attention. A recent small sample, randomized, double-blind, pilot study in an AD group showed that the modified Mediterranean-ketogenic diet might alleviate AD symptoms by modulating SCFAs (reducing fecal lactate and acetate while increasing propionate and butyrate) as well as improved AD biomarkers[28]. An animal study by Zhang et al[29] in APP/PS1 transgenic AD mice showed that the concentrations of butyric acid were lower in both feces and the brain, whereas the abundance of Butyricoccus pullicaecorum, a butyrate producer, decreased, which may compromise cognitive decline in AD. Consistent with this, a study by Govindarajan et al[30] showed that treatment involving butyrate can improve memory impairment in AD mice even when administered at an advanced stage of pathology; this is attributable to its role in HDAC inhibition. Similarly, acetate was shown to be neuroprotective and exert an anti-neuroinflammatory effect in AD mice, likely via the upregulation of GPR41 and suppression of the ERK/JNK/NF-kappaB pathway[31]. Certain SCFAs, particularly valeric acid, butyric acid, and propionic acid, can interfere with initial protein-protein interactions in vitro, which are necessary for the formation of toxic soluble Aβ aggregates[32].

PD is the second most typical neurodegenerative disorder; it is clinically characterized by motor systems and non-motor symptoms, and pathogenetically characterized by the aggregation of Lewy body and loss of dopamine in the substantia nigra. In PD, researchers have observed that gut microbiota are crucial for the development of motor symptoms. SCFAs can interact with the brain through the three major MGB axis pathways mentioned above. SCFAs can interact with the neural pathway by reinforcing BBB integrity via two major cellular mechanisms. One is to bind to and activate G protein-coupled receptors, of which GPR43 and GPR41, which were later renamed as free fatty acid receptor 2 (FFAR2) and FFAR3, respectively, are the most investigated mechanisms. They are broadly expressed in the gastrointestinal mucosa and immune system[13]. FFAR3 has been shown to be highly expressed in brain tissue and the BBB[14], based on the finding that all three major SCFAs exist in the cerebrospinal fluid, although their concentrations were relatively low[15]. Another mechanism is to induce histone deacetylase (HDAC) inhibitory effects, with butyrate being the most potent inhibitor of class I and IIa HDACs[16]. Research has shown that the effects of SCFAs on HDACs are dose dependent. It is widely accepted that HDACs are involved in brain development and various neuropsychiatric diseases. Furthermore, SCFAs can interact with the brain through the three major MGB axis pathways mentioned above. SCFAs can interact with the neural pathway by reinforcing BBB integrity[17], affecting levels of neurotrophic factors[18], promoting serotonin biosynthesis[19], or directly activating vagal afferent[20]. Furthermore, SCFAs can promote the endocrine pathway by modulating the secretion of peptide YY[21]. Additionally, SCFAs can interfere with the immune pathway by directly affecting immune cells and immune modulators to maintain homeostasis. SCFAs can regulate the differentiation, recruitment, and activation of systemic inflammatory cells, including neutrophils, dendritic cells, macrophages, monocytes, and T cells[22,23], thereby affecting systemic inflammation as well as the microglial structure, maturation, and activation involved in neuroinflammation[24,25].

In summary, SCFAs might directly or indirectly communicate along the MGB axis by activating GPRs or inhibiting HDACs. They can enter the bloodstream, activate the vagus pathway, facilitate the secretion of other hormones or neurotransmitters, interfere with the immune response, and finally participate in neuropathologies.
bodies in the nervous system. The role of gut microbiota in PD has been investigated extensively and promising results have been obtained; researchers hypothesized that the pathological process in PD may spread from the gut to the brain[33]. It is widely accepted that the gut microbiota composition differs between patients with PD and healthy individuals, and target the gut microbiota could be a promising strategy for PD[34]. Emerging evidence indicates that SCFAs are crucial for correlating PD and the gut within the enteric nervous system. A recent study showed that fecal SCFA concentrations, as well as populations of SCFA-producing microbiota reduced significantly in PD patients compared with controls [35-39]; this will induce alterations in the ENS and contribute to gastrointestinal dysmotility in PD patients with digestive symptoms, such as constipation[40]. In addition, Shin[41] et al measured the plasma concentrations of SCFAs in PD patients and controls; they discovered that the acetic acid concentration was higher in the PD group and was positively correlated with age, whereas the propionic acid concentration was negatively correlated with the UPDRS part III score and use of entacapone. Meanwhile, the butyric acid concentration was correlated with the inhibitor and anticholinergic usages of monoamine oxidase. A-synuclein (aSyn) aggregation is regarded as critical in PD development. An animal study in an alpha-synuclein-overexpressing (ASO) mouse model of PD showed that SCFA-gavage ASO mice displayed significantly impaired performance in several motor tasks, and that aSyn aggregated more seriously in the brain compared with in untreated mice, possibly owing to the promotion of the microglial morphology to a more active status within affected brain regions[25]. Additionally, sodium butyrate might have caused a-synuclein degradation via an Atg5-dependent and PI3K/Akt/mTOR-related autophagy pathway. In an in vitro model of PD, propionic acid was suggested as a potential therapy for rotenone toxicity in PD. Moreover, butyrate has been discovered in an animal model of Huntington’s disease to protect against neurotoxicity, resulting in improved motor performance by deacetylase inhibition. These results imply the potential significance of SCFAs in the onset and development of neurodegenerative diseases and provide a new perspective for their future treatment.

**SCFAs AND CEREBRAL VASCULAR DISEASES**

Stroke is the second leading cause of death worldwide, and options for its treatment remain limited. Overwhelming evidence suggests that the gut microbiome is significantly associated with most of its modifiable risk factors, those that are associated with atherosclerosis, including hypertension, hyperlipidemia, diabetes, and obesity. Studies have revealed that stroke and transient ischemic attack (TIA) patients showed significant changes in gut microbial diversity (an increased abundance of Akkermansia muciniphila and an excessive abundance of clostridial species), the abundance of opportunistic pathogens, such as Enterobacter, Megaspheara, Oscillibacter, and Desulfovibrio were increased in stroke and TIA patients, and the commensal or beneficial genera including Bacteroides, Prevotella, and Faecalibacterium were decreased[42,43]. The levels of SCFAs changed after stroke, although the results were inconsistent[44-46]. Sun et al[47] discovered that the concentration of butyric acid decreased after stroke, whereas Li et al[46] and Dragana et al[42] presented the opposite conclusion. However, SCFAs were considered to be beneficial products in most studies. Sun et al[47] indicated that the oral gavage of Clostridium butyricum can attenuate cerebral ischemic-reperfusion injury and neuronal apoptosis by regulating the composition of intestinal microflora and restoring cerebral ischemic-reperfusion induced decreases of fecal microbiota diversity in diabetic mice. Additionally, the transplant of fecal microbiota rich in SCFAs, particularly butyric acid, exhibited protective effects in a rat model of middle cerebral artery occlusion, and alleviated post-stroke neurological deficits in aged stroke mice[44]. These functions might be related to their role in modulating the immune system. A recent study identified that SCFAs improved post-stroke recovery by altering contralesional cortex connectivity and changing synapse densities after stroke, which might be associated with their effect on the recruitment of T cells to the infarcted brain and the corresponding microglial activation[48]. However, studies regarding the association between cerebral vascular diseases and SCFAs are limited, most of which are focused on ischemic stroke and completed in animal models. High-quality clinical studies pertaining to its roles in chronic vascular diseases, such as small vessel diseases or vascular dementia, should be further investigated.

**SCFAs AND EPILEPSY**

Epilepsy is a chronic brain condition characterized by persistent unprovoked seizures caused by the abnormal function of the CNS due to the excessive and synchronous discharge of neurons. More than 50 million individuals worldwide are affected by epilepsy, and this can result in cognitive decline and depression in the patients. Recent clinical studies have confirmed that the intestinal flora of patients with epilepsy differs from that of normal individuals. Fusobacteria phylum, Proteobacteria phylum and the genera of Campylobacter, Delftia, Haemophilus, Lautropia, Neisseria among Proteobacteria phylum were found to be higher in patients compared with the healthy persons[49]. Similarly, in an animal
SCFAs AND NEUROIMMUNE INFLAMMATORY DISEASES

MS is a chronic T cell-mediated autoimmune disease of the CNS that is characterized by demyelination and axonal damage in the brain and spinal cord. Recently, gut microbiota has received increasing attention in regard to their roles in the development of MS, as well as SCFAs[54]. It was discovered that fecal levels of SCFAs (acetate, propionate, and butyrate) reduced in a Chinese cohort study of MS compared to health controls, corresponding to their alterations in blood circulation[55,56]. SCFAs have been shown to exert anti-inflammatory effects in MS, possibly by interfering with T cell differentiation[57]. Specifically, oral treatment with SCFAs ameliorated the symptoms of experimental autoimmune encephalomyelitis (EAE), i.e., the most typically used animal model of MS, and reduced axonal damage by suppressing the differentiation of pro-inflammatory Th17 cells, while promoting differentiation of anti-inflammatory Tregs[58,59]. Similarly, another experiment that treated ordinary EAE mice with fecal samples from those rich in SCFAs resulted in better EAE clinical scores[60]. Moreover, butyrate might alleviate CNS demyelination and promote remyelination by facilitating oligodendrocyte maturation and differentiation[61]. Acetate supplementation is assumed to increase histone acetylation by inducing more acetyl-CoA metabolism, resulting in preserved spinal cord lipid content and reduced clinical symptoms of EAE[62]. A similar finding has been discovered in NMOSDs, which are characterized by severe immune-mediated demyelination and axonal damage predominantly affecting the optic and spinal cord nerves[63].

A recent study demonstrated that levels of SCFAs reduced in patients with anti-leucine-rich glioma-inactivated 1 encephalitis[64], which is a rare autoimmune encephalitis, related to a group of immune-mediated inflammatory neurological diseases with antibodies against CNS components, characterized by subacute disturbances of memory, behavior, mood, and seizures. Compared to health controls, the anti-leucine-rich glioma-inactivated 1 encephalitis patients exhibited a decreased microbial diversity and an altered composition of gut microbiome, the Faecalibacterium, Roseburia, Lachnospira, Ruminococcus, and Blautia, which had the ability to produce SCFAs, were obviously reduced in the patient group. However, more studies are warranted to explore the relationships or internal mechanisms between gut microbiota and anti-leucine-rich glioma-inactivated 1 encephalitis.

As both microbiota and its metabolites SCFAs have been widely proven to be associated closely to the immune system, we can expect their application in future immune-modulating therapy.

SCFAs AND MOOD DISORDER

ASD is collectively referred to as autism, Asperger’s syndrome, and pervasive developmental disorder. It is characterized by impairment in communication skills, as well as repetitive or restrictive patterns in behavior, interests, and activities. The results of the relationship between SCFAs and ASD are controversial. In a clinical study, the concentrations of fecal acetic, butyric, iso-butyric, valeric and isovaleric acids except for caproic acid were all significantly higher in children with ASD compared with controls, which indicated that the fermentation products were associated with the occurrence and progress of ASD[65]. However, a recent study reported that children with ASD had lower fecal acetate and butyrate levels, but higher fecal valeric acid level than the controls, which was related with the altered composition of the gut microbiota in ASD individuals, the abundances of butyrate-producing taxa (Ruminococcaceae, Eubacterium, Lachnospiraceae and Erysipelotrichaceae) were decreased and the abundance of valeric acid associated bacteria (Acidobacteria) was increased in autistic individuals[66]. Rats treated with propionic acid showed restricted interest and impaired social behavior, as observed in ASD[67]. Therefore, it can be speculated that the pathogenesis of ASD might be caused by the overproduction of propionate by gut microbiota[67]. The modulate of gut microbiota might be a promising model of epilepsy, it has been confirmed that a ketogenic diet exerts an anti-epileptic effect by changing the composition of gut microbiota, consequently resulting in increased expression of GABA in the hippocampus of mice. The transplantation of feces from epileptic mice with ketogenic diet intervention in the normal diet group can reduce the frequency of seizures[50]. However, studies regarding the role of gut microbiota in epilepsy remain limited, and most of them are related to treatment through a ketogenic diet[51]. Their roles in epilepsy are likely to be optimistic. A previous study based on a mouse vascular dementia model showed that injection with Clostridium butyricum significantly reduced cognitive impairment and histopathological changes in the hippocampus of mice by regulating the gut-brain axis, Clostridium butyricum increased the levels of BDNF and Bcl-2 but decreased level of Bax and induced Akt phosphorylation, ultimately reduced neuronal apoptosis[52]. Furthermore, SCFAs reversed functional abnormalities in the mitochondrial respiratory chain complex in the prefrontal cortex, hippocampus, striatum, and amygdala regions of rats in manic animal models, as well as reversed depressive and manic behaviors which was associated with histone deacetylase inhibition[53]. The studies above indirectly indicated that SCFAs can affect the anatomical structure associated closely with epilepsy. Hence, further studies regarding the relationship between SCFAs and epilepsy are warranted.
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CONCLUSION

Explosive basic and clinical studies have implicated gut microbiota dysbiosis and SCFAs to play critical roles in various neurological diseases (Figure 1). Despite the low levels of SCFA in peripheral circulation, they may actively interact with the MGB axis involving various biological processes by binding to GRPs or by inhibiting HDAC. In addition, they may interfere with immune response, exerting anti-inflammatory functions, or activate the vagus nerve and finally communicate with the brain. It is proposed that the fecal SCFA levels are decreased in most neurological disorders; this may be related to the intracranial pathology. These promising results also suggest their potential protective roles in CNS diseases, and SCFAs supplementation may be anticipated as an effective therapy in the future. An earlier systematic review summarized the human randomized clinical trials regarding the effects of gut microbiota shaping on cognitive functions, including probiotics, prebiotics, synbiotics, and fecal microbiota transplant (FMT). The results showed that probiotic supplementation and FMT could improve cognitive functions in subjects, irrespective of their health; however, supplementation with prebiotics in unhealthy subjects did not provide any cognitive improvement[71]. Most studies are descriptive research. Most current results are revealed in animal studies, and the remaining small number of clinical studies generally include small sample sizes, resulting in a low-level evidence. Relatively few studies are published in the field of epilepsy and certain other fields, such as chronic method for the treatment of ASD.

MDD is the most typical mental disorder among the disabilities worldwide. A clinical study had shown that fecal SCFA levels decreased in patients with depression although the size of groups in this clinical study is small and more participants are needed[68]. Similarly, in an animal study, three major fecal SCFAs (acetic acid, propionic acid and pentanoic acid) in the hypothalamus were discovered to be lower in depressed mice than in control mice[69]. Recently, it was reported that high-dietary fiber significantly attenuated depressive symptoms in maternal mice after weaning offspring by elevating the formation of SCFAs[70]. These studies indicate that SCFAs might be vital to the pathogenesis of MDD and may be a possible treatment strategy for MDD in the future.
vascular diseases, that are also speculated to be possibly related to microbiota dysbiosis. Moreover, most studies are elucidated around the trends of SCFAs in specified neurological diseases, whereas deeper linking or mechanisms between SCFAs and the brain are still ambiguous. Further, larger samples of clinical studies and basic mechanism research are urgently warranted.

FOOTNOTES

Author contributions: Guo C and Huo YJ are involved in drafting and writing the manuscript; Li Y and Han Y are involved in editing the manuscript; Zhou D are involved in critical revision and editing the manuscript; all authors read and approved the final version of this manuscript.

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Association between direct-acting antiviral agents in hepatitis C virus treatment and hepatocellular carcinoma occurrence and recurrence: The endless debate

Ahmed Kamal, Ahmed Elsheaita, Mahmoud Abdelnabi

Abstract

Since direct-acting antiviral agents (DAAs) have been introduced into hepatitis C virus treatment, the sustained viral response (SVR) rate has significantly increased to more than 95%. Scientific evidence supports the idea that SVR after interferon therapy has beneficial effects related to cirrhosis progression, resulting in a reduction in the incidence of hepatocellular carcinoma (HCC). However, a significant debate exists related to DAA impact on HCC development. We reviewed the current literature highlighting the controversial data related to DAA association with de novo HCC occurrence or recurrence and possible pathophysiology of HCC related to DAAs. After a review of the published literature, we believe that the current evidence does not confirm or repudiate a higher rate of de novo HCC occurrence or recurrence related to DAA therapy. More trials are needed to determine if there is an association between HCC occurrence or recurrence and DAA or if it is related to preexisting liver cirrhosis.

Key Words: Hepatitis C virus; Sustained virologic response; Direct-acting antiviral drugs; Hepatocellular carcinoma; Liver cirrhosis

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INTRODUCTION

Hepatitis C virus (HCV) is an enveloped single-stranded ribonucleic acid (RNA) virus. It is mainly transmitted through infected blood, after which it identifies the target cell through multiple molecules; it enters the host cells by clathrin-mediated endocytosis. In the cell, the viral capsid is disrupted and the RNA genome is released to be translated into a single polypeptide precursor that is later cleaved into multiple mature products[1]. Co- and post-translational cleavage steps are mediated by different viral proteins, including proteins (nonstructural protein 3 [NS3], NS4A, NS5A, and NS5B proteins) that are targets for direct-acting antiviral agents (DAAs)[2]. Hepatocellular carcinoma (HCC) occurrence reflects the integration of different host, viral, and environmental factors over many years[2]. HCV-mediated liver inflammation with subsequent tissue necrosis, fibrosis, and cellular regeneration lead to genetic mutations that lead to neoplastic transformation[2]. HCV proteins themselves are carcinogenic[2]. NS5B has a role in cell cycle disruption and accordingly HCC development, through binding to retinoblastoma protein—that controls cell proliferation—and promoting its degradation, which sequentially stimulates cell cycle progression. Other products E2, NS3, and NS5A result in aggressive HCC development through disrupting RAF/mitogen-activated protein kinase/extracellular signal-regulated kinase-regulated pathways. Some products, such as NS2 NS3, and NS5A inhibit p53, resulting in abnormal cell cycle and apoptosis[3].

The annual HCC occurrence rate in untreated HCV patients is 2%-8%[4]. HCC recurrence rates after curative treatments, namely surgical management and thermal ablation, differ between trials. A meta-analysis that included 11 studies evaluated the recurrence rates of HCC in patients who did not receive HCV treatment post radiofrequency ablation (RFA) or surgical intervention for the HCC < 3 cm in size. The 6-mo recurrence rates were between 0% and 12.5%, recurrence at 1-year was between 4.9% and 62.5%, and recurrence at 2 years was between 31.8% and 100%. Probabilities of recurrence from this meta-analysis were 7.4% at 6 mo, 20% at 1 year, and 47% at 2 years[5].

Antiviral therapy against hepatitis B virus (HBV) reduces the risk of HCC development and recurrence[6]. In HCV, the impact of HCV eradication using pegylated interferon (IFN) on HCC occurrence and recurrence has also been studied[6,7]. The studies found a decrease in HCC occurrence and recurrence over time due to turning off the necro-inflammatory process with antiviral treatment. Yet, there is still a significant risk in cirrhotic patients, and therefore, long-term surveillance for HCC is necessary[8].

HCV eradication is now better achieved using DAAs but may be lower in HCC patients. Beste et al[9] reported sustained virologic response (SVR) after different DAA regimens in 74% of HCC patients; it was 91% in non-HCC patients. Another study reported higher viral relapse after oral anti-HCV regimens in patients with active or treated HCC compared to patients without HCC history (21% vs 12%) with significantly higher relapse rates among those with active HCC[10]. In another study, ledipasvir/sofosbuvir showed lower 12-wk SVR (SVR12) among HCC patients compared with non-HCC patients. SVR rates were 94.1% and 98.7% in HCC and non-HCC groups, respectively[11]. An Egyptian cohort compared SVR rates in those with successfully managed HCC with sofosbuvir combined with ribavirin alone or sofosbuvir combined with daclatasvir or simprevir. Overall rates of SVR12 in this cohort were 64.5%. SVR rate was highest (87.5%) in treated HCV patients with a combination of sofosbuvir, daclatasvir, and ribavirin, which indicate a significant benefit of ribavirin addition to a sofosbuvir-daclatasvir regimen in HCC patients treated with ablation[12].

Another Egyptian study reported an overall SVR12 rate among patients with ablated HCC treated sofosbuvir in addition to daclatasvir with or without ribavirin was 68%, and 85.7% after sofosbuvir/ledipasvir treatment[13].

In HCV patients, lower SVR rates may be explained by decreased delivery of the drug to the cancerous hepatocytes leaving these cells as a reservoir for HCV. Again, immune and inflammatory changes in patients with HCC can explain the somewhat unfavorable response after DAAs[10,14].
IFN therapy can decrease the risk of de novo HCC development in cirrhotic patients with an adjusted relative risk of 0.54 (95% confidence interval [CI]: 0.33-0.89) compared to untreated patients. The effect is more evident in patients who achieve SVR with a relative risk of 0.05 (95% CI: 0.006-0.34) compared to untreated patients[15]. Also, IFN-based therapy has a significant impact on the reduction of all-cause mortality in chronic HCV patients[16-18]. The incidence of HCC was estimated to be 1% approximately per year in patients with SVR treated with IFN-based therapy[19,20]. Again, it was estimated that IFN-based therapy decreases HCC occurrence by 76%[19]. Unfortunately, such agreement is not present in the case of DAAs despite achieving more than 90% SVR in a 12-wk period[17,21].

A meta-analysis studied the role of IFN therapy for HCV after curative treatment for HCC showed that IFN reduced the HCC recurrence rates at 2, 3, and 5 years of follow-up in HCV patients, but no significant change was observed in the recurrence rate of HCC during the 1st year of follow-up[22]. Although higher SVR rates can be attained with DAAs, their effects on de novo HCC occurrence and recurrence are uncertain. Several papers have reported an increase in the incidence of HCC occurrence and/or recurrence after DAAs administration. Tumorigenesis after DAAs can be attributed to an imbalance between cell apoptosis and pro-survival[2,23]. The direct and rapid viral eradication caused by DAAs without immune system involvement can disrupt the natural surveillance by the immune system with subsequent dormant tumor cells progression[23,24]. This fast viral eradication induces disruption of the innate immunity and reduction of IFN receptors II and III that regulate tumor angiogenesis and tumor anti-proliferative effects[24,25]. The rapid decline in natural killer cells has been linked to HCC progression[24,26]. Several immune mediators were identified and shown to be at higher levels before DAA initiation in patients who developed HCC thereafter[27]. Moreover, the level of tumor necrosis factor alpha (TNF-α) remained high after DAA completion in those who developed HCC thereafter but was decreased in subjects who did not develop HCC later. This suggests a role for persistent high TNF-α in HCC occurrence and recurrence after DAAAs[27,28]. Vascular endothelial growth factor (VEGF) also increases during DAA therapy and persists at high levels for 3 mo[29]. In addition, higher levels of angiopoietin-2 in patients with HCC occurrence and recurrence after DAAs have been found, and the authors suggested that the increase in VEGF induced by DAAs stimulates neo-angiogenesis in the liver in patients with clinically significant portal hypertension[30]. Some studies also noted a significant reduction in microRNA 122 concentrations in serum levels in patients treated with DAAs, which has a central role in suppressing HCC development and hence that also might be implicated in tumor development[31,32].

ASSOCIATION BETWEEN DAAS AND DE NOVO HCC

A few months after wide-scale implementation of DAAs in HCV management, many reports surprisingly reported higher rates of HCC recurrence and occurrence[33,34]. In a study done by Cardoso et al[35], 7.4% of the patients who achieved SVR on DAAs were diagnosed with HCC with a median time for HCC development of 8 mo.

Conti et al[34] reported that 3% of the patients treated with DAAs developed de novo HCC within a 6-mo follow-up and concluded that attaining SVR on DAAs does not seem to reduce the incidence of HCC occurrence. Moreover, multivariate analysis found that the risk of HCC development increased with a higher Child-Pugh score.

Kozbial et al[36] also reported that in patients with SVR on DAA therapy, there was a 5% incidence of de novo HCC development, which is significantly higher than that with IFN-based therapy as mentioned before.

In a retrospective study, Ravi et al[33] observed de novo HCC occurrence in about 9% of HCV-related cirrhosis patients during or within 6 mo of DAA therapy and another 3% developed new indeterminate lesions.

A French study that followed three separate cohorts with more than 6000 patients treated with DAAs concluded that recurrence of HCC is similar in treated and untreated patients[37]. Other studies reached a similar conclusion regarding de novo HCC occurrence after DAAs[21,38].

The same results were obtained in a British study. Also, this study concluded that DAAs were associated with improved liver function in patients with decompensated liver cirrhosis compared to placebo[39]. This indicates that in contrast to IFN-based therapy, DAAs do not reduce the incidence of HCC after achieving SVR, but at the same time do not increase its incidence.

Abdelaziz et al[40] in a small retrospective study that included 89 patients who developed HCC after DAAs (either occurrence or recurrence) found that the time until HCC development was significantly longer in the de novo group compared to the recurrence group.

Zeng et al[20] suggested that DAA treatment often includes advanced age groups and patients with advanced cirrhotic disease who cannot receive IFN-based therapy.

In response to such a theory, Calvaruso et al[41] studied HCC occurrence in patients treated with DAAs with Child-Pugh class A and B. In 1 year, HCC occurred in approximately 2% of patients with Child-Pugh class A and 8% in class B (P < 0.001). Moreover, low serum albumin and thrombocytopenia were independently associated with increased risk of HCC.
A similar study that included about 4000 patients found that in a 1-year follow-up, the risk of HCC development was 0.46% (95%CI: 0.12-1.17) in patients with F3 class based on METAVIR fibrosis and activity score, 1.49% (1.03-2.08) in Child-Pugh A, and 3.61% (1.86-6.31) in Child-Pugh B patients[42].

In a large retrospective study that included more than 22000 patients, DAA-treated patients who achieved SVR had a significantly reduced HCC risk (0.90 vs 3.45 HCC/100 person-years; adjusted hazard ratio 0.28; 95%CI: 0.22-0.36). However, in patients with established cirrhosis who achieved SVR, the absolute HCC risk remained high, indicating that liver cirrhosis was the most significant risk factor for HCC development[43].

Finkelmeier et al[44] followed 819 patients for a median period of 263 d after DAA therapy and found that in 550 patients with no cirrhosis (F0-F3) none developed de novo HCC, while 9% of those with cirrhosis (F4) developed de novo HCC. In addition, HCC developed more in males, older patients, treated patients, patients with a lower SVR12 rate, and those with higher levels of liver inflammation markers. The study compared their cohort with an older cohort of IFN-treated patients and concluded that de novo HCC development is the same with DAs and IFN.

Ioannou et al[45] found a higher HCC incidence with DAs compared to IFN-based therapy, but after adjusting confounders, including age, cirrhosis severity, serum albumin, and platelet count, it was concluded that HCC risk reduction was achieved regardless of the regimen used to achieve SVR.

Mettke et al[38] found a similar finding. In a multivariate analysis, only a higher MELD-Score and α fetoprotein (AFP)-levels were associated with a higher risk of HCC.

Tani et al[46] studied 1454 patients who received DAs and found that the annual incidence of de novo HCC was 1.8%. This study identified age and AFP level after DAs as independent factors risk factors for HCC development and proposed a novel scoring system (0-2 points) to predict HCC occurrence following DAs. HCC incidence at 2 years was 0.3%, 6.27%, and 18.37% in 0-, 1-, and 2-point, groups, respectively. However, independent validation is required for this scoring system.

Shiha et al[47] studied 2400 patients in Egypt with advanced fibrosis (F3-F4) and found that the annual incidence of HCC was 2.3% (95%CI: 1.942-2.814) with a slightly higher incidence in patients with cirrhosis (2.9%, 95%CI: 2.407-3.535). Similar findings were reported from a prospective study in Latin America that reported an annual incidence of 2% in a cohort of 1400 patients; all the patients who developed HCC were classified as F3-F4 classes according to METAVIR fibrosis and activity score before initiating treatment with DAs[48].

However, another study that included 400 patients in Egypt found that HCC occurrence rate was 7.6% in patients who received DAs. All patients included had also cirrhosis and/or with fibrosis (class F3-F4)[49]. Similar findings were reported by Hassany et al[50] in a cohort of 350 Egyptian patients in which HCC occurrence after DAs was 6.7% in patients with SVR and 23.8% in patients with non-SVR.

A meta-analysis that included 26 studies found that DAA therapy was not associated with higher HCC occurrence (RR 0.68, 95%CI: 0.18-2.55,  P = 0.55), and the authors concluded that there is no difference in HCC occurrence following SVR with DAs compared to IFN-based therapy[51]. Another meta-analysis that included 138 studies found that the hazard ratio was 0.58 (95%CI: 0.20-1.07) for HCC occurrence and 0.59 (95%CI: 0.24-1.03) for HCC recurrence after DAA treatment compared to IFN-based treatment[52].

Furthermore, Abdelaziz et al[53] studied the differences in tumor behavior HCV-induced HCC in patients either treated with or without DAs and concluded that HCC behavior was more aggressive in DAA-treated patients based on portal vein thrombosis, malignant lymphadenopathy, and HCC imaging characteristics.

El Fayoumie et al[54] assessed pattern changes in HCC after DAA treatment and demonstrated that HCC after DAA treatment may occur in less advanced liver disease. Infiltrative and multiple nodules patterns of HCC after DAA treatment were significantly more frequent than among HCC patients without DAA treatment. Also, HCC was still detected up to 4 years after starting DAA therapy.

However, most of the trials did not report the long-term incidence of HCC occurrence post-DAs (e.g., see Pecoraro et al[55]), and due to the relatively short period of DAA treatment, it is difficult to draw a solid conclusion regarding the relationship between DAs and HCC. The summary of the studies is listed in Table 1.

**ASSOCIATION BETWEEN HCC RECURRENCE AND DAS**

Regarding HCC recurrence after DAs, in 2016 Reig et al[56] were the first to report high HCC recurrence rates at 28% with a 3.5-mo median time from initiating DAs. They also reported a more aggressive HCC recurrence[57]. Another Italian study reported that the recurrence rate of HCC was also 28% 6 mo after DAA therapy[34]. HCC recurrence in 30% of cases within 1 year was reported in another study[58]. In 2017, a high HCC recurrence rate after DAs was again reported by another multicenter study[59]. HCC recurrence rate after liver transplantation was also reportedly high in patients who received DAs before surgery[60]. In contrast to this study, another study reported no HCC recurrence in a group managed by liver transplantation but high rates of recurrence among those treated with RFA or liver resection. In 2018, Elkassas et al[61] reported a non-randomized trial with a significantly
Table 1 Summary of studies of the association between direct-acting antiviral agents and de novo hepatocellular carcinoma occurrence

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Type of study</th>
<th>n (treated with DAAs)</th>
<th>Follow-up period</th>
<th>Incidence of HCC occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravi et al[33]</td>
<td>Prospective</td>
<td>61</td>
<td>6 mo</td>
<td>9%</td>
</tr>
<tr>
<td>Conti et al[34]</td>
<td>Prospective</td>
<td>344</td>
<td>24 wk</td>
<td>3.16%</td>
</tr>
<tr>
<td>Cardoso et al[35]</td>
<td>Prospective</td>
<td>240</td>
<td>12 mo</td>
<td>7.4%</td>
</tr>
<tr>
<td>Mettke et al[59]</td>
<td>Prospective cohort treated with DAAs vs retrospective control matched group of untreated patients</td>
<td>158 in DAAs group vs 184 in the control group</td>
<td>440 d for DAAs group vs 592 d for the control group</td>
<td>2.9% vs 4.5%</td>
</tr>
<tr>
<td>Cheung et al[59]</td>
<td>Prospective cohort treated with DAAs vs retrospective control matched group of untreated patients</td>
<td>406 in each group</td>
<td>15 mo</td>
<td>4% in both groups</td>
</tr>
<tr>
<td>Calvaruso et al[40]</td>
<td>Prospective</td>
<td>2249</td>
<td>16 mo</td>
<td>3.5%</td>
</tr>
<tr>
<td>Romano et al[41]</td>
<td>Prospective</td>
<td>3917</td>
<td>536.2 + 197.6 d</td>
<td>1.4%</td>
</tr>
<tr>
<td>Kanwal et al[43]</td>
<td>Retrospective</td>
<td>22500</td>
<td>12 mo</td>
<td>1.18%</td>
</tr>
<tr>
<td>Finkelmeier et al[44]</td>
<td>Prospective</td>
<td>819</td>
<td>263 d</td>
<td>3.6% annually</td>
</tr>
<tr>
<td>Ioannou et al[45]</td>
<td>Retrospective</td>
<td>21348 treated with IFN free regimen</td>
<td>-</td>
<td>1.32% annually</td>
</tr>
<tr>
<td>Tani et al[46]</td>
<td>Retrospective</td>
<td>1088 (Patients with SVR)</td>
<td>4 yr</td>
<td>1.88% annually</td>
</tr>
<tr>
<td>Shih et al[47]</td>
<td>Prospective</td>
<td>2372 patients with advanced liver fibrosis or cirrhosis with SVR</td>
<td>12 mo</td>
<td>2.3% annually</td>
</tr>
<tr>
<td>Pinero et al[48]</td>
<td>Prospective</td>
<td>1400</td>
<td>16 mo</td>
<td>2% annually</td>
</tr>
<tr>
<td>Lashen et al[49]</td>
<td>Retrospective</td>
<td>392 (F3-F4) patients</td>
<td>34 mo</td>
<td>7.6%</td>
</tr>
<tr>
<td>Hassany et al[50]</td>
<td>Prospective</td>
<td>350</td>
<td>2 yr after the end of treatment</td>
<td>6.7% in patients with SVR vs 23.8% in patients with non-SVR</td>
</tr>
</tbody>
</table>

DAAs: Direct-acting antiviral agents; HCC: Hepatocellular carcinoma; IFN: Interferon; SVR: Sustained viral response.

increased HCC recurrence rate after DAAs in Egyptian patients. More microvascular invasion in tumors after DAAs was reported in another study[62].

Data from the ANRS cohorts from France showed no significant difference in HCC recurrence between those who received DAAs and those who did not[37]. In 2017, Cabibbo et al.[63] reported that the recurrence rates after DAAs at 6 and 1-year follow-up were comparable to those reported previously without HCV treatment (12% and 26.6%, respectively). In addition, another study also found no higher risk of HCC recurrence on DAAs[9]. A meta-analysis of papers published between 2000 and February 2017 found no increased risk of HCC recurrence after DAAs when compared to that after IFN[62].

In 2018, another multicenter study showed no increase in HCC recurrence on DAAs[64]. Another study reported that patients who received DAAs had a lower risk of dropping off the transplantation waiting list due to death or HCC growth. Huang et al.[65] described HCC recurrence at a rate of 17% per year in their meta-analysis, and they concluded that there was no strong evidence of increased HCC recurrence risk after DAAs.

In 2019, a multicenter study with North American cohorts reported no link between DAAs and HCC recurrence[66]. A Japanese study compared the behavior and HCC recurrence risk and found no differences after IFN or DAA therapy[67]. A meta-analysis revealed no verification of increased probability of HCC recurrence post-DAA therapy with a rate of HCC recurrence after DAAs equals 16.76% per year[32]. Another study revealed better survival in patients with ablated HCC who received DAAs thereafter[68].

In a more recent international multicenter retrospective study published in 2020, there was no increase in the risk of HCC recurrence or the risk of mortality in patients with HCC waiting for liver transplantation[69]. Another group reported no difference in the behavior of HCC recurrence or mortality rates in patients who achieved SVR after either IFN or DAAs[70].
Kamal et al[13] reported 26.9% and 42.3% HCC recurrence rates at 1- and 2-year follow-up in a cohort that received DAAs. The authors concluded that DAAs do not increase overall HCC recurrence rates, similar to the rates in untreated HCV patients with ablated curable HCC although authors included lesions up to 5 cm in their cohort.

Zeng et al[20] described no recurrence in the HCC group after DAAs. Another study also described a significant decrease in HCC recurrence after DAAs[71]. A more recent study in 2020 also described the same finding[72].

Increasing the interval between HCC management and DAA initiation is suggested to decrease the risk of early HCC recurrence after DAAs. A Japanese study recommended that to reduce the risk of HCC recurrence, at least a 120-d interval between HCC management and initiation of DAA therapy[73]. Kamal et al[13] also observed higher 6-mo HCC recurrence in those who started DAAs within 12 wk from percutaneous tumor ablation with a higher incidence of multi-centric recurrence. But the recurrence rates were nearly equal in both groups by the end of the first and second years of follow-up and close to the recurrence rates reported after curative HCC management in HCV untreated patients although they have included lesions up to 5 cm, not only 3 cm, in their study. The summary of the studies is listed in Table 2.

### Table 2 Summary of Studies of the association between direct-acting antiviral agents and hepatocellular carcinoma recurrence

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Type of study</th>
<th>Number (treated with DAAs)</th>
<th>Median follow-up period</th>
<th>Incidence of HCC recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reig et al[56]</td>
<td>Retrospective</td>
<td>58</td>
<td>5.7 mo</td>
<td>27.6%</td>
</tr>
<tr>
<td>Conti et al[34]</td>
<td>Prospective</td>
<td>59</td>
<td>24 wk</td>
<td>28.81%</td>
</tr>
<tr>
<td>Calleja et al[58]</td>
<td>Retrospective</td>
<td>70</td>
<td>12 mo</td>
<td>30%</td>
</tr>
<tr>
<td>Elkassas et al[61]</td>
<td>Prospective</td>
<td>53 vs 63 untreated patients</td>
<td>16 mo vs 23 mo in the untreated group</td>
<td>37.7% vs 25.4%</td>
</tr>
<tr>
<td>ANRS study group[37]</td>
<td>Retrospective</td>
<td>(1) ANRS CO22 HEPATHER cohort: 189 vs 78 untreated patients</td>
<td>20.2 vs 26.2 mo</td>
<td>0.73 vs 0.66/100 person-mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) ANRS CO12 CirVir cohort: 13 patients received DAAs</td>
<td>79 mo</td>
<td>7.7%</td>
</tr>
<tr>
<td>Ogawa et al[64]</td>
<td>Prospective</td>
<td>152</td>
<td>1 yr</td>
<td>6.5% in non-cirrhotic and 23% in cirrhotic patients</td>
</tr>
<tr>
<td>Cabibbo et al[68]</td>
<td>Prospective</td>
<td>143</td>
<td>18 mo</td>
<td>29.1%</td>
</tr>
<tr>
<td>Huang et al[65]</td>
<td>Retrospective</td>
<td>62 receive DAAs vs 87 did not receive DAAs</td>
<td>12 mo</td>
<td>47% vs 49.8%</td>
</tr>
<tr>
<td>Singal et al[66]</td>
<td>Retrospective</td>
<td>304 received DAAs and 489 did not</td>
<td>365 d</td>
<td>17.1 vs 46.4%</td>
</tr>
<tr>
<td>Kinoshita et al[67]</td>
<td>Retrospective</td>
<td>147 received DAAs vs 156 received IFN</td>
<td>2 yr</td>
<td>60% vs 61%</td>
</tr>
<tr>
<td>Ikeda et al[71]</td>
<td>Prospective</td>
<td>89</td>
<td>2 yr</td>
<td>22.1%</td>
</tr>
<tr>
<td>Imai et al[72]</td>
<td>Retrospective</td>
<td>13 DAAs, 14 IFN, and 64 untreated groups</td>
<td>-</td>
<td>The 3-yr recurrence-free survival was 76.2% in DAAs group vs 69.2% in the IFN group and 22.4% in the untreated group</td>
</tr>
<tr>
<td>Gorgen et al[69]</td>
<td>Retrospective</td>
<td>875</td>
<td>-</td>
<td>The 5-yr recurrence-free survival was 93.4%, 84.8%, 73.9% for the pre-liver transplant DAA, IFN, and antiviral naïve groups</td>
</tr>
<tr>
<td>Tahata et al[70]</td>
<td>Retrospective</td>
<td>63 patients in each group</td>
<td>3 yr</td>
<td>43% in the DAAs vs 34% in the IFN group</td>
</tr>
<tr>
<td>Kamal et al[13]</td>
<td>Retrospective</td>
<td>52</td>
<td>2 yr</td>
<td>42.3%</td>
</tr>
</tbody>
</table>

DAAs: Direct-acting antiviral agents; HCC: Hepatocellular carcinoma; IFN: Interferon.

**CONCLUSION**

In conclusion, although DAAs are associated with increased SVR, there is still controversial data regarding the association between DAAs with de novo HCC occurrence, recurrence, and HCC morphologic and pathological behaviors. Also, when to initiate DAA treatment in patients with treated
HCC is still uncertain. Randomized trials are required to address these issues.

FOOTNOTES

Author contributions: All authors contributed equally to the literature review, data collection, and manuscript writing, and approved the final version of the manuscript.

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S-Editor: Chang KL
L-Editor: Filipodia
P-Editor: Chang KL

REFERENCES


Retrospective Cohort Study

Effects of bilirubin on perioperative myocardial infarction and its long-term prognosis in patients undergoing percutaneous coronary intervention

Ya Li, Duan-Bin Li, Li-Ding Zhao, Qing-Bo Lv, Yao Wang, Ya-Fei Ren, Wen-Bin Zhang

Abstract

BACKGROUND
Although bilirubin is known to be an antioxidant, any relationship with coronary heart disease remains controversial. To the best of our knowledge, no previous study has investigated the association between bilirubin and perioperative myocardial infarction (PMI), including its long-term prognosis.

AIM
To investigate the impact of bilirubin levels on PMI in patients undergoing percutaneous coronary intervention (PCI), and long-term prognosis in post-PMI patients.

METHODS
Between January 2014 and September 2018, 10236 patients undergoing elective PCI were enrolled in the present study. Total bilirubin (TB) and cardiac troponin I (cTnI) levels were measured prior to PCI and cTnI at further time-points, 8, 16 and 24 h after PCI. Participants were stratified by pre-PCI TB levels and divided into three groups: < 10.2; 10.2-14.4 and > 14.4 μmol/L. PMI was defined as producing a post-procedural cTnI level of > 5 × upper limit of normal (ULN) with normal baseline cTnI. Major adverse cardiovascular events (MACEs) included cardiac death, MI, stroke and revascularization during a maximum 5-year follow-up.

RESULTS
PMI was detected in 526 (15.3%), 431 (12.7%) and 424 (12.5%) of patients with pre-
PCI TB levels of < 10.2, 10.2-14.4 and > 14.4 μmol/L (P = 0.001), respectively. Multivariate logistical analysis indicated that patients with TB 10.2-14.4 and > 14.4 μmol/L had a lower incidence of PMI [TB 10.2-14.4 μmol/L: Odds ratio (OR): 0.854; 95% confidence interval (CI): 0.739-0.987; P = 0.032; TB > 14.4 μmol/L: OR: 0.846; 95%CI: 0.735-0.975; P = 0.021] compared with patients with TB < 10.2 μmol/L. Construction of a Kaplan-Meier curve demonstrated a higher MACE-free survival time for patients with higher TB than for those with lower TB (log-rank P = 0.022). After adjustment for cardiovascular risk factors and angiographic characteristics, multivariate Cox analysis showed that a TB level > 14.4 μmol/L was associated with a reduced risk of MACEs compared with a TB level < 10.2 μmol/L (hazard ratio 0. 667; 95%CI: 0.485-0.918; P = 0.013).

CONCLUSION
Bilirubin was a protective factor in PMI prediction. For post-PMI patients, elevated bilirubin levels were independently associated with a reduced risk of MACEs during long-term follow-up.

Key Words: Bilirubin; Perioperative myocardial infarction; Percutaneous coronary intervention; Major adverse cardiovascular events; Coronary heart disease; Retrospective cohort study

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Core Tip: Perioperative myocardial infarction (PMI) is a frequent complication of percutaneous coronary intervention, with an adverse long-term outcome. Previous studies have sought to identify potential targets for PMI avoidance. The current study was designed to explore the effect of bilirubin on PMI and its utility for long-term prognosis. Bilirubin has a protective effect making it a suitable predictor of PMI. Furthermore, elevated levels of bilirubin are associated with a reduced risk of major adverse cardiovascular events during long-term follow-up of post-PMI patients. We present evidence of the suitability of bilirubin as a therapeutic target for PMI prevention and other oxidative diseases.

DOI: https://dx.doi.org/10.12998/wjcc.v10.i6.1775

INTRODUCTION
Perioperative myocardial infarction (PMI) is a frequent complication of percutaneous coronary intervention (PCI)[1,2]. Despite technological advances over the past two decades, the frequency of PMI remains between 5% and 30% with higher rates in patients with complex lesions. PMI may occur via several mechanisms, including side branch occlusion, distal embolization, inflammation and endothelial injury, all of which may contribute to myocardial damage[3]. Many other causative factors affecting PMI risk remain controversial.

Traditionally, the end product of heme catabolism, bilirubin, has been considered a cytotoxic waste product. More recently, an appreciation of its anti-oxidant and anti-inflammatory effects, involving scavenging of ROS to improve vascular and microvascular dysfunction, has emerged[4-6]. Indeed, it is more than 20 years since the antioxidant role of bilirubin in in vivo ischemia-reperfusion was established[7] and, more recently, Bösch et al[8] also found an ameliorating effect on ischemia reperfusion damage in mice[5]. A number of recent clinical studies have reported a protective role of bilirubin in coronary artery disease (CAD)[4-6], although there are also some contradictory reports[9,10]. Indeed, elevated bilirubin has been associated with increased in-hospital mortality in acute coronary syndrome[11] and positively correlated with SYNTAX score[10]. Thus, the relationship between bilirubin and CAD remains controversial. No previous study has investigated its effect on PMI and its utility for long-term prognosis.

The current study was designed to explore the relationship between bilirubin and PMI in patients undergoing PCI and its utility for predicting long-term outcomes. The following article is presented in accordance with the STROBE reporting checklist.
MATERIALS AND METHODS

Study population
The current retrospective study enrolled 10263 patients who had been diagnosed with CAD without pre-PCI elevation of cardiac troponin I (cTnI) between January 2014 and September 2018. All patients had elected to have single-vessel PCI. Patients were excluded for the following reasons: (1) Acute or chronic liver injury, biliary tract disease, hematological disease, vitamin B12 deficiency, heart failure or other factors leading to elevated bilirubin; (2) Acute myocardial infarction (MI) in the previous 4 wk; (3) Elective PCI for chronic total occlusion; and (4) Intraoperative factors leading to elevated cTnI, including side-branch occlusion during the procedure, severely calcified lesions with a rotablator or dissection, to enable evaluation of bilirubin effects with less confounding intraoperative factors. Acute liver injury was screened with an acute elevation of transaminases. Chronic liver injury was screened mainly by chronic elevation of transaminases with the case history, such as viral hepatitis, fatty liver disease, alcoholic hepatitis, autoimmune liver disease, biliopancreatic disease, drug-induced liver injury, liver cancer, liver cirrhosis and so on. Heart failure was defined according to the 2021 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure[12].

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Sir Run Run Shaw Hospital.

Procedures
Stent implantation was performed by experienced cardiac surgeons using the radial artery approach, according to current clinical practice. Patients were treated with aspirin (100 mg/night) and P2Y12 inhibitor (clopidogrel: 75 mg/d or ticlopidine: 180 mg twice daily) for three days before PCI. In the absence of pre-treatment, patients received 300 mg aspirin plus 300 mg clopidogrel or 180 mg ticlopidine before the operation as a loading dose. CTnI levels were measured by immunoassay pre-PCI and at 8, 16 and 24 h post-PCI. The peak value of cTnI over 24 h was used for analysis [upper limit of normal (ULN): 0.011 ng/mL]. Serum bilirubin level was measured before PCI.

Definitions of outcome
PMI was defined as a post-procedural cTnI > 5 × ULN (revised diagnosis criteria from the third or fourth version of the universal MI definition published in 2012 and 2018[13,14]. End points were defined as major adverse cardiovascular events (MACEs), a composite of cardiac death, MI, stroke and revascularization. PMI is not a composition of MACEs.

Statistical analysis
Statistical analyses were performed by the SPSS 22.0 statistical package (Chicago, Illinois, United States). Continuous variables were reported as mean ± SD or as median with interquartile range. Continuous variables were compared by the t-test (normal distribution) or Kruskal–Wallis test (non-normal distribution). Comparisons of continuous variables among three groups were performed by ANOVA. Categorical variables were expressed as frequencies and compared by chi-square test.

Multivariate logistical analysis was performed to determine independent predictors of PMI after adjustment for significant variables by univariate analysis (P < 0.05). Events rates were calculated using the Kaplan–Meier method. Analysis of factors relative to reported events was performed by multivariate Cox proportional hazards modeling. Hazard ratios (HRs) were presented with 95% CIs. A value of P < 0.05 was considered to show statistical significance.

RESULTS

Patient characteristics
The design of the present study is shown in Figure 1. Baseline clinical and procedural characteristics of the 10236 participants, grouped by pre-operative serum TB concentrations (< 10.2; 10.2-14.4; > 14.4 μmol/L), are shown in Table 1. Patients with lower TB were more likely to be older, female and to have a prevalence of unstable angina, hypertension, diabetes, and renal failure (estimated glomerular filtration rate: < 60 mL/min/1.73 m2). Patients in the lower TB group were also more likely to be taking angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB), calcium-channel blocker (CCB), receiving more stents and greater balloon pre-dilation.

Predictor of PMI
PMI was detected in 526 (15.3%), 431 (12.7%) and 424 (12.5%) of patients with pre-PCI TB levels of < 10.2, 10.2-14.4 and > 14.4 μmol/L (P = 0.001), respectively (Figure 2). Recorded rates of PMI were lower in patient groups with the two higher TB levels [TB 10.2-14.4 μmol/L: Odds ratio (OR): 0.854; 95% confidence interval (CI): 0.739-0.987; P = 0.032; TB > 14.4 μmol/L: OR: 0.846; 95% CI: 0.735-0.975; P = 0.021; Table 2] compared with the lowest level group after adjustment for age, gender, smoking,
<table>
<thead>
<tr>
<th>Variable</th>
<th>Tertile I &lt; 10.2 μmol/L, n = 3430</th>
<th>Tertile II 10.2-14.4 μmol/L, n = 3405</th>
<th>Tertile III &gt; 14.4 μmol/L, n = 3401</th>
<th>P value (All)</th>
<th>Tertile I vs Tertile II</th>
<th>Tertile I vs Tertile III</th>
<th>Tertile II vs Tertile III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.9 ± 10.4</td>
<td>66.3 ± 10.3</td>
<td>65.6 ± 10.0</td>
<td>&lt; 0.001</td>
<td>0.020</td>
<td>&lt; 0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1232 (36.0)</td>
<td>1017 (29.9)</td>
<td>676 (19.9)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6 ± 4.9</td>
<td>24.9 ± 11.2</td>
<td>24.9 ± 10.1</td>
<td>0.314</td>
<td>0.063</td>
<td>0.091</td>
<td>0.651</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>774 (22.6)</td>
<td>731 (21.5)</td>
<td>735 (21.6)</td>
<td>0.491</td>
<td>0.401</td>
<td>0.288</td>
<td>0.821</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1015 (29.6)</td>
<td>848 (24.9)</td>
<td>782 (23.0)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.028</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2413 (70.4)</td>
<td>2327 (68.3)</td>
<td>2276 (66.9)</td>
<td>0.008</td>
<td>0.021</td>
<td>&lt; 0.001</td>
<td>0.122</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>532 (15.5)</td>
<td>557 (16.4)</td>
<td>522 (15.3)</td>
<td>0.470</td>
<td>0.449</td>
<td>0.726</td>
<td>0.266</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
<td>353 (10.3)</td>
<td>300 (8.8)</td>
<td>253 (7.4)</td>
<td>&lt; 0.001</td>
<td>0.037</td>
<td>&lt; 0.001</td>
<td>0.110</td>
</tr>
<tr>
<td>eGFR &lt; 60 (mL/min/1.73 m²), n (%)</td>
<td>488 (14.2)</td>
<td>345 (10.1)</td>
<td>269 (7.9)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>66.8 ± 8.0</td>
<td>67.2 ± 7.8</td>
<td>67.0 ± 9.0</td>
<td>0.096</td>
<td>0.031</td>
<td>0.575</td>
<td>0.008</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>395 (11.5)</td>
<td>360 (10.6)</td>
<td>399 (11.7)</td>
<td>0.271</td>
<td>0.054</td>
<td>0.861</td>
<td>0.071</td>
</tr>
<tr>
<td>Prior PCI, n (%)</td>
<td>876 (25.5)</td>
<td>800 (23.5)</td>
<td>806 (23.7)</td>
<td>0.094</td>
<td>0.052</td>
<td>0.056</td>
<td>0.978</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>1850 (54.0)</td>
<td>1740 (51.1)</td>
<td>1708 (50.3)</td>
<td>0.006</td>
<td>0.002</td>
<td>&lt; 0.001</td>
<td>0.528</td>
</tr>
<tr>
<td>Perioperative medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>1979 (57.7)</td>
<td>1916 (56.3)</td>
<td>1825 (53.7)</td>
<td>0.003</td>
<td>0.613</td>
<td>&lt; 0.001</td>
<td>0.021</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>1746 (50.9)</td>
<td>1746 (51.3)</td>
<td>1691 (49.7)</td>
<td>0.407</td>
<td>0.835</td>
<td>0.129</td>
<td>0.082</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>1270 (37.0)</td>
<td>190 (34.9)</td>
<td>1114 (32.8)</td>
<td>0.001</td>
<td>0.004</td>
<td>&lt; 0.001</td>
<td>0.034</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.05 ± 0.88</td>
<td>2.09 ± 0.86</td>
<td>2.04 ± 0.86</td>
<td>0.053</td>
<td>0.117</td>
<td>0.843</td>
<td>0.076</td>
</tr>
<tr>
<td>Lesions in vessels, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>197 (5.7)</td>
<td>186 (5.5)</td>
<td>180 (5.3)</td>
<td>0.711</td>
<td>0.613</td>
<td>0.578</td>
<td>0.959</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>1828 (53.3)</td>
<td>1848 (54.3)</td>
<td>1837 (54.0)</td>
<td>0.702</td>
<td>0.187</td>
<td>0.321</td>
<td>0.926</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>579 (16.9)</td>
<td>524 (15.4)</td>
<td>578 (17.0)</td>
<td>0.136</td>
<td>0.068</td>
<td>0.902</td>
<td>0.051</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>983 (28.7)</td>
<td>994 (29.2)</td>
<td>955 (28.1)</td>
<td>0.597</td>
<td>0.960</td>
<td>0.196</td>
<td>0.184</td>
</tr>
<tr>
<td>AHA/ACC classification B₂/C, n (%)</td>
<td>1228 (35.8)</td>
<td>1256 (36.8)</td>
<td>1356 (39.9)</td>
<td>0.002</td>
<td>0.487</td>
<td>&lt; 0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>Calcification, n (%)</td>
<td>406 (11.8)</td>
<td>391 (11.5)</td>
<td>390 (11.5)</td>
<td>0.864</td>
<td>0.204</td>
<td>0.485</td>
<td>0.567</td>
</tr>
<tr>
<td>FFR/IVUS/OCT, n (%)</td>
<td>357 (10.4)</td>
<td>372 (10.9)</td>
<td>402 (11.8)</td>
<td>0.170</td>
<td>0.496</td>
<td>0.050</td>
<td>0.210</td>
</tr>
<tr>
<td>Number of implanted stents, median (IQR)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>&lt; 0.001</td>
<td>0.005</td>
<td>0.005</td>
<td>0.133</td>
</tr>
<tr>
<td>Mean stent size &gt; 2.5 mm, n (%)</td>
<td>3107 (90.6)</td>
<td>3077 (90.4)</td>
<td>3056 (89.9)</td>
<td>0.606</td>
<td>0.755</td>
<td>0.282</td>
<td>0.464</td>
</tr>
<tr>
<td>Balloon pre-dilation, n (%)</td>
<td>3031 (88.4)</td>
<td>2970 (87.2)</td>
<td>2921 (85.9)</td>
<td>0.009</td>
<td>0.039</td>
<td>0.001</td>
<td>0.183</td>
</tr>
<tr>
<td>Balloon post-dilation, n (%)</td>
<td>3175 (92.6)</td>
<td>3145 (92.4)</td>
<td>3156 (92.8)</td>
<td>0.793</td>
<td>0.999</td>
<td>0.828</td>
<td>0.827</td>
</tr>
</tbody>
</table>

Data are presented as n or %. ACEI: Angiotensin-Converting Enzyme Inhibitors; AHA/ACC: American Heart Association/American College of Cardiology; ARB: Angiotensin Receptor Blocker; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; FFR: Fractional flow reserve; IVUS: Intravascular ultrasound; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; OCT: Optical coherence tomography.

hypertension, renal function, left ventricular ejection fraction (LVEF), prior MI, the use of ACEI or ARB, American Heart Association/American College of Cardiology (AHA/ACC) classification, calcification, the use of fractional flow reserve (FFR)/intravascular ultrasound (IVUS)/optical coherence tomography (OCT) and number of implanted stents.
**Table 2 Factors affecting perioperative myocardial infarction in univariate and multivariate analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate model</th>
<th>Multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age &gt; 65 yr</td>
<td>1.428 (1.268, 1.607)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.225 (1.084, 1.384)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.983 (0.966, 1.000)</td>
<td>0.052</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.832 (0.721, 0.959)</td>
<td>0.011</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.134 (0.999, 1.287)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.271 (1.120, 1.443)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>1.181 (0.976, 1.428)</td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>1.309 (1.108, 1.547)</td>
<td>0.002</td>
</tr>
<tr>
<td>eGFR &lt; 60 (mL/min/1.73 m²)</td>
<td>1.645 (1.400, 1.933)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.975 (0.968, 0.982)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.116 (0.996, 1.250)</td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>1.243 (1.107, 1.395)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.992 (0.886, 1.112)</td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>1.067 (0.948, 1.201)</td>
<td></td>
</tr>
<tr>
<td>LDL-C &gt; 1.8 mmol/L</td>
<td>0.950 (0.808, 1.070)</td>
<td></td>
</tr>
<tr>
<td>AHA/ACC classification B2/C</td>
<td>1.167 (1.040, 1.311)</td>
<td>0.009</td>
</tr>
<tr>
<td>Calcification</td>
<td>1.767 (1.514, 2.063)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FFR/IVUS/OCT</td>
<td>1.391 (1.178, 1.642)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of implanted stents</td>
<td>1.868 (1.741, 2.006)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean stent size &gt; 2.5 mm</td>
<td>1.117 (0.917, 1.362)</td>
<td></td>
</tr>
<tr>
<td>Balloon pre-dilation</td>
<td>1.116 (0.937, 1.330)</td>
<td></td>
</tr>
<tr>
<td>Balloon post-dilation</td>
<td>1.330 (0.926, 1.912)</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>Tertile I</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>Tertile II</td>
<td>0.800 (0.698, 0.918)</td>
</tr>
<tr>
<td></td>
<td>Tertile III</td>
<td>0.786 (0.685, 0.902)</td>
</tr>
</tbody>
</table>

ACEI: Angiotensin-Converting Enzyme Inhibitors; AHA/ACC: American Heart Association/American College of Cardiology; ARB: Angiotensin Receptor Blocker; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; FFR: Fractional flow reserve; IVUS: Intravascular ultrasound; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; OCT: Optical coherence tomography.

**Clinical outcomes**

A total of 1310 post-PMI patients were followed up long-term. The median follow-up period was 3.2 years (interquartile range: 1.8-5.0). During follow-up, 258 (19.7%) cases of MACE were identified, including 53 (4.0%) cardiac deaths, 31 (2.4%) non-fatal MIs, 6 (0.5%) non-fatal strokes and 182 (13.9%) revascularizations. Kaplan-Meier curves were used to demonstrate that the cumulative incidence of MACEs decreased with the higher tertile of TB level (log-rank test; P = 0.022; Figure 3). The data indicated that better outcomes were correlated with higher TB levels.

Cox proportional hazard analysis was performed after adjustment for age, diabetes, unstable angina, low-density lipoprotein cholesterol (LDL-C) and number of stents implanted. The results demonstrated that patients with TB > 14.4 μmol/L had a reduced risk of long-term MACEs with an adjusted HR of 0.667 (95% CI: 0.485-0.918; P = 0.013; Table 3) compared with patients with TB < 10.2 μmol/L. Multivariate Cox models were constructed for further analysis of the relationships between TB levels and MACE component events. Patients with TB > 14.4 μmol/L were at decreased risk of revascularization (HR: 0.633; 95% CI: 0.458-0.875; P = 0.006; Table 4) compared to those with TB < 10.2 μmol/L.
Table 3 Cox proportional hazard regression model: incidence of major adverse cardiac events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate model</th>
<th>Multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age &gt; 65 yr</td>
<td>1.199 (1.080, 1.332)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>1.213 (0.921, 1.598)</td>
<td>0.170</td>
</tr>
<tr>
<td>BMI</td>
<td>1.005 (0.969, 1.042)</td>
<td>0.782</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.982 (0.733, 1.316)</td>
<td>0.905</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.135 (1.098, 1.173)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.122 (0.848, 1.484)</td>
<td>0.420</td>
</tr>
<tr>
<td>eGFR &lt; 60 (mL/min/1.73 m²)</td>
<td>1.291 (0.936, 1.780)</td>
<td>0.120</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.996 (0.984, 1.008)</td>
<td>0.540</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.284 (1.003, 1.644)</td>
<td>0.048</td>
</tr>
<tr>
<td>LDL-C &gt; 1.8 mmol/L</td>
<td>1.160 (1.650, 1.264)</td>
<td>0.001</td>
</tr>
<tr>
<td>Acei/ARB</td>
<td>1.077 (0.825, 1.340)</td>
<td>0.586</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>1.044 (0.810, 1.345)</td>
<td>0.739</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>1.197 (0.872, 1.644)</td>
<td>0.266</td>
</tr>
<tr>
<td>AHA/ACC classification B2/C</td>
<td>0.848 (0.638, 1.128)</td>
<td>0.258</td>
</tr>
<tr>
<td>Calcification</td>
<td>1.197 (0.872, 1.644)</td>
<td>0.266</td>
</tr>
<tr>
<td>Number of stents implanted</td>
<td>1.186 (1.031, 1.365)</td>
<td>0.017</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile I</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Tertile II</td>
<td>0.801 (0.604, 1.063)</td>
<td>0.125</td>
</tr>
<tr>
<td>Tertile III</td>
<td>0.640 (0.469, 0.875)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

ACEI: Angiotensin-Converting Enzyme Inhibitors; AHA/ACC: American Heart Association/American College of Cardiology; ARB: Angiotensin Receptor Blocker; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; FFR: Fractional flow reserve; IVUS: Intravascular ultrasound; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; OCT: Optical coherence tomography.

Adjusted HRs for different TB tertiles did not differ significantly with regard to cardiac death, non-fatal MI and non-fatal stroke (Table 4).

DISCUSSION

The current study presents data to demonstrate an independent association between higher preoperative TB levels and a lower incidence of PMI in patients receiving PCI. Furthermore, a high TB level is a protective factor producing a better long-term prognosis in post-PMI patients.

Persistent high rates of PMI, which are of particular concern among patients with complex lesions, are thought to be largely due to oxidative stress causing free radical and inflammatory damage to vascular endothelial cells[3,15,16]. There is an adverse impact on long-term morbidity for patients with PMI[17,18] which has stimulated the search for potential targets or risk factors to avoid development of the condition. Patients, lesion and procedure-related factors are all implicated[3]. Consistent with previous studies, current findings also indicate that age, gender, renal impairment, complexity of lesions and the number of stents implanted are all predictors of PMI development. Interestingly, the present study also suggests that use of FFR, OCT or IVUS may increase the likelihood of PMI. All these would not only increase additional procedures, but also prolong the operating time and increase the dose of contrast agent, which may aggravate myocardial damage.

Antioxidant properties have been attributed to bilirubin[19] and this breakdown product of heme may directly scavenge ROS[20] and inhibit NADPH oxidase[21]. Furthermore, bilirubin has been shown to inhibit peroxidation of lipids and lipoproteins, especially low-density lipoprotein[22-24], indirectly improving microvascular dysfunction. Any resulting improvement in endothelial function will be...
Table 4 Association between serum total bilirubin and clinical outcomes

<table>
<thead>
<tr>
<th>Events</th>
<th>Tertile I</th>
<th>Tertile II</th>
<th>Tertile III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite MACE(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number events/participants</td>
<td>118 (23.2)</td>
<td>81 (19.6)</td>
<td>59 (15.3)</td>
</tr>
<tr>
<td>Adjust HR and 95%CI</td>
<td>1.0 (ref)</td>
<td>0.837 (0.627, 1.119)</td>
<td>0.667 (0.485, 0.918)(^a)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number events/participants</td>
<td>27 (5.3)</td>
<td>13 (3.1)</td>
<td>13 (3.4)</td>
</tr>
<tr>
<td>Adjust HR and 95%CI</td>
<td>1.0 (ref)</td>
<td>0.546 (0.28, 1.065)</td>
<td>0.588 (0.295, 1.171)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number events/participants</td>
<td>13 (2.6)</td>
<td>11 (2.7)</td>
<td>7 (1.8)</td>
</tr>
<tr>
<td>Adjust HR and 95%CI</td>
<td>1.0 (ref)</td>
<td>1.113 (0.487, 2.547)</td>
<td>0.736 (0.286, 1.898)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number events/participants</td>
<td>2 (0.4)</td>
<td>20 (5.5)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Adjust HR and 95%CI</td>
<td>1.0 (ref)</td>
<td>1.534 (0.213, 11.067)</td>
<td>1.888 (0.251, 14.211)</td>
</tr>
<tr>
<td>Revascularization(^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number events/participants</td>
<td>84 (16.5)</td>
<td>59 (14.3)</td>
<td>39 (10.1)</td>
</tr>
<tr>
<td>Adjust HR and 95%CI</td>
<td>1.0 (ref)</td>
<td>0.814 (0.608, 1.089)</td>
<td>0.633 (0.458, 0.875)(^a)</td>
</tr>
</tbody>
</table>

\(^{1}\)Major cardiovascular adverse event was defined as a composite of cardiac death, myocardial infarction, stroke and revascularization.

\(^{2}\)Adjusted model included age, diabetes, unstable angina, LDL-C and numbers of stents implanted.

\(^a\)P < 0.05.

Cl: Confidence intervals; HR: Hazard ratio; MACE: Major cardiovascular adverse events.

Figure 1 The study design. CKMB: Creatine kinase myocardial-band; cTnI: Cardiac troponin I; PCI: Percutaneous coronary intervention; PTCRA: Percutaneous Transluminal Coronary Rotational Ablation.

instrumental in inhibiting the development of atherosclerosis and reducing cardiovascular complications.

Several clinical studies have demonstrated a negative correlation between serum bilirubin concentrations and cardiovascular disease risk. Schwertner et al[4] were the first to report serum bilirubin as an inverse risk factor for CAD and several other studies supported this protective role[4-6,25]. Interestingly, patients with Gilbert's syndrome, a hereditary disorder resulting in mild hyperbilirubinemia, have lower rates of ischemic heart disease than the general population (2% vs 12%)[19]. In contrast to previous studies, the present study focused on PMI, finding a negative association between the incidence of PMI and TB levels. After adjustment for age, gender, body mass index, hypertension, diabetes and LDL-C, plasma TB levels were inversely correlated with C-reactive protein (r = -0.023; P =
0.019) and white blood cell count (r = -0.062; P < 0.001), suggesting an anti-inflammatory effect of elevated bilirubin. Peyton et al\cite{26} demonstrated that bilirubin blocks the proliferation and migration of vascular smooth muscle cells, thus reducing post-PCI stenosis. The present study also found a lower risk of post-PMI revascularization in patients with elevated TB levels.

However, a number of studies found contradictory results. Kaya et al\cite{10} demonstrated a positive association between high TB levels and the severity of CAD in non-ST-elevation MI. Similarly, Gul et al\cite{27} and Celik et al\cite{28} found an association between high TB level and increased in-hospital adverse outcomes in patients with ST-elevation MI. Contrary findings among these studies may be attributed to differences in study populations. Previous trials included AMI patients while the present study focused on patients with normal pre-PCI cTnI. Heme oxygenase 1 (HO-1), a rate-limiting enzyme in bilirubin breakdown, can be activated by cellular stresses due to MI, resulting in elevated bilirubin levels\cite{29,30}. Xu et al\cite{31} reported a positive correlation between TB levels and C-reactive protein in AMI patients, reflecting inflammatory activation. Thus, upregulated HO-1 activity and bilirubin would seem to be a defense mechanism to protect the myocardium via antioxidant activity. Previous experiments found that exogenous bilirubin decreased infarct size and ameliorated left ventricular function in the post-ischemic rat heart\cite{32,33}.

The findings of the present study assist our understanding of bilirubin actions and our search for therapeutic targets for the management of PMI and other oxidative diseases. A number of drugs are known to induce HO-1, including aspirin and statins\cite{34}. Inhibition of bilirubin UDP-glucuronosyl transferase (the key enzyme responsible for bilirubin conjugation) or prevention of bilirubin oxidation may be other routes to elevated bilirubin concentrations\cite{35}. Moreover, synthetic materials or naturally occurring tetrapyrrolic molecules structurally related to bilirubin may act as mimetics\cite{36}.

**Limitations**

We acknowledge several limitations in the present study. Firstly, due to its retrospective nature, data regarding ischemic symptoms and electrocardiographs were difficult to collect. PMI in our study was alternatively defined as an isolated rise in cTnI, which did not fulfill the requirement of the revised...
diagnosis criteria published in 2012 and 2018[13,14]. In addition, patients with abnormal pre-PCI cTnl levels were excluded since AMI may affect pre-PCI bilirubin. Secondly, PMI is known to be associated with surgical factors, such as branch occlusion and distal embolism. Patients with intraoperative factors, including side-branch occlusion and severely calcified lesions with a rotablator or dissection, were excluded to reduce the influence of surgical complications. However, although adjustment for many known predictors of PMI was made, confounding factors may not have been completely eliminated. For example, plaque characteristics, such as \textit{via} IVUS/OCT, were only available for a proportion of patients. Thirdly, since HO-1 enzyme activity was not measured, the association between HO-1 level, bilirubin and the risk of PMI could not be assessed. Lastly, our findings show that indirect bilirubin, rather than direct bilirubin, has the predictive value for PMI. Although a previous study has shown that patients with mildly elevated indirect serum bilirubin have a much lower incidence of CAD[37], any difference in mechanism between the two forms remains unconfirmed. Due to potential bias, results regarding the different effects of the two forms on PMI and its long-term outcome are not shown.

**CONCLUSION**

Bilirubin was an inverse predictor of PMI and has a protective effect. In patients who experienced PMI, elevated levels of bilirubin were independently associated with a reduced risk of MACEs during long-term follow-up.

**ARTICLE HIGHLIGHTS**

**Research background**
As a frequent complication of percutaneous coronary intervention (PCI), the rate of perioperative myocardial infarction (PMI) remains high and patients suffering from PMI have poor outcomes.

**Research motivation**
To identify whether bilirubin could be a potential target for PMI avoidance.

**Research objectives**
To explore the impact of bilirubin levels on PMI and long-term prognosis in post-PMI patients.

**Research methods**
Logistic regression and Cox regression analyses were used to explore the association between bilirubin, PMI and its long-term prognosis.

**Research results**
Higher bilirubin was associated with a reduced rate of PMI and major adverse cardiovascular events.

**Research conclusions**
Bilirubin was a protective factor in PMI prediction and produced a better long-term prognosis in post-PMI patients.

**Research perspectives**
The study provides evidence of bilirubin as a therapeutic target in PMI prevention.

**FOOTNOTES**

**Author contributions:** Li Y and Li DB reviewed the literature and contributed to manuscript drafting; Lv QB, Wang Y, Zhao LD and Ren YF contributed to data collection, interpretation, and analysis; Zhang WB was responsible for revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

**Institutional review board statement:** The study was reviewed and approved by Sir Run Run Shaw Hospital.

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

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

**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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86


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Retrospective Cohort Study

Disease exacerbation is common in inflammatory bowel disease patients treated with immune checkpoint inhibitors for malignancy

Samuel J S Rubin, Tatiana Balabanis, John Gubatan, Aida Habtezion

**Abstract**

**BACKGROUND**

Colitis is a known potential toxicity of immune checkpoint inhibitors (ICIs). Studies evaluating the risk of disease exacerbation following ICI treatment in patients with pre-existing inflammatory bowel disease (IBD) are limited.

**AIM**

To assess the clinical characteristics of IBD patients treated with ICIs and determine prevalence of subsequent IBD exacerbations.

**METHODS**

We conducted a retrospective cohort study of all patients in the Stanford Research Repository database with pre-existing IBD who were exposed to ICIs.

**RESULTS**

The prevalence of IBD exacerbation following ICI was 36.8% amongst 19 patients meeting inclusion criteria. Patients with exacerbations had more gastrointestinal-related hospitalizations (4 of 7) than patients without exacerbations (0 of 12; \( P = 0.0090 \)).

**CONCLUSION**

The prevalence of IBD exacerbations following ICI was higher than reported rates of ICI-induced colitis and diarrhea in the general population and was associated with hospitalization.

**Key Words**: Inflammatory bowel disease; Immune checkpoint inhibitors; Immunotherapy; Malignancy
Core Tip: Immune checkpoint inhibitor (ICI)-mediated colitis is increasingly recognized as a complication of ICI therapy. The clinical outcomes of ICI therapy on underlying inflammatory bowel disease (IBD) in patients with malignancy is poorly understood. In this retrospective cohort study of IBD patients treated with ICIs for malignancy, we demonstrate that the prevalence of IBD exacerbation following ICI therapy was higher than reported ICI-induced colitis and diarrhea in the general population. ICI use among patients with IBD who had a disease exacerbation was also associated with increased rates of hospitalization.

INTRODUCTION

Immune checkpoint inhibitor (ICI) monoclonal antibodies block surface receptors on leukocytes, triggering profound immune responses. Use of ICIs for cancer treatment is increasing; the number of Food and Drug Administration-approved indications is growing, with additional ICIs in development [1]. Immune-related adverse events (irAEs) and disease exacerbations following ICIs have been documented for pre-existing inflammatory diseases and are typically managed with prompt steroids, immunomodulators, and/or tumor necrosis factor inhibitors [2,3]. Thus, clinical benefit of ICIs for malignancy in patients with certain pre-existing conditions may be limited due to serious risks.

Gastrointestinal (GI) irAEs, including diarrhea and ICI-mediated colitis (IMC), are amongst the most common ICI-associated irAEs [4]. In the general population treated with ICIs, the incidence of diarrhea was 12.1%-13.7% for anti-programmed cell death protein (PD)-1, 30.2%-35.4% for anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), and 9.1%-10.6% for combination ICIs, while the incidence of colitis was 0.7%-1.6% for anti-PD-1, 5.7%-9.1% for anti-CTLA-4, and 13.6% for combination ICIs [1]. Use of anti-CTLA-4 ICIs is considered to increase the risk of IMC [5,6]. Recent reports suggest that the incidence of GI irAEs following ICI administration in patients with pre-existing inflammatory bowel disease (IBD) may be higher than the general population [7-9]. While these studies provided insight into IBD exacerbation rates following ICI therapy in small cohorts at a limited number of study centers, data on patient comorbidities, medications, and baseline IBD activity were lacking and might affect irAE occurrence and recognition. Understanding the prevalence, detailed clinical characteristics and outcomes of ICI-induced IBD exacerbation in broader patient populations remains an ongoing challenge. We aimed to assess the clinical characteristics of IBD patients treated with ICIs at our previously unreported center and determine IBD exacerbation prevalence in this novel population.

MATERIALS AND METHODS

We performed a retrospective cohort study of all IBD patients exposed to ICIs from 2000 through August 13, 2020 at Stanford Healthcare using the Stanford Research Repository Tool database, as approved by the Stanford Institutional Review Board. Patients were screened by International Classification of Diseases codes (K50, CD; K51, ulcerative colitis; K52, other unspecified noninfective gastroenteritis and colitis; 555, regional enteritis; 556, other ulcerative colitis) and ICI (ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, or cemiplimab). Pre-existing IBD diagnosis and subsequent ICI administration were confirmed by chart review. All subjects with these inclusion criteria were reported. Patients whose IBD diagnosis did not predate ICI were excluded. Demographics, comorbidities, medications, disease phenotypes, and clinical outcomes were collected by chart review.

The primary outcome was prevalence of IBD exacerbation following ICI, as defined by new onset bloody stool, rectal bleeding, diarrhea, and/or increased bowel movements. No patients with IBD exacerbations had documented GI infections following ICI use, as determined by GI polymerase chain reaction panel, Clostridium difficile toxin testing, and/or stool culture. One patient with IBD exacerbation had chronic hepatitis C virus infection, and another had a postoperative wound infection. Missing data is indicated in table footnotes. No data was imputed. Statistical analyses were performed in Microsoft Excel (16.43), GraphPad Prism (8.4.3) and R (3.3.2).
### Table 1 Baseline demographics and inflammatory bowel disease characteristics stratified by inflammatory bowel disease diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
<th>Indeterminate IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 4 )</td>
<td>( n = 14 )</td>
<td>( n = 1 )</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first ICI use, yr, median, IQR</td>
<td>63, 4</td>
<td>69, 12.5</td>
<td>60, 0</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>2 (50.0)</td>
<td>2 (14.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>3 (75.0)</td>
<td>11 (78.6)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Black race, n (%)</td>
<td>1 (25.0)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asian race, n (%)</td>
<td>0 (0)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other race, n (%)</td>
<td>0 (0)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Non-Hispanic ethnicity, n (%)</td>
<td>4 (100)</td>
<td>12 (85.7)</td>
<td>1 (100)</td>
</tr>
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<td>Hispanic/Latino ethnicity, n (%)</td>
<td>0 (0)</td>
<td>2 (14.3)</td>
<td>0 (0)</td>
</tr>
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<td>Never smoker, n (%)</td>
<td>2 (50.0)</td>
<td>5 (35.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>2 (50.0)</td>
<td>9 (64.3)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Body mass index, median, IQR</td>
<td>21.6, 1.7</td>
<td>25.5, 6.1</td>
<td>24.1, 0</td>
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<tr>
<td><strong>IBD characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at IBD onset, yr, median, IQR</td>
<td>( ^1 ) 56, 0</td>
<td>39.5, 32.8</td>
<td>54, 0</td>
</tr>
<tr>
<td>IBD duration, yr, median, IQR</td>
<td>( ^1 ) 7, 1</td>
<td>20, 29.25</td>
<td>6, 0</td>
</tr>
<tr>
<td>Disease location, n (%)</td>
<td>( L1 ): 1 (25.0)</td>
<td>( E1 ): 1 (7.1)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>( L2 ): 1 (25.0)</td>
<td>( E2 ): 4 (28.6)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>( L3 ): 2 (50.0)</td>
<td>( E3 ): 7 (50.0)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Unknown: 2 (14.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disease behavior, n (%)</td>
<td>( B1 ): 2 (50.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>( B2 ): 1 (25.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>( B3 ): 0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Unknown: 1 (25.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perianal disease, n (%)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Extra-intestinal manifestations, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

\(^1\)Unknown for 2 CD and 4 UC patients because date of IBD onset was not available.

Disease location and behavior were categorized using the Montreal classification: Location (L): L1, ileal disease; L2, colonic disease; L3, ileocolonic disease; Behavior (B): B1, inflammatory phenotype; B2, obstructive/stricturing phenotype; B3, penetrating/fistulizing phenotype; Extent (E): E1, proctitis; E2, left-sided colitis; E3, extensive/pan colitis. IQR: Interquartile range; IBD: Inflammatory bowel disease; ICI: Immune checkpoint inhibitor.

### Table 2 All baseline clinical characteristics stratified by prevalence of inflammatory bowel disease exacerbation

<table>
<thead>
<tr>
<th></th>
<th>Exacerbation</th>
<th>No exacerbation</th>
<th>( P ) value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 7 )</td>
<td>( n = 12 )</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>0 (0)</td>
<td>4 (33.3)</td>
<td>0.2451</td>
</tr>
<tr>
<td>Age at first ICI use, yr, median, IQR</td>
<td>60, 12.5</td>
<td>66, 9.3</td>
<td>0.6055</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>4 (57.1)</td>
<td>11 (91.7)</td>
<td>0.1174</td>
</tr>
<tr>
<td>Black race, n (%)</td>
<td>1 (14.3)</td>
<td>1 (8.3)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Asian race, n (%)</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
<td>0.3684</td>
</tr>
<tr>
<td>Other race, n (%)</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
<td>0.3684</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Non-Hispanic ethnicity, n (%)</td>
<td>5 (71.4)</td>
<td>12 (100)</td>
<td>0.1228</td>
</tr>
<tr>
<td>Hispanic/Latino ethnicity, n (%)</td>
<td>2 (28.6)</td>
<td>0 (0)</td>
<td>0.1228</td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>3 (42.9)</td>
<td>9 (75.0)</td>
<td>0.3261</td>
</tr>
<tr>
<td>Body mass index, median, IQR</td>
<td>24.3, 1.8</td>
<td>25.2 (6.7)</td>
<td>0.9018</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1 (14.3)</td>
<td>6 (50.0)</td>
<td>0.1733</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>3 (42.9)</td>
<td>6 (50.0)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>0 (0)</td>
<td>3 (25.0)</td>
<td>0.2632</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>0 (0)</td>
<td>2 (16.7)</td>
<td>0.5088</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>0 (0)</td>
<td>2 (16.7)</td>
<td>0.5088</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (28.6)</td>
<td>1 (8.3)</td>
<td>0.5232</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease, n (%)</td>
<td>1 (14.3)</td>
<td>1 (8.3)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Asthma, n (%)</td>
<td>0 (0)</td>
<td>2 (16.7)</td>
<td>0.5088</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>1 (14.3)</td>
<td>1 (8.3)</td>
<td>1.0000</td>
</tr>
<tr>
<td>IBD characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn's disease, n (%)</td>
<td>0 (0)</td>
<td>4 (33.3)</td>
<td>0.2451</td>
</tr>
<tr>
<td>Ulcerative colitis, n (%)</td>
<td>6 (85.7)</td>
<td>8 (66.7)</td>
<td>0.6027</td>
</tr>
<tr>
<td>Indeterminate IBD, n (%)</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
<td>0.3684</td>
</tr>
<tr>
<td>Age at IBD onset, yr, median, IQR²</td>
<td>47, 28.3</td>
<td>56, 24.5</td>
<td>0.9668</td>
</tr>
<tr>
<td>IBD duration, yr, median, IQR²</td>
<td>11.5, 19.75</td>
<td>20, 24</td>
<td>0.9184</td>
</tr>
<tr>
<td>History of GI surgery before ICI use, n (%)</td>
<td>2 (28.6)</td>
<td>5 (41.7)</td>
<td>0.6562</td>
</tr>
<tr>
<td>Latest known disease state before ICI use, n (%)</td>
<td>Active: 0 (0)</td>
<td>Active: 0 (0)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Latest available 25 (OH) D before ICI use, ng/mL, median, IQR²</td>
<td>38.9, 11.2</td>
<td>29.0, 9.5</td>
<td>0.8857</td>
</tr>
<tr>
<td>GI medications at start of ICI use, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminosalicylate</td>
<td>3 (42.9)</td>
<td>3 (25.0)</td>
<td>0.6169</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>1 (14.3)</td>
<td>2 (16.7)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Cholecalciferol (vitamin D3)</td>
<td>3 (42.9)</td>
<td>3 (25.0)</td>
<td>0.6169</td>
</tr>
<tr>
<td>Laxative (PEG, senna glycoside, docusate)</td>
<td>3 (42.9)</td>
<td>3 (25.0)</td>
<td>0.6169</td>
</tr>
<tr>
<td>Anti-diarrheal (diphenoxylate-atropine, loperamide)</td>
<td>1 (14.3)</td>
<td>3 (25.0)</td>
<td>1.0000</td>
</tr>
<tr>
<td>TNF inhibitor</td>
<td>0 (0)</td>
<td>1 (8.3)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
<td>0.3684</td>
</tr>
<tr>
<td>Other medications at start of ICI use, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral antibiotics</td>
<td>0 (0)</td>
<td>2 (16.7)</td>
<td>0.5088</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>3 (42.9)</td>
<td>2 (16.7)</td>
<td>0.3047</td>
</tr>
<tr>
<td>Famotidine</td>
<td>0 (0)</td>
<td>2 (16.7)</td>
<td>0.5088</td>
</tr>
<tr>
<td>Metformin</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
<td>0.3684</td>
</tr>
<tr>
<td>Insulin secretagogue</td>
<td>0 (0)</td>
<td>1 (8.3)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Insulin</td>
<td>1 (14.3)</td>
<td>1 (8.3)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>2 (28.6)</td>
<td>4 (33.3)</td>
<td>1.0000</td>
</tr>
</tbody>
</table>
Rubin SJS et al. IBD exacerbation following ICI treatment

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

<table>
<thead>
<tr>
<th></th>
<th>In patients Without ICI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>0 (0)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin receptor blocker</td>
<td>3 (42.9)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>HMA-CoA reductase inhibitor</td>
<td>4 (57.1)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Anticoagulant or antiplatelet</td>
<td>1 (14.3)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drug</td>
<td>3 (42.9)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Donepezil</td>
<td>1 (14.3)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>1 (14.3)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>2 (28.6)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Chemotherapeutic kinase inhibitor</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Cancer characteristics and management

Primary cancer origin, n (%)

<table>
<thead>
<tr>
<th>Primary cancer origin</th>
<th>In patients Without ICI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>0 (0)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3 (42.9)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Lung</td>
<td>2 (28.6)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>GI</td>
<td>1 (14.3)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (14.3)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Radiation therapy for cancer, n (%)</td>
<td>5 (71.4)</td>
<td>9 (75.0)</td>
</tr>
</tbody>
</table>

Checkpoint inhibitor, n (%)

<table>
<thead>
<tr>
<th>Checkpoint inhibitor</th>
<th>In patients Without ICI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>2 (28.6)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>2 (28.6)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>4 (57.1)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>0 (0)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Avelumab</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>0 (0)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Cemiplimab</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Any anti-PD-1 or -PD-L1</td>
<td>6 (85.7)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Combination anti-CTLA-4 and -PD-1/PD-L1</td>
<td>1 (14.3)</td>
<td>1 (8.3)</td>
</tr>
</tbody>
</table>

1 P-values from Fisher’s exact test for categorical variables or Mann-Whitney U test for continuous variables.
2 Unknown for 1 patient with and 5 patients without immune checkpoint inhibitor (ICI)-attributed inflammatory bowel disease (IBD) exacerbations because date of IBD onset was not available.
3 Unknown for 3 patients with and 8 patients without ICI-attributed IBD exacerbations.

RESULTS

Nineteen patients met inclusion criteria of pre-existing IBD and subsequent ICI therapy. Four had Crohn’s disease (CD), fourteen ulcerative colitis (UC), and one indeterminate IBD (Table 1). The median age of patients with CD was 63 [interquartile range (IQR), 4] and UC was 69 (IQR, 12.5). Patients were predominantly of male sex and white race. No patients had extraintestinal IBD manifestations nor pediatric onset IBD; the median age of onset was 56 (IQR, 0) for CD and 39.5 (IQR, 32.8) for UC.

All patients had controlled asymptomatic IBD when beginning ICI therapy, after which seven developed GI irAEs consistent with IBD exacerbation (Tables 2 and 3). Median length of ICI use was 12 mo (IQR, 10) and 6.5 mo (IQR, 9.3) in patients with and without exacerbations, respectively (P = 0.3685; Table 3). Median follow-up time was 435 d (IQR, 306) and 572 d (IQR, 450) from beginning ICI therapy for patients with and without exacerbations, respectively (P = 0.4824). Demographics, comorbidities, IBD characteristics (location, behavior, etc.), and medications were evaluated and not associated with ICI-induced IBD exacerbation (Table 2).
Rubin SJS et al. IBD exacerbation following ICI treatment

| Table 3 Inflammatory bowel disease management and clinical outcomes following immune checkpoint inhibitor treatment stratified by prevalence of inflammatory bowel disease exacerbation |
|-------------------------------------------------|------------------------------------------|-------------------|
| **Exacerbation** | **No exacerbation** | **P value** |
| **n = 7** | **n = 12** | |
| Follow up time, d, median, IQR | 435, 306 | 572, 450 | 0.4824 |
| Length of ICI use, mo, median, IQR | 12, 10 | 6.5, 9.3 | 0.3685 |
| Reason for ICI discontinuation, n (%) | |
| Cancer remission | 1 (14.3) | 1 (8.3) | 1.0000 |
| Cancer non-response | 0 (0) | 2 (16.7) | 0.5088 |
| Side effect(s) | 1 (14.3) | 3 (25.0) | 1.0000 |
| Patient preference | 0 (0) | 1 (8.3) | 1.0000 |
| Deceased | 1 (14.3) | 2 (16.7) | 1.0000 |
| Unknown | 0 (0) | 1 (8.3) | 1.0000 |
| Not discontinued | 4 (57.1) | 2 (16.7) | 0.1287 |
| GI-related hospitalization, n (%) | 4 (57.1) | 0 (0) | 0.0090 |
| GI-related surgery, n (%) | 2 (28.6) | 0 (0) | 0.1228 |
| IBD medications used after ICI initiation, n (%) | |
| Aminosalicylates | 4 (57.1) | 4 (33.3) | 0.3765 |
| Glucocorticoids | 3 (42.9) | 4 (33.3) | 1.0000 |
| TNF inhibitor | 2 (28.6) | 1 (8.3) | 0.5232 |
| Mercaptopurine | 1 (14.3) | 0 (0) | 0.3684 |
| None | 2 (28.6) | 5 (41.7) | 0.6562 |
| Deceased, n (%) | 1 (14.3) | 4 (33.3) | 0.6027 |

\(^1\)P-values from Fisher’s exact test. IQR: Interquartile range; IBD: Inflammatory bowel disease; ICI: Immune checkpoint inhibitor; GI: Gastrointestinal; TNF: Tumor necrosis factor.

Four of seven patients with IBD exacerbations required GI-related hospitalization following ICI treatment, compared to none of 12 patients without exacerbations (57.1% vs 0%; P = 0.0090); two patients with exacerbations required GI surgery (Table 3). IBD medical therapy following ICI was not significantly different between patients with and without IBD exacerbations (Table 3). Importantly, no patients with IBD exacerbations had documented GI infections following ICI, consistent with exacerbation due to flare of underlying IBD. One patient who had an exacerbation after ICI underwent flexible sigmoidoscopy, demonstrating circumferential colitis from the anus to distal sigmoid colon, consistent with a flare of pre-existing left-sided UC.

**DISCUSSION**

Recent reports suggest higher incidence of GI irAEs in patients with pre-existing IBD following ICI therapy (28%-41%) compared to the general population (diarrhea: 9.1%-35.4%; colitis: 0.7%-13.6%) [1,7-9]. We observed GI irAEs consistent with IBD exacerbations in 36.8% of IBD patients treated with ICIs in a novel patient population, which parallels this emerging pattern.

Patients with IBD exacerbations experienced more GI-related hospitalizations, half accompanied by surgery. There was no association between ICI type and IBD exacerbation. Although only three patients were on antibodies directed against CTLA-4, this is consistent with another recent report [9]. We found no associations between IBD exacerbation and non-IBD medications, including proton pump inhibitors, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, antidiabetic agents, antihypertensive agents, and others analyzed (Table 2).

Our study adds to developing literature on ICIs in IBD, providing detailed data on prevalence of IBD exacerbation and outcomes in this vulnerable population. Importantly, while GI symptoms are common amongst IBD and cancer patients and could resemble GI irAEs, all patients had controlled asymptomatic IBD prior to ICI use, and no patients with subsequent IBD exacerbations had GI...
infections. Another strength of our study was inclusion of additional clinical characteristics, including medications, comorbidities, race, and ethnicity, relative to previous studies. Cohort size was limited due to the single-center nature of our study and the rarity of IBD preceding ICI therapy.

CONCLUSION
In conclusion, our data highlight that relative to non-IBD patients, those with pre-existing IBD are a vulnerable population at increased risk of ICI-induced IBD flare. These findings demonstrate the importance of closely monitoring ICIs in the setting of IBD and the need for larger prospective studies to define factors associated with ICI-induced flare in IBD patients.

ARTICLE HIGHLIGHTS
Research background
Colitis and diarrhea are immune-related adverse events associated with immune checkpoint inhibitor (ICI) therapy.

Research motivation
The risk of inflammatory bowel disease (IBD) exacerbation following ICI treatment of malignancy in these patients is poorly understood.

Research objectives
We aimed to understand clinical characteristics of IBD patients treated with ICIs for malignancy and their clinical outcomes.

Research methods
We conducted a retrospective cohort study of all IBD patients treated with ICIs for malignancy and Stanford Healthcare.

Research results
The prevalence of IBD exacerbation amongst patients treated with ICI therapy for malignancy was 36.8%. Individuals with exacerbation of pre-existing IBD had more gastrointestinal-related hospitalizations.

Research conclusions
IBD exacerbation amongst patients treated with ICIs for malignancy was higher than reported rates of colitis and diarrhea in the general population treated with ICIs for malignancy.

Research perspectives
IBD patients are vulnerable to disease exacerbation when treated with ICIs for malignancy, and close monitoring should be implemented. Further studies will aim to better understand what factors modulate risk of IBD exacerbation in patients following ICI administration.

ACKNOWLEDGEMENTS
We thank Dr. Alexa R. Weingarden, MD, PhD for helpful discussions, critiques, and feedback on the study design and manuscript.

FOOTNOTES
Author contributions: Rubin SJS, Gubatan J and Habtezion A helped plan the study, interpret data, and draft the manuscript. Rubin SJS, Balabanis T, Gubatan J and Habtezion A interpreted data; Balabanis T collected data; all authors approved the final draft submitted.

Supported by: the Stanford Medical Scholars Fellowship Program to Rubin SJS.

Institutional review board statement: The study is approved by the Stanford Institutional Review Board (57160).
Informed consent statement: Because of the retrospective and anonymous character of this study, the need for informed consent was waived by the institutional review board.

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

Data sharing statement: The full data underlying this article cannot be shared publicly due to privacy of the individuals that participated in the study. The de-identified data will be shared on reasonable request to the corresponding authors.

STROBE statement: 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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Country/Territory of origin: United States

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

REFERENCES


Retrospective Cohort Study

Multidrug-resistant organisms in intensive care units and logistic analysis of risk factors

Ying Han, Jin Zhang, Hong-Ze Zhang, Xin-Ying Zhang, Ya-Mei Wang

BACKGROUND

Intensive care unit (ICU) patients are critically ill and have low immunity. They will undergo various trauma medical procedures during diagnosis and treatment. The use of high-dose hormones and broad-spectrum antibiotics will increase the incidence of nosocomial infection in ICU patients. Therefore, it is necessary to explore the causes of nosocomial infection in ICU and provide basis for the prevention and control of nosocomial infection in ICU.

AIM

To explore major pathogens of nosocomial infection in ICUs, methods of detection and drug resistance trends.

METHODS

Risk factors of multidrug-resistant infection were analyzed to provide a basis for clinical rational use of antimicrobial drugs in the ICU. These findings were used to standardize rational use of antimicrobial agents. BD PhoenixTM100 automatic bacterial identification analyzer was used to for cell identification in specimens collected from the ICU between January 2016 and December 2019. Drug sensitivity tests were carried out and drug resistance trends were analyzed using the optical disc diffusion method. Odds ratios and corresponding 95%CI of independent variables were calculated using a logistic regression model. Backward elimination (trend = 0.1) was used as an inclusion criterion for multivariate analysis. All data were analyzed using SPSS version 22.0, and $P < 0.05$ was considered statistically significant.

RESULTS

We collected 2070 samples from ICU patients between January 2016 and December 2019. Sample types comprised sputum (1139 strains, 55.02%), blood (521 strains, 25.17%), and drainage fluid (117 strains, 5.65%). A total of 1051 strains of major pathogens, including Acinetobacter baumannii, Escherichia coli (E.
E. coli), Pseudomonas aeruginosa (P. aeruginosa), Klebsiella pneumoniae (K. pneumoniae) and Staphylococcus aureus, were detected, with a detection rate of 35.97% (378/1051). Most of these strains were resistant to antibiotics. Detection rate of E. coli was 21.79% (229/1051), and it was generally sensitive to many antimicrobial drugs. Detection rate of P. aeruginosa was 24.74% (260/1051), and showed low sensitivity to most antibiotics. Detection rate of K. pneumoniae was 9.42% (99/1051), which was generally resistant to multiple antimicrobial drugs and resistant forms. K. pneumoniae was resistant to imipenem for approximate 4 years, and showed a 19.9% (19/99) and 20.20% (20/99) rate of meropenem resistance. Logistic analysis showed that mechanical ventilation and ureteral intubation were risk factors for multidrug-resistant bacterial infections.

CONCLUSION
This study showed a high incidence of ICU infections. Mechanical ventilation and urine tube intubation were risk factors for infection with multidrug-resistant bacteria.

Key Words: Multidrug-resistant organisms; Intensive care; Antibiotics; Drug resistance

INTRODUCTION
Intensive care unit (ICU) patients are critically ill and have low immunity. They undergo various traumatic medical procedures during diagnosis and treatment. The use of high-dose hormones and broad-spectrum antibiotics increase the incidence of nosocomial infection in ICU patients. Therefore, it is necessary to explore the causes of nosocomial infection in the ICU and provide a basis for the prevention and control of nosocomial infection in the ICU. This study described multidrug-resistant bacterial infection in ICU patients from January 2016 to December 2019, and analyzed the risk factors for infection by multidrug-resistant bacteria in ICU patients.

MATERIALS AND METHODS
Research methods
Bacteria were isolated from collected samples for identification and analysis following the National Operating Rules for Clinical Examination (third edition). BD PhoenixTM100 automatic bacterial identification and analysis instrument was used for cell identification. Drug sensitivity test was carried out by paper disk (provided by Oxoid) Agar diffusion method (Kirby–Bauer method). Pseudomonas aeruginosa (P. aeruginosa) ATCC27853, Staphylococcus aureus (S. aureus) ATCC25923 and Escherichia coli (E. coli) ATCC25922 were used as quality control strains.

Inclusion and exclusion criteria
Inclusion criteria were: (1) According to the definition of diagnostic criteria for nosocomial infection (2001) issued by the Ministry of Health of the People’s Republic of China, and the etiological diagnosis was multidrug-resistant bacterial infection; and (2) Inpatients in the ICU.

Exclusion criteria were: (1) Diagnosis did not meet the diagnostic criteria for nosocomial infection issued by the Ministry of Health of the People’s Republic of China; (2) Diagnosis of multidrug-resistant bacterial colonization without clinical infection symptoms; (3) Contaminated samples of multidrug-resistant organisms were detected; (4) The samples were contaminated or failed to be cultured within 48 hours; (5) Antibiotics were used within 3 days before sampling.

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resistant bacteria; and (4) Natural resistant strains.

**Statistical analysis**
Pathogenic bacteria detected in nosocomial samples were analyzed and sorted out by real-time monitoring system for nosocomial infection control in Xinglin. Retrospective analysis was used to investigate and collect patient records and test data. Data analysis was performed using SPSS 22.0. Logistic regression analysis was used to perform univariate and multivariate analyses for independent risk factors for multidrug-resistant infection.

**RESULTS**

**Sample collection**
A total of 2070 cases of ICU infection were recorded. The causative pathogens were mainly collected from sputum in 1139 cases (55.02%), blood in 521 (25.17%), and drainage in 117 (5.65%) (Table 1).

**Distribution of pathogenic bacteria**
Among the 1051 strains of main pathogens identified in ICU, 966 were Gram-negative bacteria, accounting for 91.91% of the total number of pathogens. *Acinetobacter baumannii (A. baumannii)* was most common strain, accounting for 35.97% (378/1051) of the total strains, followed by *P. aeruginosa* (24.74%), *E. coli* (21.79%) and *Klebsiella pneumoniae* (*K. pneumoniae*) (9.42%). *S. aureus* was the most common Gram-positive bacteria strain with 8.09% (85/1051) (Table 2).

**Drug-resistance trends and analysis of main pathogens**
*A. baumannii*: Resistance rates of *A. baumannii* to minocycline in 2017 and 2019 were 28.41% and 32.42%, respectively. Resistance rates of this strain to other antimicrobials were > 40% (Table 3). Energy allocation rate to the antimicrobial drug meropenem was 74.6%, and imipenem resistance rate was 75.66% (Table 4).

*E. coli*: Carbapenem, piperacillin/tazobactam, amikacin, and cefoperazone/sulbactam showed inhibitory activity against *E. coli*. Analysis of 2019 data showed 21.4% (5/22) rate of resistance against cefotaxime and 13.6% (3/22) against tobramycin (Table 4). Resistance rate of *E. coli* against meroxifen was 14.41% (33/229), whereas resistance rate against imipenem was 15.28% (35/229) (Table 3).

*P. aeruginosa*: In 2017, *P. aeruginosa* was generally resistant to a variety of antibiotics such as piperacillin/tazobactam, aminoglycosides, quinolones and carbapenem. Analysis of 2016, 2018 and 2019 data showed that a variety of antibiotics showed good antibacterial activity against *P. aeruginosa* (Table 4). Energy allocation rate of Meropenem against *P. aeruginosa* in the previous 4 years was 20.38% (53/260), whereas imipenem resistance rate was 26.5% (68/260) (Table 3).

*K. pneumoniae*: Analysis of 2019 data showed that *K. pneumoniae* was 12.5% resistant to cefoperazone/sulbactam (3/27) and generally insensitive to other antibiotics. Drug resistance against *K. pneumoniae* in 2019 was severe compared with previous years (Table 4). Resistance rate of *K. pneumoniae* to Meropenem in the previous 4 years was 20.20% (20/99), whereas resistance rate of *K. pneumoniae* to imipenem was 19.9% (19/99) (Table 3).

*S. aureus*: Incidence of methicillin resistance of *S. aureus* at the time of the study was 64.71% (55/85). In the previous 4 years, no resistance was recorded for linezolid and vancomycin antibiotics against *S. aureus* (Table 3).

**Logistic regression analysis**
A ratio of 1:1 was used to analyze risk factors for multidrug-resistant bacterial infection in 208 patients hospitalized in ICU with nosocomial infection. In addition, 208 patients hospitalized at the same time, and with comparable age, sex and symptoms were selected as a control group. Factors with $P \leq 0.05$ were included in the logistic regression model to avoid the influence of confounding factors. Logistic regression analysis showed that mechanical ventilation and urine tube intubation were risk factors for infection with multidrug-resistant bacteria (Tables 5 and 6).

**DISCUSSION**
ICU patients are in critical condition, and are often accompanied with multiple organ dysfunction and severe immune dysfunction. Ventilator and invasive operation may result in damage to physiological barriers of patients, and risk of infection in ICU patients is higher compared with patients in other departments[1]. ICU patients use antibiotics at a higher frequency, higher dose and longer duration, and
Table 1 Specimen type distribution and composition ratio in 2016-2019

<table>
<thead>
<tr>
<th>Source of specimen</th>
<th>n</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum</td>
<td>1139</td>
<td>55.02</td>
</tr>
<tr>
<td>Blood</td>
<td>521</td>
<td>25.17</td>
</tr>
<tr>
<td>Drainage fluid</td>
<td>117</td>
<td>5.65</td>
</tr>
<tr>
<td>Urine</td>
<td>105</td>
<td>4.98</td>
</tr>
<tr>
<td>Peritoneal drainage fluid</td>
<td>72</td>
<td>3.48</td>
</tr>
<tr>
<td>Secretion</td>
<td>39</td>
<td>1.88</td>
</tr>
<tr>
<td>Bile</td>
<td>15</td>
<td>0.72</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>12</td>
<td>0.58</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>12</td>
<td>0.58</td>
</tr>
<tr>
<td>Ascites</td>
<td>3</td>
<td>0.14</td>
</tr>
<tr>
<td>Puncture fluid</td>
<td>3</td>
<td>0.14</td>
</tr>
<tr>
<td>Pus</td>
<td>2</td>
<td>0.10</td>
</tr>
<tr>
<td>Other</td>
<td>28</td>
<td>1.35</td>
</tr>
<tr>
<td>Catheter</td>
<td>4</td>
<td>0.19</td>
</tr>
<tr>
<td>Total</td>
<td>2070</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2 Distribution of pathogenic bacteria

<table>
<thead>
<tr>
<th>Types of pathogens</th>
<th>n</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. baumannii</td>
<td>378</td>
<td>35.97</td>
</tr>
<tr>
<td>E. coli</td>
<td>229</td>
<td>21.79</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>260</td>
<td>24.74</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>99</td>
<td>9.42</td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>85</td>
<td>8.09</td>
</tr>
<tr>
<td>Total</td>
<td>1051</td>
<td>100</td>
</tr>
</tbody>
</table>

A. baumannii: Acinetobacter baumannii; E. coli: Escherichia coli; P. aeruginosa: Pseudomonas aeruginosa; K. pneumoniae: Klebsiella pneumoniae; S. aureus: Staphylococcus aureus.

Infection with multiple drug-resistant bacteria (multidrug-resistant organisms; MDROs) is severe compared with patients in other departments. Surveillance results of the European Centers for Disease Control and Prevention show that drug resistance of common pathogenic bacteria such as A. baumannii increased from 1997 to 2018[2]. Therefore, studies on nosocomial infections should be carried out. Intervention with drugs that are effective against drug-resistant pathogenic bacteria can reduce the incidence of MDROs. This study explored distribution of pathogens implicated in nosocomial infections in ICU and degree of drug resistance to a variety of antibiotics. The findings of this study will guide on rational use of drugs in clinics, to reduce the occurrence of drug-resistant bacteria. Furthermore, this study provides an effective scientific basis for improving clinical efficacy of antibiotics.

Antibiotics with a resistance rate > 40% to major pathogenic bacteria should be used cautiously. Antibiotics with a resistance rate > 50% to major pathogenic bacteria must be selected and used based on drug sensitivity test results. Use of antibiotics must be stopped if the drug resistance rate of the main pathogenic bacteria is > 75%. Feedback results of bacterial resistance must be investigated and analyzed, to determine whether clinical use of the drug can be continued. Therefore, it is important to explore detection and analysis of drug resistance of pathogenic bacteria in hospitals[3]. A. baumannii is a common cause of opportunistic infection in humans[4]. Drug-resistance and isolation rates of this strain have gradually increased in recent years with higher rates compared with the incidence of P. aeruginosa.
### Table 3 Main pathogens resistance rate in 2016-2019

<table>
<thead>
<tr>
<th></th>
<th>A. baumannii</th>
<th>E. coli</th>
<th>P. aeruginosa</th>
<th>K. pneumoniae</th>
<th>S. aureus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>78.17</td>
<td>78.41</td>
<td>63.1</td>
<td>68.75</td>
<td>17.57</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>45.95</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>89.44</td>
<td>94.32</td>
<td>79.76</td>
<td>80.03</td>
<td>/</td>
</tr>
<tr>
<td>Cefepime</td>
<td>81.69</td>
<td>78.57</td>
<td>72.62</td>
<td>80.95</td>
<td>48.65</td>
</tr>
<tr>
<td>Cefoperazone / sulbactam</td>
<td>61.27</td>
<td>60.71</td>
<td>48.81</td>
<td>68.4</td>
<td>25.68</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>88.73</td>
<td>94.32</td>
<td>77.38</td>
<td>77.3</td>
<td>74.32</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>54.05</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>82.39</td>
<td>77.27</td>
<td>71.43</td>
<td>81.25</td>
<td>/</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>48.65</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>83.1</td>
<td>73.86</td>
<td>80.95</td>
<td>81.36</td>
<td>55.41</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Compound sulfanilamide</td>
<td>77.46</td>
<td>75</td>
<td>76.19</td>
<td>67.19</td>
<td>54.05</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>55.41</td>
</tr>
<tr>
<td>Imipenem</td>
<td>81.69</td>
<td>62.5</td>
<td>75</td>
<td>85.54</td>
<td>24.32</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>52.7</td>
</tr>
<tr>
<td>Meropenem</td>
<td>78.87</td>
<td>67.05</td>
<td>77.38</td>
<td>72</td>
<td>24.32</td>
</tr>
<tr>
<td>Meticillin</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Minocycline</td>
<td>78.17</td>
<td>28.41</td>
<td>59.52</td>
<td>32.42</td>
<td>/</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Piperacillin / tazobactam</td>
<td>80.99</td>
<td>70.45</td>
<td>80.95</td>
<td>72.1</td>
<td>27.03</td>
</tr>
<tr>
<td>Ticarcillin / clavulanic acid</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>56.76</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>83.8</td>
<td>78.57</td>
<td>76.19</td>
<td>81.36</td>
<td>52.7</td>
</tr>
</tbody>
</table>
A. baumannii: Acinetobacter baumannii; E. coli: Escherichia coli; P. aeruginosa: Pseudomonas aeruginosa; K. pneumoniae: Klebsiella pneumoniae; S. aureus: Staphylococcus aureus.

infections. A. baumannii was the main pathogen causing ICU colonization and nosocomial infection. Several studies have reported that A. baumannii is the most sensitive strain to imipenem. In addition, A. baumannii is highly sensitive to combination therapies of β-lactam and enzyme inhibitors such as cefoperazone/sulbactam and ampicillin/sulbactam. Sulbactam, an enzyme inhibitor, has direct antibacterial properties and an inhibitory effect against β-lactamases. Therefore, sulbactam is used in combination with cefoperazone and ampicillin. This strain is resistant to most antimicrobial agents and can be cloned and spread rapidly among strains. Surveillance data of drug resistance of CHINET bacteria in China in 2018 showed that resistance rates of imipenem and meropenem against this strain were 73.2% and 73.9%, respectively. In addition, resistance rates to cefoperazone/sulbactam and minocycline were 49.7% and 38.8% respectively. Resistance rates to polymyxin B and tigecycline were low (0.7% and 5.0%), whereas resistance rates to other tested drugs were > 40%. Resistance rate of A. baumannii to imipenem and meropenem significantly increased between 2005 and 2018. Resistance rates of 378 strains of A. baumannii isolated from ICU between 2016 and 2019 to imipenem and meropenem were 75.66% and 74.6%, respectively. Resistance rates to cefoperazone/sulbactam during the 4 years were 61.27%, 60.71%, 48.81% and 68.4%, respectively. Further, resistance rates to quinolones in the 4 years were 89.10%, 73.86%, 80.95% and 81.36%, respectively. These rates were higher compared with rates recorded in data released in 2016 on sensitivity of bacteria to antimicrobial agents in CHINET in China. In addition, the report showed that rates of resistance to minocycline in 2017 and 2019 were 28.41% and 32.42% respectively. Notably, > 40% resistance rates to other antibiotics were recorded. These findings indicate that hospitals should monitor resistance of A. baumannii to a variety of antimicrobial agents in real time. Furthermore, mechanisms of antimicrobial resistance should be explored, accurate clinical use of antibiotics should be ensured, and infection control measures should be improved. These measures will prevent increases in multidrug resistance of A. baumannii to a variety of antibiotics thus reducing occurrence of multidrug-resistant strains[5].

E. coli infection in ICU patients is often serious, accompanied by multiorgan dysfunction and serious immune dysfunction. The rapid increase of infections caused by Salmonella and K. pneumoniae has become the current concern[6]. Previous studies have reported that uncontrolled use and abuse of carbapenem, third-and fourth-generation cephalosporins and quinolone antibiotics are independent risk factors for high incidence of multidrug-resistant bacteria[7]. Moreover, the strains showed high sensitivity to cefoperazone/sulbactam, amikacin, and piperacillin/tazobactam. Analysis of 2019 data showed that resistance rate of E. coli to cefotaxime and tobramycin was lower compared with previous years. These findings provide an important basis for hospital clinicians for choosing antibiotics. Hospital Enterobacteriaceae are used to study drug resistance of a variety of antimicrobials and rational use of antibiotics in clinical treatment.

P. aeruginosa was sensitive to a variety of antibiotics in 2016, 2018 and 2019. Energy allocation rates of imipenem and Meropenem resistance in the 4 years were 26.5% and 20.38%, respectively. This finding is important for clinicians when choosing antibiotics. Antibiotics with high sensitivity and low price should be selected based on characteristics and drug sensitivity of common infection pathogens in the ICU, to improve therapeutic effect and reduce economic burden of treatment to patients.
Table 4 Carbapenem-resistance rate against main Gram-negative bacteria

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>A. baumannii</th>
<th>E. coli</th>
<th>P. aeruginosa</th>
<th>K. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>75.66</td>
<td>15.28</td>
<td>26.15</td>
<td>19.19</td>
</tr>
<tr>
<td>Meropenem</td>
<td>74.6</td>
<td>14.41</td>
<td>20.38</td>
<td>20.2</td>
</tr>
</tbody>
</table>

A. baumannii: Acinetobacter baumannii; E. coli: Escherichia coli; P. aeruginosa: Pseudomonas aeruginosa; K. pneumoniae: Klebsiella pneumoniae.

Table 5 Data on patients with multidrug-resistant organisms in intensive care units

<table>
<thead>
<tr>
<th>Factors</th>
<th>Patient group, n = 208</th>
<th>Control group, n = 208</th>
<th>t/(\chi^2)</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td>2.648</td>
<td>0.104</td>
</tr>
<tr>
<td>Male</td>
<td>105 (50.5)</td>
<td>98 (47.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>103 (49.5)</td>
<td>110 (52.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.803</td>
<td>0.422</td>
</tr>
<tr>
<td></td>
<td>67.71 ± 12.83</td>
<td>66.72 ± 12.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operation experience, n (%)</td>
<td></td>
<td></td>
<td>0.471</td>
<td>0.492</td>
</tr>
<tr>
<td></td>
<td>105 (50.5)</td>
<td>98 (47.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total length of hospital stay</td>
<td></td>
<td></td>
<td>8.52</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>27.13 ± 25.96</td>
<td>10.47 ± 11.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20.96 ± 17.14</td>
<td>9.13 ± 9.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td></td>
<td></td>
<td>101.65</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>204 (98.1)</td>
<td>118 (56.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central venous catheterization, n (%)</td>
<td></td>
<td></td>
<td>5.872</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>180 (86.5)</td>
<td>161 (77.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine tube intubation, n (%)</td>
<td></td>
<td></td>
<td>24.755</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>207 (99.5)</td>
<td>182 (87.5%)</td>
<td></td>
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</tr>
</tbody>
</table>

Table 6 Risk factor analysis results

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp (B)</th>
<th>95% CI for Exp (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1.089</td>
<td>0.260</td>
<td>17.588</td>
<td>1</td>
<td>0.000</td>
<td>2.972</td>
<td>1.786</td>
</tr>
<tr>
<td>Urine tube intubation</td>
<td>0.816</td>
<td>0.195</td>
<td>17.424</td>
<td>1</td>
<td>0.000</td>
<td>2.261</td>
<td>1.542</td>
</tr>
</tbody>
</table>

CI: Confidence interval.

*K. pneumoniae* is commonly resistant against extended-spectrum \(\beta\)-lactamase and cephalosporin. Carbapenem antibiotics are some of the most effective for treatment of *K. pneumoniae* infection. In recent years, carbapenem-resistant *K. pneumoniae* has been widely spread around the world, resulting in a high resistance rate to almost all \(\beta\)-lactam antibiotics and increase in mortality. In 2013, the US Center for Disease Control and Prevention published threat of antibiotic resistance, including carbapenem-resistant Enterobacteriaceae as one of the three bacteria in the urgent threat category. In addition, in the 4 years, resistance rates of *K. pneumoniae* to imipenem and meropenem were 19.9% and 20.20%, respectively. The CHINET surveillance report shows that resistance rates of *K. pneumoniae* to meropenem and imipenem in 2013 were 13.5% and 10%, respectively. On the contrary, Enterobacteriaceae are highly sensitive to carbapenem antibiotics, however, drug resistance rate is gradually increasing. Previous studies have reported that infection with carbapenem-resistant *K. pneumoniae* causes a high number of in-hospital deaths[8,9]. Case fatality rate of *K. pneumoniae* infections, which is sensitive to carbapenem, is 25.7%. The case fatality rate of patients infected with carbapenem-resistant
K. pneumoniae is 50%, which is significantly higher compared with that of carbapenem-sensitive K. pneumoniae. Long-term use of central venous intubation is an independent factor for infections caused by carbapenem-resistant K. pneumoniae[10]. Restrictions on clinical use of broad-spectrum cephalosporins can effectively reduce resistance rate of K. pneumoniae to cephalosporins. Therefore, studies should explore characteristics of nosocomial infection of K. pneumoniae, analyze characteristics of antibiotic resistance, and implement rational distribution of antibiotics, to avoid further evolution of drug-resistant strains.

S. aureus is an important pathogen of nosocomial and community infection. The detection rate of multidrug-resistant S. aureus in a general hospital was approximately 65.82%[11]. No strains resistant to linezolid and vancomycin were detected among the strains isolated for the 4 years. Linezolid and vancomycin can be used to treat severe infection caused by Gram-positive cocci. However, widespread use of these antimicrobials will aggravate drug toxicity. These drugs can be used to prevent S. aureus resistance against vancomycin. Further studies should explore measures to control drug resistance against vancomycin[12]. Clinical management on use of antibiotics should be carried out, and vancomycin should not be used as the first choice for prevention and routine treatment of staphylococcal bacterial infections.

Logistic regression analysis showed that mechanical ventilation and urinary tube intubation were risk factors for infections caused by multidrug-resistant bacteria. This implies that medical staff should carefully consider the necessity before performing the above procedures, to reduce infections caused by multidrug-resistant bacteria. Mechanical ventilation, urinary catheterization and other invasive procedures increase point of entry for pathogens, thus increasing resistance level of multidrug-resistant bacteria. Therefore, the important task of preventing and controlling MDRO infection in the ICU is to improve the prevention and control measures as soon as possible, in the face of the increasing rate of multidrug-resistant infection worldwide[13].

CONCLUSION

Although bacteria have their own drug-resistance mechanism, the primary reason for high incidence of multidrug-resistant bacteria infection in ICUs is inappropriate use of antibiotics, especially abuse of third-generation cephalosporins[14-17]. Studies have reported that nosocomial infection in ICU patients is a major source of mortality. Adoption of clear evidence-based prevention and control methods to significantly reduce incidence of nosocomial infection is an important measure to improve treatment efficacy and prognosis of ICU patients. However, advocacy should be carried out to control nosocomial infection and reduce the rate of antibiotic resistance. The purpose of this study was to explore and analyze the main pathogens of ICU nosocomial infections and their drug resistance[18]. The study reports on main pathogenic bacteria of nosocomial infection and corresponding mechanism of drug resistance in the ICU at a specific time, and analyzed drug resistance of pathogenic bacteria after use of antibiotics in the same period. These findings provide a theoretical basis for hospital control of drug-resistant infections, so as to improve efficacy of antibiotics and safety of diagnosis and treatment of patients, rational use of antibiotics, and reduce pressure on patients, family members and the wider economy.

ARTICLE HIGHLIGHTS

Research background
There intensive care unit (ICU) patients are critically ill and have low immunity. They will undergo various trauma medical procedures during diagnosis and treatment. The use of high-dose hormones and broad-spectrum antibiotics will increase the incidence of nosocomial infection in ICU patients.

Research motivation
To explore the causes of nosocomial infection of multi drug resistant bacteria in ICU, and to provide basis for the prevention and control of nosocomial infection in ICU.

Research objectives
To provide basis for the prevention and control of nosocomial infection in ICU.

Research methods
BD PhoenixTM100 automatic bacterial identification and analysis instrument was used for cell identification. Inclusion criteria were: (1) The etiological diagnosis was multidrug-resistant bacterial infection; and (2) Inpatients in the ICU. Exclusion criteria were: (1) Diagnosis of multidrug-resistant bacterial colonization without clinical infection symptoms; (2) Contaminated samples of multidrug-resistant
bacteria; and (3) Natural resistant strains. Retrospective analysis was used to investigate and collect patient records and test data. Logistic regression analysis was used to perform univariate and multivariate analyses for independent risk factors for multidrug-resistant infection.

**Research results**
(1) Sample collection: The causative pathogens were mainly collected from sputum in 1139 cases (55.02%), blood in 521 (25.17%), and drainage in 117 (5.65%) (Table 1); (2) Distribution of pathogenic bacterial: *Acinetobacter baumannii* (A. baumannii) was most common strain, accounting for 35.97% (378/1051) of the total strains, followed by *Pseudomonas aeruginosa* (P. aeruginosa) (24.74%), *Escherichia coli* (E. coli) (21.79%) and *Klebsiella pneumoniae* (K. pneumoniae) (9.42%). *Staphylococcus aureus* (S. aureus) was the most common Gram-positive bacteria strain with 8.09% (85/1051) (Table 2); (3) Drug-resistance trends and analysis of main pathogens *A. baumannii*: Resistance rates of *A. baumannii* to minocycline in 2017 and 2019 were 28.41% and 32.42%, respectively. Resistance rates of this strain to other antimicrobials were > 40% (Table 3). Energy allocation rate to the antimicrobial drug meropenem was 74.6%, and imipenem resistance rate was 75.66% (Table 4); E. coli: Analysis of 2019 data showed 21.4% (5/22) rate of resistance against cefotaxime and 13.6% (3/22) against tobramycin (Table 4). Resistance rate of *E. coli* against meropenem was 14.41% (33/229), whereas resistance rate against imipenem was 15.28% (35/229) (Table 5); *P. aeruginosa*: Analysis of 2016, 2018 and 2019 data showed that a variety of antibiotics showed good antibacterial activity against *P. aeruginosa* (Table 4). Energy allocation rate of meropenem against *P. aeruginosa* in the previous 4 years was 20.38% (53/260), whereas imipenem resistance rate was 26.5% (68/260) (Table 3); *K. pneumoniae*: Analysis of 2019 data showed that *K. pneumoniae* was 12.5% resistant to cefoperazone/sublactam (3/27). Drug resistance against *K. pneumoniae* in 2019 was severe compared with previous years (Table 4). Resistance rate of *K. pneumoniae* to meropenem in the previous 4 years was 20.20% (20/99), whereas resistance rate of *K. pneumoniae* to imipenem was 19.9% (19/99) (Table 3); S. aureus: Incidence of methicillin resistance of *S. aureus* at the time of the study was 64.71% (35/58) (Table 3). And (4) Logistic regression analysis: A ratio of 1:1 was used to analyze risk factors for multidrug-resistant bacterial infection in 208 patients hospitalized in ICU with nosocomial infection. In addition, 208 patients hospitalized at the same time, and with comparable age, sex and symptoms were selected as a control group. Factors with $P \leq 0.05$ were included in the logistic regression model to avoid the influence of confounding factors. Logistic regression analysis showed that mechanical ventilation and urine tube intubation were risk factors for infection with multidrug-resistant bacteria (Tables 5 and 6).

**Research conclusions**
Although bacteria have their own drug-resistance mechanism, the primary reason for high incidence of multidrug-resistant bacteria infection in ICUs is inappropriate use of antibiotics, especially abuse of third-generation cephalosporins. Studies have reported that nosocomial infection in ICU patients is a major source of mortality. The purpose of this study was to explore and analyze the main pathogens of ICU nosocomial infections and their drug resistance. The study reports on main pathogenic bacteria of nosocomial infection and corresponding mechanism of drug resistance in the ICU at a specific time, and analyzed drug resistance of pathogenic bacteria after use of antibiotics in the same period.

**Research perspectives**
Logistic analysis results showed that mechanical ventilation and urinary tube intubation were risk factors for infections caused by multidrug-resistant bacteria. This finding implies that our medical staff should carefully consider the necessity before performing the above procedures, to reduce infections caused by multidrug-resistant bacteria. Mechanical ventilation, urinary catheterization and other invasive procedures increase point of entry for pathogens thus increasing resistance level of multi-drug-resistant bacteria. Therefore, the important task of preventing and controlling MDRO infection in ICU is to improve the prevention and control measures as soon as possible in the face of the increasing rate of multidrug-resistant infection in the world.

**ACKNOWLEDGEMENTS**
The authors will thank for Yan JP great help.

**FOOTNOTES**
*Author contributions*: Han Y and Zhang J made equal contributions to the work; Han Y, Zhang J and Zhang HZ designed the study; Han Y, Zhang J, Zhang HZ, Wang YM, Zhang XY and Zhou XL studied; Zhang J and Zhang HZ analyze data and write articles; all authors have read and approved the final manuscript.

Supported by Drug resistance trend analysis and prevention and control of main pathogens in tertiary hospitals of...
Logistic analysis of ICU MDR

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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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Retrospective Study

Change and impact of left ventricular global longitudinal strain during transcatheter aortic valve implantation

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Abstract

BACKGROUND
Although transcatheter aortic valve implantation (TAVI) is a safe and effective treatment for aortic stenosis, it still carries some risks, such as valve leaks, stroke, and even death. The left ventricular global longitudinal strain (LVGLS) measurement may be useful for the prediction of adverse events during this operation.

AIM
To explore the change of LVGLS during TAVI procedure and the relationship between LVGLS and perioperative adverse events.

METHODS
In this study, 61 patients who had undergone percutaneous transfemoral TAVI were evaluated by transthoracic echocardiography. Before surgery, data on left ventricular ejection fraction (LVEF) and LVGLS were collected separately following balloon expansion and stent implantation. Difference in values of LVGLS and LVEF during preoperative balloon expansion (pre-ex), preoperative stent implantation (pre-im) and balloon expansion-stent implantation (ex-im) were also examined. Adverse events were defined as perioperative death, cardiac rupture, heart arrest, moderate or severe perivalvular leakage, significant mitral regurgitation during TAVI, perioperative moderate or severe mitral regurgitation, perioperative left ventricular outflow tract obstruction, reoperation, and acute heart failure.

RESULTS
The occurrence of perioperative adverse events was associated with differences in pre-ex LVGLS, but not with difference in pre-ex LVEF. There were significant differences between pre-LVGLS and ex-LVGLS, and between pre-LVGLS and im-LVGLS ($P = 0.037$ and $P = 0.020$, respectively). However, differences in LVEF were not significant ($P = 0.358$, $P = 0.254$); however differences in pre-ex LVGLS were
associated with pre-LVGLS (P = 0.045). Compared to LVEF, LVGLS is more sensitive as a measure of left heart function during TAVI and the perioperative period. Moreover, the differences in LVGLS were associated with the occurrence of perioperative adverse events, and changes in LVGLS were apparent in patients with undesirable LVGLS before the surgery. Furthermore, LVGLS is useful to predict changes in cardiac function during TAVI.

**CONCLUSION**

Greater attention should be paid to the patients who plan to undergo TAVI with normal LVEF but poor LVGLS.

**Key Words:** Aortic stenosis; Ejection fraction; Longitudinal strain; Transcatheter aortic valve implantation; Left ventricular global longitudinal strain

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**INTRODUCTION**

As the prevalence of calcified aortic stenosis (AS) is increasing in aging societies[1], transcatheter aortic valve implantation (TAVI) provides an option for this population with intermediate-high surgical risks[2,3]. Recently studies have proved the feasibility and safety of this invasive method in short- and mid-term follow-up periods[4,5]. Echocardiography is the most widely used method to evaluate left ventricle (LV) function before and after the operation. Traditionally in echocardiographic measurements, LV systolic function is measured through left ventricular ejection fraction (LVEF) referring to the fraction of LV end-diastolic volume ejected during systole. LVEF is the most widely used measure for the assessment of LV systolic function and has been extensively used in clinical trials as well as in guidelines. Even so, LVEF is load dependent, and LVEF may thus be maintained despite reduced myocardial contractility using preload reserve or changes in LV geometry. In contrast, a decreased LVEF may be determined in spite of preserved contractility due to afterload mismatch, but could represent LV failure[6]. As to subclinical dysfunction, LVEF seems not to be an ideal indicator. Therefore, left ventricular global longitudinal strain (LVGLS), which is derived from speckle tracking echocardiography, is introduced to quantize subtle myocardial dysfunction. In valvular heart disease, LVGLS provides additional diagnostic and prognostic value. It has been demonstrated that LVGLS is depressed while LVEF is still preserved in AS patients[7], and recovery of LVEF and LVGLS after TAVI was also observed[8]. However, the impact of LVGLS and LVEF to TAVI operation procedure and perioperative adverse events is seldom noticed. The aim of the present study was to detect how the baseline and changes of LVGLS during operation affect the perioperative outcomes.

**MATERIALS AND METHODS**

**Study population**

From November 2019 to November 2020, we retrospectively studied patients who had undergone transfemoral TAVI. Inclusion criteria for TAVI were the following: (1) 2D echocardiography showed severe native AS with peak aortic valve (AV) velocity ≥ 400 cm/s or mean AV gradient ≥ 40 mmHg or AV area < 1 cm²; (2) 70 years of age or at high surgical risks; and (3) Severe AS with relevant symptoms and above New York Heart Association functional classification class II.
Transthoracic echocardiography (TTE) was performed before, during, and immediately after the operation using EPIQ7C ultrasound machines (Philips Healthcare, Bothell, WA, United States). In total, 98 patients underwent TAVI, and 37 patients were excluded due to incomplete image collection or unanalyzable poor trace or TEE performance. From the original set of patients, 61 patients with AS were included in the study. Table 1 presents the clinical characteristics of the study subjects. These patients were divided into two groups, a normal LVEF group and a reduced LVEF group based on a threshold of 50% for normal LVEF. With a threshold of -20% for LVGLS[9], the normal LVEF group was further stratified into a normal LVGLS subgroup and an increased LVGLS subgroup.

Definitions of perioperative adverse events
Perioperative adverse events were pre-specified as following: perioperative death, cardiac rupture, heart arrest, moderate or severe perivalvular leakage (PVL), significant mitral regurgitation (MR) during TAVI and moderate or severe postoperative residual MR, perioperative residual ventricular outflow tract obstruction, perioperative reoperation, and perioperative acute heart failure. The observation period was from the initiation of TAVI to hospital discharge.

Echocardiography
Patients included in the study underwent standard echocardiography using EPIQ7C ultrasound system (Philips Healthcare). Offline analyses were performed for LV measurements using TomTec software (GE Healthcare, Chicago, IL, United States). The mean transvalvular gradient was calculated using the Bernoulli formula. The AV area was measured using the continuity equation. LVEF was obtained using Biplane Simpson methods. Short axis view at AV level was used to observe morphological characteristics. The global 2D LVGLS was acquired in the apical long axis view, in apical four chamber, and in apical two chamber view. The speckle-tracking echocardiography-derived measurements were performed with software package (TomTec Imaging Systems, Unterschleissheim, Germany). For speckle tracking analysis, 3 cycles were recorded at a frame rate between 40 and 80 frames per second and were averaged for strain analysis. LVGLS was defined as the peak negative value from the strain curve at end-systole. From 3 manually selected landmark points (lateral and septal mitral annulus and LV apex) in apical views, LV endocardial borders were automatically detected by the software. Automatic tracking of myocardial speckles was performed in the cardiac cycle, manually correction was performed if automatic tracing was not appropriate. LVEF and LVGLS data were collected preoperatively immediately after anesthesia introduction, following balloon expansion and following stent implantation respectively. Value variant of LVGLS and LVEF during preoperative balloon expansion (pre-ex), preoperative stent implantation (pre-im) and balloon expansion-stent implantation (ex-im) were then calculated.

Statistical analysis
All results are expressed as mean ± SD. Student’s t test was used to compare echocardiographic data between baseline and values during and after the operation. Linear regression analysis was conducted to test the correlation among the variations before, during, and after the procedure of LVEF, LVGLS and perioperative adverse events. Differences were considered statistically significant if the P value was less than 0.05. All statistical analyses were performed with SPSS version 24.0 statistical analysis software (IBM Corp., Armonk, NY, United States).

RESULTS

Baseline patient characteristics
Sixty-one patients underwent transfemoral TAVI and TTE tests. Self-expanding prosthetic valves were used in this operation. Table 1 presented the clinical characteristics of participants in the study. Twenty patients were female. The mean age of the participants was 73.42 ± 7.60 years. Based on the results of echocardiographic tests, all patients had AS, with an average AV area of 0.66 ± 0.29 cm². Peak flow velocity of aortic flow was 478.21 ± 103.36 cm/s, and pressure gradient across AV was 56.47 ± 22.33 mmHg. Thirty patients had more than moderate aortic regurgitation simultaneously. 2D echocardiography was used to assess the valve morphology at the short axis view. Among all the participants, 28 patients (45.9%) had bicuspid aortic valve (BAV) and 33 patients (54.1%) had tricuspid aortic valve (TAV). Complications included hypertension (32 patients, 52.5%), coronary heart disease (18 patients, 29.5%), diabetes (14 patients, 23%), impaired pulmonary function (11 patients, 18%) and stroke (11 patients, 18%).

Clinical events during TAVI
Totally perioperative adverse events occurred in 16 patients during the observation. Neither aortic dissection nor procedural coronary flow impairment was observed in the entire study population. Details of the events are listed in Table 2. The most common adverse event was moderate or severe PVL.
Table 1 Clinical characteristics of participants undergoing transcatheter aortic valve implantation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n = 61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (n)</td>
<td>28</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>73.42 ± 7.60</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.67 ± 7.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.88 ± 10.61</td>
</tr>
<tr>
<td>NYHA class III/IV (n)</td>
<td>43/5</td>
</tr>
<tr>
<td>Other diseases</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>32</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
</tr>
<tr>
<td>Hyperlipemia</td>
<td>8</td>
</tr>
<tr>
<td>Coronary heart diseases</td>
<td>18</td>
</tr>
<tr>
<td>Impaired pulmonary function</td>
<td>11</td>
</tr>
<tr>
<td>Stroke</td>
<td>11</td>
</tr>
</tbody>
</table>


Table 2 Adverse events during the perioperative period

<table>
<thead>
<tr>
<th>Perioperative adverse events</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac rupture</td>
<td>2</td>
</tr>
<tr>
<td>Heart arrest</td>
<td>1</td>
</tr>
<tr>
<td>Perioperative death</td>
<td>2</td>
</tr>
<tr>
<td>Perioperative reoperation</td>
<td>2</td>
</tr>
<tr>
<td>Perioperative acute heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Moderate or severe perivalvular leakage</td>
<td>5</td>
</tr>
<tr>
<td>Perioperative LVOTO</td>
<td>1</td>
</tr>
<tr>
<td>Significant mitral regurgitation</td>
<td>2</td>
</tr>
</tbody>
</table>

LVOTO: Left ventricular outflow tract obstruction.

(5 patients, including 3 patients with BAV and 2 patients with TAV). No evidence showed the development of PVLs was related to the morphology of AV (OR = 1.008, 95% CI: 0.582-1.745, P = 0.978). During linear regression analyses, only deviation of pre-ex LVGLS was associated with perioperative adverse events (OR = 1.384, 95% CI: 1.030-1.861, P = 0.031). Other factors that might have effects on the occurrence of adverse events but showed no statistical significance are listed in Table 3.

**Effects of TAVI on echocardiographic parameters**

Both peak AV velocity (478.21 ± 103.36 cm/s vs 232.77 ± 56.03 cm/s; P = 0.000) and mean pressure gradient (56.47 ± 22.33 mmHg vs 11.95 ± 5.48 mmHg; P = 0.000) significantly decreased after TAVI. Concomitant AR decreased from 30 to 5 cases. However, AV area increased evidently (0.66 ± 0.29 cm² vs 1.78 ± 0.3 cm²).

The TAVI procedure was divided into three sections in the study: preoperatively after the induction of anesthesia, following balloon expansion and following stent implantation. LVEF and LVGLS at the three sections and the deviations of LVEF and LVGLS over the three sections were calculated. There was a decline in LVEF over the three sections, but the decrease was not statistically significant. There was also declining trend in LVGLS and the pre-ex and pre-im mean values of LVGLS increased significantly (P = 0.037 and P = 0.020, respectively) while no significant increase was noted in the ex-im mean value (P = 0.835). Some patients’ LVGLS became better (18 patients, -15.00 ± 4.92) after prothesis implantation, while some others became worse (43 patients, -12.36 ± 4.62). By comparing the baseline LVGLS between these 2 types of patients, it was found that the patients whose LVGLS increased had worse baseline
Table 3 Factors influencing perioperative adverse events

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.089</td>
<td>0.003-2.425</td>
<td>0.152</td>
</tr>
<tr>
<td>Age</td>
<td>1.141</td>
<td>0.974-1.335</td>
<td>0.102</td>
</tr>
<tr>
<td>Weight</td>
<td>0.929</td>
<td>0.823-1.048</td>
<td>0.228</td>
</tr>
<tr>
<td>Height</td>
<td>1.233</td>
<td>0.942-1.615</td>
<td>0.127</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.579</td>
<td>0.309-21.515</td>
<td>0.381</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.512</td>
<td>0.398-76.356</td>
<td>0.203</td>
</tr>
<tr>
<td>Hyperlipemia</td>
<td>0.721</td>
<td>0.027-19.079</td>
<td>0.845</td>
</tr>
<tr>
<td>Coronary heart diseases</td>
<td>1.919</td>
<td>0.218-16.924</td>
<td>0.557</td>
</tr>
<tr>
<td>Impaired pulmonary function</td>
<td>2.656</td>
<td>0.154-45.870</td>
<td>0.502</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.290</td>
<td>0.240-21.846</td>
<td>0.472</td>
</tr>
</tbody>
</table>

CI: Confidence interval; OR: Odds ratio.

LVGLS ($P = 0.049$).

When the threshold for LVEF was set at $\geq 50\%$, patients were divided into a preserved LVEF group (39 patients) and a decreased LVEF group (22 patients). In the preserved LVEF group, changes in LVGLS were greater than in LVEF. The mean pre-ex and pre-im LVGLS values decreased obviously. In total, 13 adverse events occurred in this group. In the decreased LVEF group, neither LVEF nor LVGLS displayed significant changes and 3 adverse events occurred. Details for the two groups are showed in Table 4 and Table 5.

We further subdivided the normal LVEF group into a normal LVGLS group (11 patients) and an increased LVGLS group (28 patients) with a threshold $\leq -20\%$ for LVGLS. An increasing trend can be observed in LVGLS in both groups. Adverse events occurred 10 times in the increased LVGLS group and 3 times in the normal LVGLS group. When comparing difference in the values of LVGLS between pre-ex and pre-im sections, it revealed that rise in the mean values of LVGLS was more significantly in the increased group than in the normal group ($P = 0.039$, $P = 0.015$).

DISCUSSION

TAVI is a guideline recommended as an alternative treatment in AS patients with or without AR who deemed to have moderate or severe surgical risk\[10]. As reported previously, these patients can benefit from the operation with decreased peak velocity, pressure gradient, and degree of AR and increased AV area. It has been demonstrated that TAVI resulted in continued beneficial changes in LVEF and LVGLS \[11,12]. However, the change in LV function during the procedure has seldom been noted. The present study revealed that (1) The baseline LV function could have effect on the change in subtle LV function during TAVI procedure; (2) LVGLS was more sensitive than LVEF to reflect the changes in subtle LV function during the operation; and (3) The changes in LVGLS during TAVI may have an influence on the occurrence of perioperative adverse events.

We categorized the TAVI procedure into three sections based on balloon expansion and rapid pacing. Balloon expansion would do obstruction in left ventricular outflow tract within a short time, and rapid pacing was needed to bring down the blood pressure. These actions may be exerted several times if necessary; however, both manipulations might do harm to the LV function in case of improper actions or taking too much time. We collected TTE images immediately after anesthesia introduction, balloon expansion, and protheses implantation in consideration of the possible injuries.

All the patients in the study suffered from AS. Although LVEF exceeded 50% in the preserved LVEF group (39 patients), the mean value of LVGLS had declined in severe AS patients, which was consistent with the previous studies\[13,14]. Conventional LVEF is useful in detecting global LV dysfunction, but it is not sensitive enough. As reported earlier, our data also suggest that the myocardium of patients with severe AS is intrinsically dysfunctional despite preserved LV function based on the level of LVEF. The subtle injury of LV function might lead to a downtrend in the tolerance to manipulations during TAVI procedure. It should be noted that strain is load dependent, and the reduction in LVGLS may be partially explained by an increase in LV afterload pressure\[12,15].

Compared with baseline data, both LVEF and LVGLS became worse over the operation. The manipulation of TAVI was presumed when the LV function had already been injured. However, LVEF only showed obvious change in pre-ex section, while LVGLS changed significantly in both pre-ex and pre-im
Table 4 Changing trend in left ventricular ejection fraction and left ventricular global longitudinal strain in the preserved left ventricular ejection fraction group

<table>
<thead>
<tr>
<th></th>
<th>Preserved LVEF group</th>
<th>Pre-ex</th>
<th>Pre-im</th>
<th>Di-im</th>
<th>Inter-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LVEF</td>
<td>64.57 ± 7.63</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LVEF after expansion</td>
<td>60.17 ± 9.73</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LVEF after implantation</td>
<td>58.38 ± 11.39</td>
<td></td>
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<tr>
<td>P value</td>
<td>0.081</td>
<td>0.013</td>
<td>0.432</td>
<td>0.040</td>
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</tr>
<tr>
<td>Baseline LVGLS</td>
<td>-18.09 ± 3.30</td>
<td></td>
<td></td>
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<tr>
<td>LVGLS after expansion</td>
<td>-13.99 ± 4.22</td>
<td></td>
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<tr>
<td>LVGLS after implantation</td>
<td>-12.94 ± 5.59</td>
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<tr>
<td>P value</td>
<td>0.003</td>
<td>0.000</td>
<td>0.309</td>
<td>0.000</td>
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<tr>
<td>PAEs</td>
<td>13</td>
<td></td>
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</tr>
</tbody>
</table>

Ex-im: Balloon expansion-stent implantation; LVEF: Left ventricular ejection fraction; LVGLS: Left ventricular global longitudinal strain; PAEs: Perioperative adverse events; Pre-ex: Preoperative balloon expansion; Pre-im: Preoperative stent implantation.

Table 5 Changing trend in left ventricular ejection fraction and left ventricular global longitudinal strain in the decreased left ventricular ejection fraction group

<table>
<thead>
<tr>
<th></th>
<th>Decreased LVEF group</th>
<th>Pre-di</th>
<th>Pre-im</th>
<th>Di-im</th>
<th>Inter-group</th>
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</thead>
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<td>34.34 ± 9.74</td>
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<tr>
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<td>35.23 ± 9.98</td>
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<tr>
<td>LVEF after implantation</td>
<td>35.91 ± 11.52</td>
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<tr>
<td>P value</td>
<td>0.780</td>
<td>0.623</td>
<td>0.833</td>
<td>0.884</td>
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<tr>
<td>Baseline LVGLS</td>
<td>-9.07 ± 3.31</td>
<td></td>
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<tr>
<td>LVGLS after expansion</td>
<td>-7.72 ± 4.09</td>
<td></td>
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<tr>
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<td>-8.24 ± 4.00</td>
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<tr>
<td>P value</td>
<td>0.245</td>
<td>0.472</td>
<td>0.654</td>
<td>0.500</td>
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<td>PAEs</td>
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</tbody>
</table>

Ex-im: Balloon expansion-stent implantation; Pre-ex: Preoperative-balloon expansion; Pre-im: Preoperative-stent implantation; LVEF: Left ventricular ejection fraction; LVGLS: Left ventricular global longitudinal strain; PAEs: Perioperative adverse events.

sections. The LVGLS changed less if the baseline LVGLS was in normal range, while normal baseline LVEF could not guarantee the change during the operation. This again showed that while subtle variations in baseline LV function could affect the degree of tolerance to the manipulation of TAVI to some extent, LVGLS was a more sensitive index.

Some LVGLS became worse in patients during TAVI after protheses implantation compared with the baseline data, while some LVGLS would improve in others. Patients with declined LVGLS had worse baseline LVGLS (-15.00 ± 4.92% vs -12.36 ± 4.62%; P = 0.049) compared to those with normal LVGLS. This implied that the patients with better baseline LV function may be more tolerable to the procedure and could restore better after the overload of LV had been resolved.

According to the statistical data of present study, the deviation of pre-ex LVGLS was associated with the happening of clinical events. It may demonstrate the dysfunction occurring during the procedure could result in complications in some circumstances. When comparing the normal LVGLS subgroup and increased LVGLS subgroup in the preserved LVEF group, there were totally 13 clinical events in the normal LVEF group with 10 events occurring in 28 patients in the increased LVGLS subgroup and 3 events occurring in 11 patients in the normal LVGLS subgroup. Fewer events were observed in the relatively good LVGLS subgroup. In both pre-ex and pre-im sections, the mean value of deviations in the increased subgroup changed more significantly than that of normal LVGLS subgroup. Previous studies have suggested the presence of ischemia and myocardial fibrosis in the endocardium from sustained pressure loading in severe AS. The biopsy results proving myocardial fibrosis in aortic
stenosis is directly related to the reduction in GLS\textsuperscript{16,17}. In this study, the different levels in LVGLS change in the three sections during TAVI may be explained by the fibrosis in endocardium. LVGLS variation could reflect the change of LV function in a certain range, and the variation may have implications for the outcome of TAVI in the perioperative period. However, if low enough, neither LVEF nor LVGLS could be reflective of the change of subtle LV function. As many of this group showed eccentric hypertrophy, it was assumed that the fibrosis and myocardial apoptosis were too severe to react with operation in a short time\textsuperscript{18-20}. We did not find additional adverse clinical events in the declined LVEF group, which may be due to more protective measures carried out in this group. Other factors, such as advanced age, low weight, hypertension, diabetes, coronary heart disease and stroke, might also slightly stimulate the occurrence of clinical events. In line with previous reports, there was an improvement in LVGLS both at septal and lateral level as early as 72 h after the procedure, and constant beneficial could also be observed in early and late periods\textsuperscript{5,21}. Although the benefits are obvious, the subtle change during operation should not be ignored, which may influence the perioperative clinical events.

Limitations
The following are several limitations of this study. Firstly, this was a single center retrospective study, the follow-up period is limited to perioperative time, and this study was designed to assess the acute effects of the procedure on LV strain. A long-term study is necessary to observe whether any alteration of the changes in myocardial strain and clinical outcomes. Secondly, we excluded many patients due to the poor imaging or the failure in collecting all the needed images. That maybe lead to the bias of the results. Thirdly, LVGLS was affected by arrhythmia, and the results would be influenced to some degree. However, it was unavoidable when images collected after balloon expansion and stent implantation. Finally, all the data in the present study were collected under anesthesia. It may be different with the results in normal physiological conditions, and LV function could be affected by cardiotonic agents. Further and detailed research is needed.

CONCLUSION
In conclusion, LVGLS is more sensitive than conventional LVEF to detect subtle change in LV systolic function during TAVI operation in patients with severe AS. The change ranges of LVGLS during the procedure were associated with the baseline LVGLS and can affect the perioperative outcomes of TAVI. More attention should be paid to patients who had preserved LVEF with increased LVGLS and who had a wide variation in LVGLS during the operation. These findings can provide new insights into the understanding of LV mechanics and pathophysiology in patient with sever AS and play an important role in intraoperative monitoring.

ARTICLE HIGHLIGHTS

Research background
The efficacy of transcatheter aortic valve implantation (TAVI) and prognosis of aortic stenosis (AS) is usually restricted by perioperative adverse events. Global longitudinal strain is a commonly used echocardiographic parameter for the detection of left ventricular function. Whether there is an association between the changes in global longitudinal strain and the occurrence of perioperative adverse events during TAVI remains unknow.

Research motivation
If global longitudinal strain is useful for the predication of perioperative adverse events, monitoring of global longitudinal strain can be carried out before the operation and corresponding measures can be taken to reduce the operational risk.

Research objectives
To assess changes in left ventricular global longitudinal strain (LVGLS) during the surgery of TAVI and the association between LVGLS and perioperative adverse events in patients with calcified aortic stenosis.

Research methods
A retrospective study was carried in 61 patients with calcified AS undergoing TAVI. These patients underwent standard echocardiography examination. LVEF and LVGLS data were collected during preoperative balloon expansion, preoperative stent implantation, and balloon expansion-stent implantation. The patients were categorized into a normal left ventricular ejection fraction (LVEF) group...
and a reduced LVEF group, and the normal LVEF group was further stratified into a normal LVGLS subgroup and an increased LVGLS subgroup. The association between changes in LVEF and LVGLS and the occurrence of perioperative adverse events were analyzed.

**Research results**

In the preserved LVEF group, LVEF only showed obvious change in preoperative balloon expansion section, while LVGLS declined significantly in both preoperative balloon expansion and preoperative stent implantation sections. In the decreased LVEF group, neither LVEF nor LVGLS displayed significant changes. Changes in LVGLS in preoperative balloon expansion section and preoperative stent implantation section were associated with perioperative adverse events which indicating changes in LVGLS during TAVI may have an influence on the occurrence of perioperative adverse events.

**Research conclusions**

In the preserved LVEF group, changes in LVGLS were greater than in LVEF. LVGLS can be a marker to be used for the prediction of changes in cardiac function during TAVI.

**Research perspectives**

The optimal cut-off value for LVGLS and timing for measurement of LVGLS still needs to be guaranteed by large scale multi-center studies.

**FOOTNOTES**

**Author contributions:** Zhang H, Xie JJ, Li RJ, Wang YL, Niu BR, Song L, Li J, and Yang Y contributed to the writing and revising of the manuscript.

**Institutional review board statement:** The study was reviewed and approved by the Beijing Anzhen Hospital.

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

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

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

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L-Editor: Filipodia

P-Editor: Wang JL

**REFERENCES**


Zhang H et al. LVGLS and transcatheter aortic valve implantation


Observational Study

Early detection of noise-induced hearing loss

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Abstract

BACKGROUND
Noise-induced hearing loss (NIHL) is the second most common acquired hearing loss following presbycusis. Exposure to recreational noise and minimal use of hearing protection increase the prevalence of NIHL in young females. NIHL is irreversible. Identifying minor hearing pathologies before they progress to hearing problems that affect daily life is crucial.

AIM
To compare the advantages and disadvantages of extended high frequency (EHF) and otoacoustic emission and determine an indicator of hearing pathologies at the early sub-clinical stage.

METHODS
This cross-sectional study was implemented in West China Hospital of Sichuan University from May to September 2019. A total of 86 participants, aged 18-22 years, were recruited to establish normative thresholds for EHF. Another 159 adults, aged 18-25 years with normal hearing (0.25-8 kHz ≤ 25 dBHL), were allocated to low noise and noise exposure groups. Distortion otoacoustic emission (DPOAE), transient evoked otoacoustic emissions (TEOAE), and EHF were assessed in the two groups to determine the superior technique for detecting early-stage noise-induced pathologies. The chi-square test was used to assess the noise and low noise exposure groups with respect to extended high-frequency
RESULTS
A total of 86 participants (66 females and 20 males) aged between 18 and 22 (average: 20.58 ± 1.13) years were recruited to establish normative thresholds for EHF. The normative thresholds for 9, 10, 11.2, 12.5, 14, 16, 18, and 20 kHz were 15, 10, 20, 15, 15, 20, 28, and 0 dBHL, respectively. A total of 201 participants were recruited and examined for eligibility. Among them, 159 adults aged between 18 and 25 years were eligible in this study. No statistical difference was detected between the noise exposure and the low noise exposure groups using EHFA, DPOAE, and TEOAE (P > 0.05) except in the right ear at 4 kHz using TEOAE (abnormal rate 20.4% vs 5.2%, respectively; P = 0.05).

CONCLUSION
These results showed TEOAE as the earliest indicator of minor pathology compared to DPOAE and EHF. However, a multicenter controlled study or prospective study is essential to verify these results.

Key Words: Early detection superiority; Noise-induced hearing loss; Otoacoustic emission; Extended high frequency; Noise; Hearing loss

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Core Tip: Noise-induced hearing loss is irreversible. Identifying minor pathologies of hearing before they progress to hearing problems that affect daily life is crucial. Our study recruited adults aged between 18 and 25 years with normal hearing (0.25-8 kHz ≤ 25 dBHL). The participants were allocated into a high noise exposure group or low noise exposure group based on their noise exposure history. The distortion otoacoustic emission (DPOAE), transient evoked otoacoustic emissions (TEOAE), and extended high frequency were assessed in the two groups to determine the superior technique for detecting early-stage noise-induced pathologies. The current study showed TEOAE as the earliest indicator of minor pathology compared to DPOAE and extended high-frequency audiometry.

INTRODUCTION
Noise can be social or occupational[1]. Noise-induced hearing loss (NIHL) is caused by repeated exposure to loud sounds over an extended period, very loud impulse sound(s), or a combination of both [2]. NIHL can be divided into temporary threshold shift (TTS) and permanent threshold shift (PTS). TTS is defined as a threshold shift that recovers to baseline levels in hours, days, or weeks following exposure, while PTS is defined as a noise-induced threshold shift that persists after a period of recovery. It results from damage to and loss of cochlear hair cells[3].

NIHL is the second most common acquired hearing loss following presbycusis[4,5]. Occupational and social noise-induced PTS affects a large number of individuals with NIHL as the leading occupational disease[6]. Interestingly, a marked incidence was observed in the young population (12-35 years old) as a result of recreational noise exposure[4,7]. In addition, increased exposure to recreational noise and minimal use of hearing protection may be responsible for the increased prevalence of NIHL in young females[6]. Thus, social noise might play a major role in inducing NIHL in modern society.

Noise has several effects on human health, including concentration disturbance, memory loss, anxiety, depressive behavior, muscular contraction, tachycardia, and hypertension[5]. Although the noise exposure does not damage or result in loss of inner and outer hair cells, and the auditory detection thresholds are unaffected, the encoding of sound at suprathreshold levels is impaired[8,9]. In noise-exposed humans, this phenomenon manifests as difficulty in processing speech in a noisy background in the absence of clinically elevated thresholds[8,9].

NIHL is diagnosed based on the pure-tone audiogram. The typical patterns in hearing thresholds are a noise notch at 3, 4, and/or 6 kHz combined with a relatively normal threshold at 8 kHz[2]. The characteristic of NIHL is sensorineural hearing loss that is typically bilateral[10]. Although NIHL is irreversible and progressive while exposure to noise continues, it is also predictable and preventable...
Consequently, identifying minor pathologies of hearing before they progress to hearing problems that affect daily life is crucial for preventing the deterioration of hearing by changing the lifestyle, i.e., reducing noise exposure.

The commonly used methods to detect NIHL include conventional audiometry (CA), otoacoustic emission (OAE), and extended high-frequency audiometry (EHFA).

CA presents 0.25-8 kHz pure tones, which constitute the speech spectrum, and hence, the hearing loss in this frequency range can influence the daily communication that might be noticed by the affected individual. OAE comprises sounds of cochlear origin that can be recorded by a microphone fitted into the ear canal[11]. OAEs are sensitive to minor pathologies, thereby rendering them as an indicator of damage compared to CA[12]. EHFA presents a 9-20 kHz pure tone that has proved to be a promising tool for the early diagnosis of many hearing disorders[13]. The higher hearing thresholds of 10-16 kHz were observed in individuals < 31 years old following the use of personal listening devices for > 5 years [14]. Consequently, OAE and EHFA are promising tools for detecting NIHL at the early stages than by CA.

Some studies explored the types of measurements in the early detection of NIHL[5,15,16], albeit the results were inconsistent. Job et al[15] emphasized the use of distortion otoacoustic emission (DPOAE) measurements in public health and occupational noise prevention policies. Other studies stated that EHFA was sensitive in detecting NIHL[5,16]; these studies were designed differently and involved various participants.

This study aimed to compare the advantages and disadvantages of extended high frequency (EHF) and otoacoustic emission and determined an early indicator of minor pathologies of hearing in sub-clinical disease, so that further hearing loss can be prevented. Three measurements, EHFA, DPOAE, and transient-evoked otoacoustic emission (TEOAE), were compared in the patient group with normal hearing thresholds at CA. Several studies had compared the CA, EHFA, and DPOAE for the early diagnosis of NIHL[5,16,17]. These results were inconsistent and TEOAE was not discussed previously.

**MATERIALS AND METHODS**

**Participants**

This cross-sectional study was implemented at the West China Hospital of Sichuan University from May 2019 to September 2019. Young adults, aged 18-25 years, were recruited randomly and sequentially according to the sequence to Hearing Center of West China Hospital. In the current study, only young adults aged 18-25 years were recruited. Because of the age factor, the early hearing pathology did not interfere with the test results. According to ISO 7029, little change occurred in this age group[12].

Participants with normal CA and acoustic reflexes were included in this study. Normal CA was defined as the threshold ≤ 25 dBHL at each frequency from 0.25-8 kHz. According to the World Health Organization (WHO) definition, normal hearing means the average thresholds of 0.5, 1, 2, and 4 kHz at ≤ 25 dBHL[18]. In this study, normal hearing was considered if all the frequencies from 0.25-8 kHz were ≤ 25 dBHL instead of the average thresholds at 0.5, 1, 2, and 4 kHz defined by the WHO. For early detection, only minor pathologies existed before the patient identified the problem. The normal hearing could be defined only if minor hearing loss occurred at one or two frequencies at 0.5, 1, 2, and 4 kHz according to the WHO’s normal hearing definition. We could not detect the minor hearing pathology early if the normal hearing was defined according to the WHO. Thus, the normal hearing was designated if all the frequencies from 0.25-8 kHz were ≤ 25 dBHL.

Participants with disorders of middle ear function, who underwent otoscopic examination, tympanometry, and audiometry, were excluded. The participants were considered to have middle ear dysfunction in case of one of the following conditions: The tympanic membrane was perforated as observed by otoscopy, tympanogram was type B or type C, and the air-bone gap was > 10 dB at conventional audiometry[19].

**Grouping of subjects**

In the present society, all types of social media are popular, for example, listening to music through a cell phone, wearing headphones when playing games, prolonged use of the phone each day, playing a musical instrument, and attending a music concert. Consequently, it was difficult to differentiate young adults into noise and no noise exposure groups. Noise exposure cannot be avoided in the present society, and it is difficult to measure the amount of social and occupational noise exposure accurately. Thus, it is reasonable to differentiate young adults into noise exposure and low noise exposure groups instead of noise exposure and no noise exposure groups.

Participants were allocated to noise or low noise exposure groups according to their noise exposure history. The noise exposure was estimated using the Lutman structured noise questionnaires[12]. Occupational noise and social noise questionnaires were used during the interview with the participants [12]. The gunshot and explosive noise questionnaires were not used because none of the participants had this history. According to the information mentioned in the questionnaires, the noise exposure was estimated using the following equation: \( U = 10^{(L-A-90)/10} \times Y \times W \times D \times H/2080 \), where \( U \) is units of...
cumulative noise exposure, L is estimated noise level in dB(A), A is hearing protection attenuation in dB, Y is years of exposure, W is weeks/year of exposure, D is days/week of exposure, and H is hours/day of exposure[12]. Noise immission rating (NIR) was determined according to U = 10^{0.1 \times 90/10 \times Y \times W \times D \times H / 2080}. Lutman et al categorized NIR into five degrees based on the units of cumulative noise exposure: 0 (U up to 5), 1 (U = 6-50), 2 (U = 51-500), 3 (U = 501-5000), and 4 (U = 5000+) [12]. The NIR values are equivalent to continuous exposure for 8 h/d, 5 d/wk, 48 wk/year, throughout a full 50-year working lifetime[12]. NIR = 0 is equivalent to continuous noise < 80 dB(A), NIR = 1 to 81-90 dB(A), NIR = 2 to 91-100 dB(A), NIR = 3 to 101-110 dB(A), and NIR = 4 to > 110 dB(A) [12]. Participants were grouped into the low noise group if NIR = 0 and the noise group if NIR = 1, 2, 3, or 4.

**Study size**
Assuming that there would be a 55% incidence of NIHL in the noise group and 32% in the low noise group [1], we calculated that 141 patients would need to be enrolled to provide 80% power to test for the difference between the groups in the incidence of NIHL, at a two-sided significance level of 5%. Assuming a 10% rate of loss to follow-up, we planned to enroll a total of 160 patients.

**Blind method**
CA, EHFA, DPOAE, and TEOAE were performed by a trained audiology technician who was unaware of the noise exposure history of each participant. The social noise exposure history of each participant was collected by another trained audiology technician who did not know the participant’s CA, EHFA, DPOAE, and TEOAE results.

**Test tools**
CA was performed in the range 0.25-8 kHz using Interacoustic AC-40 and TDH 39 headphones calibrated according to ANSI S3.6-2010 type 1 and ANSI S3.6-2010. EHFA was measured at 9, 10, 11.2, 11.5, 14, 16, 18, and 20 kHz using the same Interacoustic AC-40 and HDA200 high-frequency headphones calibrated according to ANSI S3.6-2010. Threshold values at each frequency were obtained using a modified Hughson-Westlake up-down procedure, which obtained thresholds at the lowest response in a minimum of 50% of the ascending trials, two per level, using a 10-dB ascending and a 5-dB ascending measurement approach [20,21].

DPOAE and TEOAE were measured using an Interacoustic Titan that fulfilled the criterion of Medical Device Directive 93/42/EEC. For DPOAE, the ratio of the two frequencies was f2:f1 = 1.22; the intensity of the two frequencies was L1/L2 = 65/55 dBSPL. The frequency of f2 was 1, 1.5, 2, 3, 4, and 6 kHz, respectively. The result was considered a pass if the signal to noise ratio (SNR) ≥ 6 dB. The stimuli for TEOAE were 1, 1.5, 2, 3, and 4 kHz. The intensity of the stimulus was 83 dB peSPL. The result was considered pass if the SNR was ≥ 6 dB, and the repetition was ≥ 70%.

Tympanometry was measured using Interacoustic AT235, according to the standard of Medical Device Directive 93/42/EEC. The ipsilateral (1 and 2 kHz) and contralateral (0.25, 0.5, 1, and 2 kHz) stimuli were calibrated according to ISO3889-1 and 389-2, respectively.

**Setting up normative thresholds of EHFA**
The comparison of normative thresholds between conventional audiometry did not achieve a consensus that described the normal parameters for children or adults with respect to EHFA [13,22,23,24]. Thus, normative thresholds from 9-20 kHz need to be established, otherwise the EHFA results using DPOAE and TEOAE cannot be compared.

To develop a normative threshold of EHFA, participants aged 18-25 years, who had a low noise exposure history and complied with the inclusion criteria for a control group, were included in this study. Thresholds at 9, 10, 11.2, 12.5, 14, 16, 18, and 20 kHz were obtained using a modified Hughson-Westlake up-down procedure [20,21]. The percentile method was used to determine 95% normal range of 8-20 kHz.

**Statistical analysis**
Statistical analyses were performed by an expert statistician at the Chinese Evidence-Based Medicine/Cochrane Center using SPSS20.0 (SPSS Inc., Chicago, IL, USA). A Shapiro-Wilk normality test was used to assess the normal distribution for the group and set normative thresholds. As mentioned above, the percentile method was used to establish the normative thresholds from 9-20 kHz. The EHFA results were converted into normal and abnormal according to the normative thresholds. The results of DPOAE and TEOAE were recorded as normal if they passed, or else were considered abnormal. The chi-square test was used to test for normal and abnormal in the noise and low noise exposure groups with respect to EHFA, DPOAE, and TEOAE. \( P \leq 0.05 \) was considered statistically significant.

**RESULTS**
A total of 86 participants (66 females and 20 males), aged 18-22 (20.58 ± 1.13) years, were included to set up normative thresholds of EHFA. The Shapiro-Wilk test revealed that the sample did not conform to a normal distribution \( (P < 0.001) \) for 9, 10, 11.2, 12.5, 14, 16, 18, and 20 kHz, respectively. The upper limit...
Table 1 Lower limit at 95% of extended high-frequency audiometry thresholds (n = 86)

<table>
<thead>
<tr>
<th>EHF (kHz)</th>
<th>mean ± SD</th>
<th>Min</th>
<th>Max</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>95th</th>
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<td>9</td>
<td>3.14 ± 5.26</td>
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<td>15.00</td>
<td>0.00</td>
<td>5.00</td>
<td>5.00</td>
<td>15.00</td>
</tr>
<tr>
<td>10</td>
<td>0.93 ± 5.34</td>
<td>-15.00</td>
<td>15.00</td>
<td>-5.00</td>
<td>0.00</td>
<td>5.00</td>
<td>10.00</td>
</tr>
<tr>
<td>11.2</td>
<td>2.50 ± 7.19</td>
<td>-15.00</td>
<td>25.00</td>
<td>0.00</td>
<td>0.00</td>
<td>5.00</td>
<td>20.00</td>
</tr>
<tr>
<td>12.5</td>
<td>-0.52 ± 6.90</td>
<td>-15.00</td>
<td>20.00</td>
<td>-5.00</td>
<td>0.00</td>
<td>5.00</td>
<td>15.00</td>
</tr>
<tr>
<td>14</td>
<td>0.52 ± 7.97</td>
<td>-10.00</td>
<td>20.00</td>
<td>-5.00</td>
<td>0.00</td>
<td>5.00</td>
<td>15.00</td>
</tr>
<tr>
<td>16</td>
<td>-3.08 ± 13.15</td>
<td>-20.00</td>
<td>25.00</td>
<td>-15.00</td>
<td>-5.00</td>
<td>5.00</td>
<td>20.00</td>
</tr>
<tr>
<td>18</td>
<td>-4.48 ± 16.09</td>
<td>-20.00</td>
<td>30.00</td>
<td>-20.00</td>
<td>-10.00</td>
<td>10.00</td>
<td>28.25</td>
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<tr>
<td>20</td>
<td>-13.78 ± 7.39</td>
<td>-25.00</td>
<td>15.00</td>
<td>-20.00</td>
<td>-15.00</td>
<td>-10.00</td>
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</tr>
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</table>

EHF: Extended high frequency.

Table 2 Age distribution for noise exposure and low noise exposure groups (n = 159)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Female</th>
<th>Male</th>
<th>Mean ± SD</th>
<th>Min</th>
<th>Max</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low noise exposure</td>
<td>61</td>
<td>45</td>
<td>16</td>
<td>21.59 ± 2.00</td>
<td>18</td>
<td>25</td>
<td>20.00</td>
<td>21.00</td>
<td>23.50</td>
</tr>
<tr>
<td>Noise exposure</td>
<td>98</td>
<td>64</td>
<td>34</td>
<td>21.17 ± 1.55</td>
<td>18</td>
<td>25</td>
<td>20.00</td>
<td>21.00</td>
<td>22.00</td>
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</tbody>
</table>

Table 3 Thresholds of participants for conventional audiometry (n = 159)

<table>
<thead>
<tr>
<th>Ear</th>
<th>Group</th>
<th>n</th>
<th>0.25 kHz (mean ± SD)</th>
<th>0.5 kHz (mean ± SD)</th>
<th>1 kHz (mean ± SD)</th>
<th>2 kHz (mean ± SD)</th>
<th>4 kHz (mean ± SD)</th>
<th>8 kHz (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td></td>
<td>7.30 ± 5.21</td>
<td>7.82 ± 4.91</td>
<td>6.97 ± 4.50</td>
<td>6.97 ± 5.42</td>
<td>4.26 ± 5.69</td>
<td>7.54 ± 6.50</td>
</tr>
<tr>
<td></td>
<td>Low noise exposure</td>
<td>61</td>
<td>7.30 ± 5.21</td>
<td>7.82 ± 4.91</td>
<td>6.97 ± 4.50</td>
<td>6.97 ± 5.42</td>
<td>4.26 ± 5.69</td>
<td>7.54 ± 6.50</td>
</tr>
<tr>
<td></td>
<td>Noise exposure</td>
<td>98</td>
<td>6.99 ± 5.91</td>
<td>7.65 ± 5.14</td>
<td>8.06 ± 4.90</td>
<td>8.21 ± 5.62</td>
<td>5.87 ± 5.65</td>
<td>8.78 ± 6.70</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td></td>
<td>6.80 ± 5.70</td>
<td>8.06 ± 4.48</td>
<td>5.66 ± 4.42</td>
<td>6.07 ± 5.99</td>
<td>5.57 ± 5.63</td>
<td>8.28 ± 6.18</td>
</tr>
<tr>
<td></td>
<td>Low noise exposure</td>
<td>61</td>
<td>6.80 ± 5.70</td>
<td>8.06 ± 4.48</td>
<td>5.66 ± 4.42</td>
<td>6.07 ± 5.99</td>
<td>5.57 ± 5.63</td>
<td>8.28 ± 6.18</td>
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<tr>
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<td>Noise exposure</td>
<td>98</td>
<td>7.45 ± 5.38</td>
<td>8.32 ± 5.70</td>
<td>7.14 ± 5.13</td>
<td>6.99 ± 5.78</td>
<td>5.15 ± 5.54</td>
<td>9.03 ± 6.37</td>
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</table>

Figure 1 Flow diagram of the procedure. CA: Conventional audiometry; EHFA: Extended high-frequency audiometry; NIR: Noise immission rating; TEOAE: Transient-evoked otoacoustic emissions; DPOAE: Distortion otoacoustic emission; EHFA: Extended high-frequency audiometry.

of the one-sided clinical normal hearing threshold range was set up.
We used the percentage method to establish the normative thresholds of EHFA at the upper limit of 95% (Table 1). The normative thresholds for 9, 10, 11.2, 12.5, 14, 16, 18, and 20 kHz were 15, 10, 15, 15, 15, 20, 28, and 0 dBHL, respectively.
Meng ZL et al. Early detection of noise-induced hearing loss

Table 4 Chi-square test results for extended high-frequency audiometry (n = 159)

<table>
<thead>
<tr>
<th>Ear</th>
<th>Frequency (kHz)</th>
<th>Group</th>
<th>Normal (N)</th>
<th>Abnormal (N)</th>
<th>Abnormalrate (%)</th>
<th>$\chi^2$</th>
<th>$P$ value</th>
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</tr>
<tr>
<td>Right</td>
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<td>1.33</td>
<td>0.25</td>
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<td>14.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Fisher’s exact probability. 0: Low noise exposure group; 1: Noise exposure group.

A total of 201 participants were recruited, of which 159 were eligible (Table 2) for this study. No data were missed. The procedure is illustrated in Figure 1. These individuals displayed an intact tympanic membrane, good gloss in the tympanic membrane, and a clear view of the manubrium of malleus and cone of light when examined through otoscopy by an ENT doctor. Also, the participants had type A tympanometry along with an ipsilateral acoustic reflex at 1 and 2 kHz and a contralateral acoustic reflex at 0.5, 1, 2, and 4 kHz. None of the participants had ≥ 15 dB air-bone gap in CA. The thresholds of conventional audiometry are shown in Table 3. The chi-square test results of EHFA, DPOAE, and TEOAE are shown in Tables 4, 5, and 6, respectively. No statistical difference was detected between the noise and low noise exposure groups with respect to EHFA, DPOAE, and TEOAE ($P > 0.05$) except in the right ears at 4 kHz in TEOAE ($P =$
### Table 5 Chi-square test results for distortion otoacoustic emission (n = 159)

<table>
<thead>
<tr>
<th>Ear</th>
<th>Frequency(kHz)</th>
<th>Group</th>
<th>Normal (n)</th>
<th>Abnormal (N)</th>
<th>Abnormal rate (%)</th>
<th>Fisher P value</th>
</tr>
</thead>
<tbody>
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<td></td>
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</tr>
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DISCUSSION

The present study aimed to develop the tools to detect NIHL at the early stage. The definition of early detection is that the conventional frequency audiometry is normal. NIHL accrues progressively and often goes unnoticed until it has reached a degree of irreversible damage\(^2\). Thus, detecting NIHL before CA indicates a hearing loss. The evaluation of the sub-clinical condition is initiated by the patient to prevent the worsening of the noise-induced pathology such that it has an impact on the quality of life and clinical intervention.

Abnormal TEOAE was found at 4 kHz in one ear in this study. The result complied with the typical NIHL pattern with a noise notch at 3, 4, and 6 kHz\(^2\). Thus, we speculated that this phenomenon was an indication of the failure of the outer hair cells at 4 kHz and the first minor pathology at the site of sub-clinical conditions.

No statistical difference between noise exposure and low noise exposure groups was observed for DPOAE. This result complied with the trait of TEOAE that is sensitive to the changes in the cochlea manifested as subtle changes in the TEOAE waveform\(^1\). Compared to TEOAE, DPOAE offers a wider frequency range of observation (> 10 kHz) with a lower sensitivity to minor and sub-clinical conditions in adults\(^1\).

Other studies comparing these measures stated that EHFA is more sensitive than OAE\(^5,16\). Mehrparvar et al compared CA, EHFA, and DPOAE for the early diagnosis of NIHL. The study concluded that EHFA is the most sensitive test for the detection of hearing loss in workers exposed to hazardous noise\(^5\). The participants worked in the tile and ceramic industry, and normal CA was not

0.05).
Table 6 Chi-square test results for transient evoked otoacoustic emission (n = 159)

<table>
<thead>
<tr>
<th>Ear</th>
<th>Frequency (kHz)</th>
<th>Group</th>
<th>Normal (n)</th>
<th>Abnormal (n)</th>
<th>Abnormal rate (%)</th>
<th>Fisher P value</th>
</tr>
</thead>
<tbody>
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</tr>
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</table>

<sup>a</sup>Significant difference was observed at 4 kHz for the right ear.

undertaken. The study also included participants > 50 years old<sup>5</sup>. Somma <i>et al</i> conducted a study in cement workers and demonstrated that EHFA was more sensitive than CA in detecting NIHL<sup>16</sup>. Other studies concluded that EHAF and DPOAE can reveal early changes in the auditory function compared to CA. For example, in the study by Knight <i>et al</i>, children and adolescents receiving platinum-based chemotherapy were evaluated<sup>17</sup>. The different conclusions may be due to the varying study designs and the various participants included. Only a few studies compared these measurements using TEOAE. TEOAE is a rapid and convenient test tool. It can be used to detect early minor pathologies of hearing when the disease is sub-clinical. Thus, it can serve as a screening instrument among the population with a noise exposure history. It also can be used for those who complained of hearing problem and had noise exposure history but resented normal hearing in CA.

Since this was a cross-sectional study and the sample size was small, the results need to be interpreted cautiously. Further follow-up of the noise exposure group with TEOAE, DPOAE, and EHFA is still needed. A multicenter controlled study or prospective study is essential to substantiate the current findings.

**CONCLUSION**

In this study, we found that TEOAE is the optimal early indicator of minor pathology with normal CA compared to DPOAE and EHFA. However, multicenter, controlled, prospective studies are required to verify the results.

**ARTICLE HIGHLIGHTS**

<i>Research background</i>
Noise-induced hearing loss (NIHL) is the second most common acquired hearing loss following presbycusis. A marked incidence was observed in the young population (12-35 years old) as a result of recreational noise exposure. Noise has several effects on human health, including concentration disturbance, memory loss, anxiety, depressive behavior, muscular contraction, tachycardia, and hypertension.

Research motivation

NIHL is irreversible and progressive while exposure to noise continues. Consequently, identifying minor pathologies of hearing before they progress to hearing problems that affect daily life is crucial for preventing the deterioration of hearing by changing the lifestyle, i.e., reducing noise exposure. The authors motivated to find an indicator that can predict the minor pathologies of hearing in sub-clinical disease, so that further hearing loss can be prevented.

Research objectives

To compare the advantages and disadvantages of extended high frequency (EHF) and otoacoustic emission and determine an indicator of hearing pathologies at the early sub-clinical stage.

Research methods

This cross-sectional study was implemented at West China Hospital of Sichuan University from May-September 2019. A total of 86 participants, aged 18-22 years, were recruited to establish normative thresholds for EHF. Another 159 adults, aged 18-25 years with normal hearing (0.25-8 kHz ≤ 25 dBHL), were allocated to low noise and noise exposure groups. Distortion otoacoustic emission (DPOAE), transient evoked otoacoustic emission (TEOAE), and EHF were assessed in the two groups to determine the superior technique for detecting early-stage noise-induced pathologies. The chi-square test was used to assess the noise and low noise exposure groups with respect to extended high-frequency audiometry (EHFA), DPOAE, and TEOAE. \( P \leq 0.05 \) was considered statistically significant.

Research results

A total of 86 participants (66 females and 20 males) aged between 18 and 22 (average: 20.58 ± 1.13) years were recruited to establish normative thresholds for EHF. The normative thresholds for 9, 10, 11.2, 12.5, 14, 16, 18, and 20 kHz were 15, 10, 20, 15, 20, 28, and 0 dBHL, respectively. A total of 201 participants were recruited and examined for eligibility. Among them, 159 adults aged between 18 and 25 years were eligible in this study. No statistical difference was detected between the noise exposure and the low noise exposure groups using EHFA, DPOAE, and TEOAE \(( P > 0.05)\) except in the right ear at 4 kHz using TEOAE (abnormal rate 20.4% vs 5.2%, respectively; \( P = 0.05 \)).

Research conclusions

These results showed TEOAE as the earliest indicator of minor pathology compared to DPOAE and EHFA. However, multicenter, controlled, prospective studies are essential to verify these results.

Research perspectives

Since this was a cross-sectional study and the sample size was small, the results need to be interpreted cautiously. Further follow-up of the noise exposure group with TEOAE, DPOAE, and EHFA is still needed. Multicenter, controlled, prospective studies are essential to substantiate the current findings.

ACKNOWLEDGEMENTS

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FOOTNOTES

Author contributions: Meng ZL and Zheng Y guarantied the study; Meng ZL designed the study, interpreted the data, and drafted the initial manuscript; Gu HL performed the study and analyzed the data; Chen F and Zhao F revised the article critically for intellectual content.

Institutional review board statement: The study was reviewed and approved by the West China Hospital, Sichuan University Institutional Review Board.

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

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Empathetic nursing with mindful cognitive therapy for fatigue, depression, and negative emotions in leukemia patients undergoing long-term chemotherapy

Ying-Ying Lu, Xiao-Min Lu, Chun-Yan Shao, Chen-Chen Wang, Ting-Ting Xu, Bei-Lei Zhang

BACKGROUND
Leukemia is a broad term for blood cell cancer. Leukemia is divided into acute or chronic, depending on cell differentiation. Leukemia patients are prone to adverse reactions during chemotherapy, such as anxiety, depression, and even suicide, affecting prognosis. As a nursing model developed by three well-known cognitive psychologists, empathetic nursing with mindfulness cognitive therapy (ENMCT) can effectively reduce anxiety and depression and improve the quality of life in patients with chronic disease.

AIM
To explore the effect of ENMCT on cancer-induced fatigue, hope level, and negative emotions in patients with long-term leukemia chemotherapy.

METHODS
A total of 103 patients with long-term leukemia chemotherapy diagnosed and treated in our hospital from July 2017 to October 2019 were enrolled and randomly assigned to observation and control groups using the random number table approach. Fifty-one patients in the control group received routine nursing, while 52 patients in the observation group received empathic nursing with mindfulness cognitive therapy. After three months of nursing care, cancer-induced fatigue was measured with the Piper Fatigue Scale (PFS), hope level with the Herth Hope Index (HHI), and negative emotion with the Hamilton Anxiety Scale (HAMA)/Hamilton Depression Scale (HAMD). Self-management (Chinese Strategies Used by People to Promote Health) was also recorded.

RESULTS
The observation group’s total scores in behavior, cognition, emotion, feeling, and
PFS were lower than the control group after the intervention \( (P < 0.05) \). Keeping close contact with others, the attitude of taking positive actions, the attitude toward reality and future, and the total HHI score were higher in the observation group than the control group \( (P < 0.05) \). The observation group’s HAMA and HAMD scores were lower than the control group \( (P < 0.05) \). The observation group’s positive attitude, self-decision, and self-relief scores were greater than the control group \( (P < 0.05) \).

**CONCLUSION**

Empathetic nursing with cognitive mindfulness therapy is beneficial in improving cancer-related fatigue, negative emotions, expectation level, and self-management ability in patients with long-term leukemia chemotherapy.

**Key Words:** Mindfulness-based cognitive therapy; Empathetic nursing; Leukemia; Chemotherapy; Cancer-induced fatigue; Hope level; Negative emotions

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**Core Tip:** Leukemia often results in a heavy burden to patients’ families and society. A total of 103 patients with long-term leukemia chemotherapy were assessed to explore the effect of empathetic nursing with mindfulness cognitive therapy (ENMCT) on leukemia-induced fatigue, hope level, and negative emotions. After three months of nursing care, various indicators, such as the Piper fatigue scale, and the Herth hope index, provided conclusion. Our results suggest that ENMCT improves cancer-related fatigue, negative emotions, expectation level, and self-management in patients with long-term leukemia chemotherapy.

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**URL:** https://www.wjgnet.com/2307-8960/full/v10/i6/1826.htm

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**INTRODUCTION**

Leukemia is a white blood cell cancer characterized by rapid, out-of-control proliferation of aberrant cells in the bone marrow. It is classified as acute or chronic depending on cell differentiation[1]. Leukemia prevalence has been increasing yearly, especially in middle-aged and older populations. Leukemia patients are prone to adverse reactions during chemotherapy, which affects prognosis. Leukemia easily relapses, resulting in a heavy burden to patients’ families and society. Therefore, patients are prone to negative emotions, such as anxiety and depression, and even suicide[2,3]. Studies have shown that the incidence of depression in leukemia patients is about 30%[4]. Empathetic nursing with mindfulness cognitive therapy (ENMCT) is a nursing model developed by three well-known cognitive psychologists. ENMCT uses cognitive behavior as the basis of treatment and integrates mindfulness decompression therapy concepts plus trained exercises proposed by Kabajin. The integration of Eastern Zen meditation and Western cognitive insight can effectively reduce anxiety and depression and improve the quality of life of patients with chronic diseases.

ENMCT has had a good clinical effect in other countries[5]. However, these methods have rarely been used in China, especially leukemia patients. Therefore, this study analyzed the clinical data of 103 Leukemia patients undergoing long-term chemotherapy in our hospital and explored the impact of empathetic care with mindfulness cognitive therapy on cancer-related fatigue, hope level, and negative emotion in leukemia patients with long-term chemotherapy.

**MATERIALS AND METHODS**

**General information**

This study included 103 patients diagnosed with leukemia in our hospital who underwent long-term chemotherapy between July 2017 and October 2019. Inclusion criteria were the patient met the conditions for leukemia therapy[6], had no history of anxiety and depression treatment, had received chemotherapy for three months or more, and had an expected survival time greater than six months. Patients and family members signed a written informed consent form. Exclusion criteria were a history
of an intracranial aneurysm or other malignant tumors, severe heart, liver, kidney, or other important organ damage, asthma, mental illness, and communication disorders. Patients were randomly assigned to the observation and control groups by the random number table approach. The observation group included 52 patients, 32 men and 20 women ranging in age from 18 to 81 years, with a mean age of 54.17 ± 16.48, chemotherapy of 1 to 3 years, and mean chemotherapy time of 1.23 ± 0.47 years; two cases with religious beliefs and remaining 50 cases without religious beliefs. The control group included 30 men and 21 women, aged 22–92 years, with a mean age of 54.81 ± 16.94, chemotherapy time of 1 to 3 years, a mean chemotherapy time of 1.27 ± 0.49 years; three cases with religious beliefs, and the others without religious beliefs. The above-mentioned general information was not significantly different between the two groups (P > 0.05). This research was reviewed and approved by the Medical Ethics Committee of our hospital.

Methods
A routine nursing method was used for the control group. According to nursing norms, patients were first introduced to the surrounding ward environment, attending physicians, responsible nurses, and related ward rules and regulations for admitted patients. Second, possible adverse effects of chemotherapy were introduced to help patients master the coping methods. Finally, patient health education was conducted to patiently answer questions sent by the patients, strengthen communication with the patients, eliminate patients’ doubts, and intervene for three consecutive months. For the observation group, ENMCT was externally added to the control group. The specific methods were: initially establish an empathetic group to conduct empathetic psychological intervention training for nursing staff. The training included concepts, content, communication skills, human-orientated caring theory, cognitive theory, etc., to improve the nursing staff’s ability to care for patients and cultivate the cognitive ability to respond to patients’ psychological changes. At the end of the training, an assessment was carried out, and the nursing staff with better performance was selected to form an empathetic group. The criteria to be in the empathetic group also included qualifications and intentions, to be able to listen eagerly, to ask the patient about the situation kindly and tell them to express their inner thoughts actively, listen carefully, encourage the patient through eye contact and body movement; pay attention to changes in the patient’s facial expression and body language during communication, and further understand the patient’s needs. To think for patients while communicating with them, the nursing staff had to intentionally think about the problem from the patient’s perspective, their misfortune, and inner pain; to sort out relevant information expressed by patients, summarizing the causes of the patients’ negative emotions, and have an in-depth understanding of patients’ feelings. To be able to give information feedback, the nursing staff provided positive feedback to the patient’s expression through body movements such as a handshake, hug, etc., and guided patients to express their deep inner feelings; to lighten up the patients’ minds with different traditional (touching) stories or other proper empathy experiences; for example, joking, laughing, and adjusting expressions to make the patient feel recognized or understand a positive feeling, and instruct family members to actively communicate with their loved one, encourage support, and maximize the satisfaction of patient needs.

Observed indicators
The Piper fatigue scale (PFS)[7], which includes four dimensions, behavior, cognition, emotion, and sensation, was used before and after the intervention. The scale has 22 items with a total score of 0–40 points. The lower the score, the lighter the fatigue caused by cancer observed through behavior. The hope level, or the Herth Hope Index[7] (HHI), includes three dimensions, keeping close contact with others, taking positive actions, and attitude toward reality and future. It was used before and after the intervention and contained items for 12 dimensions, using a 4-level scoring method; the higher the score, the better the patient’s hopes. The Hamilton Anxiety Scale (HAMA)[8] was used for anxiety assessment, < 7 points for no anxiety, 7–14 points for existing anxiety, > 14 points for obvious anxiety; depression was assessed with the Hamilton Depression (HAMD) scale[8], < 7 points for no depression, 7–14 points for depression, > 14 points for obvious depression. The higher the score, the more serious the anxiety and depression. Self-management ability was assessed before and after the intervention with the Chinese version of the Cancer Self-Management Efficacy Scale[9], the Chinese version Strategies Used by People to Promote Health (SUPPH), or the C-SUPPH, including positive attitudes, self-decision-making, and self-relief decompression. A total of 28 measurements were made using a 5-point Likert scale. The higher the score, the stronger the self-management ability. Cronbach’s a coefficient of the total scale was 0.970, and Cronbach’s a coefficient of the subscale was between 0.849–0.959.

Statistical analysis
SPSS 20.0 was used to perform the statistical analysis. Data were expressed as mean ± SD. An independent sample t-test was used between the groups and a paired sample t-test within groups. Categorical variables were expressed as a percentage, and the χ² test was used to compare the groups. A P-value < 0.05 was statistically significant.
RESULTS

**PFS score comparison between the two groups**  
There was no significant difference in the PFS scores of the two groups before the intervention ($P > 0.05$). After the intervention, the two groups’ total behavior, cognition, emotion, feeling, and PFS scores decreased. The observation group had a significantly larger decline ($P < 0.05$) than the control group (Table 1).

**Comparison of HHI scores of the two groups**  
As shown in Table 2, there was no significant difference in the PFS scores of the two groups before the intervention ($P > 0.05$). However, after the intervention, the two groups had higher scores in maintaining close contact, taking positive actions, attitudes toward reality and future, and the total HHI score. The observation group had a significantly greater increase than the control group ($P < 0.05$).

**Comparison of HAMA and HAMD scores of the two groups**  
HAMA and HAMD scores showed no significant difference between the two patient groups before the intervention ($P > 0.05$). After the intervention, the HAMA and HAMD scores of the two groups decreased, and the observation group had a significantly greater decline than the control group ($P < 0.05$) (Table 3).

**Comparison of C-SUPPH scores of the two groups**  
As shown in Table 4, there was no statistically significant difference between the C-SUPPH score in the two groups before the intervention ($P > 0.05$). After the intervention, positive attitude, self-decision, and self-relief, the decompression scores of the two groups increased, and the observation group had a significantly greater increase than the control group ($P < 0.05$).

DISCUSSION

With the reform of medical models and improved quality of life, contemporary medicine has higher requirements for clinical nursing, gradually forming a biological-psychological-social model. This model is related to patient prognosis[10]. It is easy for patients diagnosed with malignant tumors to have negative and psychological stress, affecting medication. As a malignant tumor in the blood system, patients with leukemia will have a long drug treatment course, a high recurrence rate, and long-term chemotherapy. This situation makes patients prone to varying degrees of anxiety, depression, other emotions, and worry about the prognosis[11,12]. Therefore, choosing appropriate nursing measures is significant to cure disease with the help of the patient’s psychological state, quality of life, and the effect of chemotherapy.

As a kind of psychotherapy, mindfulness cognitive therapy can effectively reduce ruminating thoughts and avoid recurrent negative emotions such as periodic anxiety and depression. Among these, empathetic nursing is clinically effective[13]. Expression of empathy is the recognition of patients and their motivations to touch their inner feelings (and simultaneously avoid personal matters). Through three aspects: understanding the essence of the problem, experiencing the emotion, thinking of the patient’s feeling, and conveying empathy to the patient through communication skills, influence the patient to obtain emotional feedback spontaneously[14]. To achieve these goals, nurses must first actively gain the information expressed by the patient, and second, empathize and think about the problem from the patient’s perspective. With a computer, information sorting will elucidate the content and hidden information expressed by the patient. The nursing staff can feel the patient’s inner world; understand the painful motivation and their attitude and desire. Thus, information feedback can provide timely help.

Research has shown that the degree of cancer-related fatigue determines patients' quality of daily life. Reducing cancer-related fatigue impacts the daily quality of life and even improves the prognosis[15]. ENMCT has been consistently positive since we adopted the method. This study showed that behavior, cognition, emotion, and feeling by the respective PFS total scores, and the HAMA and HAMD scores of the observation group were lower than those of the control group after the ENMCT intervention. It shows that ENMCT improves the emotional rejuvenation of leukemia patients with long-term chemotherapy. It reduces the patient’s tension, strengthens their self-regulation ability, reduces stress response, further improves adaptability, and finally, reduces the degree of cancer-related fatigue. As a subjective feeling, hope is a potential force that can continuously produce positive effects and greatly impact people’s psychological and physical health[16]. Studies have shown that the hope level of patients with malignant tumors negatively correlates with negative emotions and positively correlates with social support; that is, the lower the negative emotions, the higher the social support[17]. Studies have shown that implementing integrated psychological care for patients with cervical cancer radiotherapy and chemotherapy is conducive to improving their level of expectation[18]. Our results showed that the observation group’s attitude toward maintaining close contact with others, taking
Table 1 Comparison of Piper Fatigue Scale scores of the two groups (mean ± SD, points)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>Behavior</th>
<th>Cognition</th>
<th>Emotion</th>
<th>Feelings</th>
<th>Total PFS scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before intervention</td>
<td>5.15 ± 1.49</td>
<td>4.09 ± 1.38</td>
<td>5.37 ± 1.48</td>
<td>4.19 ± 1.35</td>
<td>18.80 ± 2.74</td>
</tr>
<tr>
<td>Observation group</td>
<td>After intervention</td>
<td>2.60 ± 0.82</td>
<td>2.44 ± 1.01</td>
<td>3.46 ± 1.13</td>
<td>2.25 ± 0.77</td>
<td>18.55 ± 2.85</td>
</tr>
<tr>
<td>Control group</td>
<td>Before intervention</td>
<td>5.06 ± 1.42</td>
<td>4.03 ± 1.24</td>
<td>5.34 ± 1.41</td>
<td>4.12 ± 1.38</td>
<td>10.75 ± 1.76</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>4.63 ± 1.37</td>
<td>3.78 ± 1.13</td>
<td>4.47 ± 1.26</td>
<td>3.03 ± 0.95</td>
<td>15.92 ± 2.45</td>
</tr>
</tbody>
</table>

T_{after intervention} = 9.190, P_{after intervention} < 0.001

\*Group comparison before treatment.

PFS: Piper Fatigue Scale.

Table 2 Comparison of Herth hope Index scores of the two groups (mean ± SD, points)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>Maintain close contact with others</th>
<th>Take positive attitude</th>
<th>Attitudes toward reality and the future</th>
<th>Total HHI scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before intervention</td>
<td>9.14 ± 2.28</td>
<td>9.53 ± 2.72</td>
<td>10.93 ± 2.43</td>
<td>29.61 ± 4.57</td>
</tr>
<tr>
<td>Observation group</td>
<td>After intervention</td>
<td>14.06 ± 1.78*</td>
<td>14.28 ± 1.89*</td>
<td>14.52 ± 1.76*</td>
<td>42.86 ± 3.52*</td>
</tr>
<tr>
<td>Control group</td>
<td>Before intervention</td>
<td>9.33 ± 2.64</td>
<td>9.48 ± 2.66</td>
<td>10.85 ± 3.16</td>
<td>29.69 ± 5.24</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>10.67 ± 1.69*</td>
<td>11.08 ± 1.46*</td>
<td>12.03 ± 1.39*</td>
<td>33.78 ± 2.58*</td>
</tr>
</tbody>
</table>

T_{after intervention} = 9.909, P_{after intervention} < 0.001

\*Group comparison before treatment.

HHI: Herth hope Index.

Table 3 Comparison of Hamilton Anxiety Scale and Hamilton Depression Scale scores of the two groups (mean ± SD, points)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>HAMA</th>
<th>HAMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before intervention</td>
<td>20.22 ± 2.55</td>
<td>22.07 ± 4.57</td>
</tr>
<tr>
<td>Observation group</td>
<td>After intervention</td>
<td>9.11 ± 3.12*</td>
<td>9.98 ± 3.21*</td>
</tr>
<tr>
<td>Control group</td>
<td>Before intervention</td>
<td>20.06 ± 3.12</td>
<td>22.25 ± 4.22</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>13.97 ± 3.32*</td>
<td>16.88 ± 3.55*</td>
</tr>
</tbody>
</table>

T_{after intervention} = 7.657, P_{after intervention} < 0.001

\*Group comparison before treatment.

HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale.

positive actions, attitudes toward reality and the future, and the total HHI score were higher than the control group. ENMCT might truly touch the inner needs of leukemia patients with long-term chemotherapy, encourage and support family members and friends, increase the patient’s social support level, reduce negative emotions, and finally promote the patient’s hope of survival. Studies have shown that empathy care based on mindfulness cognitive therapy can effectively improve patients’ unhealthy emotions\cite{19}. Our research findings indicate that the observation group’s positive attitude, self-decision-making, and self-decompression scores were greater than those of the control group. Our findings revealed that ENMCT was beneficial to the self-management ability of leukemia patients with long-term chemotherapy.
Table 4 Comparison of Chinese Strategies Used by People to Promote Health scores between the two groups (mean ± SD, points)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>Positive attitude</th>
<th>Self-determination</th>
<th>Self-relief</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observation group (n = 52)</strong></td>
<td>Before intervention</td>
<td>39.48 ± 9.19</td>
<td>8.33 ± 2.35</td>
<td>29.57 ± 6.71</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>52.87 ± 7.72¹</td>
<td>11.29 ± 2.49¹</td>
<td>35.46 ± 6.42¹</td>
</tr>
<tr>
<td><strong>Control group (n = 51)</strong></td>
<td>Before intervention</td>
<td>40.40 ± 9.54</td>
<td>7.82 ± 1.83</td>
<td>28.78 ± 5.92</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>47.80 ± 9.18¹</td>
<td>9.04 ± 2.65¹</td>
<td>31.42 ± 5.98¹</td>
</tr>
</tbody>
</table>

¹Group comparison before treatment.
C-SUSSFH: Chinese Strategies Used by People to Promote Health.

This study was conducted in one medical center with a homogeneous group of patients. We did not consider whether the selected sample represented the target population and whether more sites and a more heterogeneous population would produce different results. This fact needs further experimentation. Overall, the need for additional research in the care of leukemia patients related to mindfulness is evident. We hope that the intervention can provide a long-lasting impact on patients' lives and that they will continuously apply the intervention after the study.

CONCLUSION

ENMCT is beneficial to leukemia patients with long-term chemotherapy to improve cancer-related fatigue and negative emotions and improve prognosis by enhancing hope and self-management ability.

ARTICLE HIGHLIGHTS

Research background
Leukemia is a group of blood cancers that usually begin in the bone marrow and result in high numbers of abnormal blood cells. Treatment may involve some combination of chemotherapy, radiation therapy, targeted therapy, and bone marrow transplant. Among these, chemotherapy is a standard treatment and beneficial for most patients. However, patients may experience many different chemotherapy-related side effects, such as discomfort, anxiety, and fatigue, significantly affecting comfort and well-being during and after cancer treatment. Empathetic nursing with mindfulness cognitive therapy (ENMCT) is a mild form of therapy that can reconcile the body and spirit through the mindfulness-based method. Numerous studies have shown that ENMCT enormously empowers patients with chronic pain, hypertension, heart disease, and psychological problems, such as depression and anxiety, and improves the well-being of cancer patients. However, these methods have rarely been used in China. Thus, we performed this randomized controlled trial to explore the effect of ENMCT on cancer-induced fatigue, hope level, and negative emotions in patients with long-term leukemia chemotherapy.

Research motivation
This article aims to explore the effect of ENMCT on cancer-induced fatigue, hope level, and negative emotions in patients with long-term leukemia chemotherapy.

Research objectives
A randomized control study was designed and performed to assess whether ENMCT can improve the health outcomes of Chinese leukemia patients. This research proved that ENMCT is an inexpensive, non-invasive, effective complementary therapy for leukemia associated with relaxation and pain reduction.

Research methods
In this study, a total of 103 patients with long-term leukemia chemotherapy diagnosed and treated were enrolled and randomly assigned to the observation and control groups using the random number table approach. After three months of nursing care, cancer-induced fatigue was measured with the PFS, hope level with the HHI, and negative emotion with the HAMA Scale/HAMD Scale. In addition, self-management ability was also recorded.
**Research results**

After the intervention, the observation group’s total scores in behavior, cognition, emotion, feeling, and Piper Fatigue Scale were lower than the control group. Moreover, keeping close contact with others, the attitude of taking positive actions, the attitude toward reality and the future, and the total Herth Hope Index score were higher in the observation group than the control group. The observation group’s Hamilton Anxiety Scale and Hamilton Depression Scale scores were lower than the control group. The observation group’s positive attitude, self-decision, and self-relief scores were greater than the control group.

**Research conclusions**

Empathetic nursing with cognitive mindfulness therapy is beneficial in improving cancer-related fatigue, negative emotions, expectation level, and self-management ability in patients with long-term leukemia chemotherapy.

**Research perspectives**

This research proved ENMCT is a mild and effective intervention that benefits leukemia patients receiving chemotherapy. It can be carried out in a nursing environment and is easily acceptable by leukemia patients, which might improve leukemia treatment schemes.

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**FOOTNOTES**

**Author contributions:** Lu YY performed the data analysis and wrote the manuscript; Lu XM designed the study and prepared the figures and tables; Shao CY corrected the manuscript; Wang CC, Xu TT, and Zhang BL participated in data collection; all authors approved the final manuscript.

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**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:** Wang JL

**L-Editor:** A

**P-Editor:** Wang JL

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</tbody>
</table>
Prospective Study

Superior pancreatic lymphadenectomy with portal vein priority via posterior common hepatic artery approach in laparoscopic radical gastrectomy

Yu-Jia Zhang, Rong-Chao Xiang, Jun Li, Yong Liu, Si-Ming Xie, Liang An, Hua-Lin Li, Gang Mai

Abstract

BACKGROUND

D2 lymph node dissection for advanced gastric cancer is advocated, and station 8p lymph node should be considered in selected patients, which is, however, technically difficult.

AIM

To introduce a new and easy-to-perform procedure for dissection of the lymph nodes superior to the pancreas.

METHODS

A series of patients who underwent laparoscopic gastrectomy for gastric cancer were retrospectively included with utilization of a new procedure for superior pancreatic lymphadenectomy (LND) with portal vein priority via the posterior common hepatic artery approach (SPLD-PPPH) based on a newly defined portal triangle. The surgical outcome of the patients, as well as the efficacy and safety of SPLD-PPPH are reported.

RESULTS

A total of 51 patients were included with most of them being male ($n = 34, 66.7\%$). According to the 8th edition of AJCC TNM staging, there were four (7.8\%) patients in stage I, 13 (25.5\%) in stage II, 33 (64.7\%) in stage III and one (2.0\%) in stage IV. The average duration for LND was about 1 h (67.7 ± 6.9 min). After surgery, four patients developed morbidities, but all were treated successfully with no perioperative mortality. Among the 51 patients included, the percentage of patients who had lymph node metastasis at station 8p was 9.8\%. Of note, with a total of 14 lymph nodes harvested at station 8p, the incidence of nodal metastasis was 14.3\%.
CONCLUSION
About one in 10 patients with advanced gastric cancer had nodal metastasis at station 8p. The new approach of SPLD-PPPH is safe and effective for D2+ LND during laparoscopic radical gastrectomy.

Key Words: Laparoscopic radical gastrectomy; Lymphadenectomy; Lymph node metastasis; Portal vein priority; Lymph node

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Core Tip: D2 radical operation has been the standard treatment of gastric cancer. One in 10 advanced gastric cancer patients had lymph node metastasis at station 8p, but D2 lymphadenectomy (LND) remains technically difficult. The new superior pancreatic LND with portal vein priority via the posterior common hepatic artery approach achieved safe removal of 8p lymph nodes.

INTRODUCTION
Laparoscopic gastrectomy for gastric cancer has been demonstrated as safe, feasible and less invasive with comparable long-term outcomes vs open surgery[1-3]. At present, D2 lymphadenectomy (LND) has been the standard treatment for locally advanced gastric cancer[4-7]. However, the overall complication rate after D2 radical operation is about 20%[4-7]. The most serious complications are bleeding, pancreatic fistula, anastomotic leakage and abdominal infection. In fact, during the procedure of D2 radical LND, it is difficult to dissect the local lymph nodes due to the limitation of the range of movement of the instruments, and the pancreas is compressed during upper pancreatic dissection, resulting in a higher incidence of postoperative pancreatic fistula.

Although D2 LND has achieved global consensus for advanced gastric cancer, whether station 8p should be dissected routinely remains controversial[8-10]. Some studies have found that the incidence of station 8p nodal metastasis increases as the AJCC T category is upstaged, with rate of station 8p lymph node metastasis (LNM) of advanced gastric cancer ranging from 12.9% to 16.4%[3]. In addition, residual station 8p LNM was one of the major causes of local recurrence of gastric cancer after initial resection. An increased number of surgeons have advocated dissection of station 8p during surgical resection for advanced gastric cancer[11-13]. However, the lymph nodes of station 8p are located behind the common hepatic artery, making complete dissection difficult. How to safely remove the station 8p lymph node remains to be optimized. Based on the anatomy of the portal triangle, the current study investigated the safety and efficacy of superior pancreatic LND with portal vein priority via the posterior common hepatic artery approach (SPLD-PPPH) for laparoscopic radical gastrectomy.

MATERIALS AND METHODS
Cohort
Data from 51 consecutive patients with gastric cancer who underwent laparoscopic D2+ radical resection between June 2018 and June 2020 in our hospital were retrospectively included. Among all the patients included, superior pancreatic LND was performed with portal vein priority via the posterior common hepatic artery approach. The scope of regional LND included stations 5, 7, 8a, 8p, 9, 11p, 12a and 12p. A standard datasheet was utilized to collect data at each institution. Demographic factors, including age, gender and body mass index (BMI), operation time, intraoperative blood loss were documented, whereas the tumor-related characteristics, total number and station of lymph node examined, as well as number and station of the positive nodes were collected based on final pathological report. The study was approved by the Ethics Committee of Deyang City People’s Hospital. A waiver of informed consent was obtained, since the data were analyzed from the electronic medical record and reported without personal identifiers.
Surgical procedures
Patients were placed in the supine position with 10-15° height difference between the head and feet and lower limbs abduction. The surgeon stood on the left side of the patient, with the assistant on the right side, and the scope-holding assistant stood between the legs of the patients (Figure 1).

An arc shape 5-port method was utilized. The observation port was placed at the lower edge of the umbilicus with a 12-mm trocar, and a pneumoperitoneum was introduced to maintain the intra-abdominal CO₂ pressure between 12 and 13 mmHg. Another 12-mm trocar was placed below the costal margin of the left anterior axillary line as the main operation port, whereas a 5-mm trocar on the left side of the umbilicus was used as an auxiliary operation port. In addition, 5-mm and 12-mm trocars were respectively placed at the right anterior axillary line and the umbilicus of the right midclavicular line as assistant operation ports (Figure 1).

The concept of the portal triangle was defined as a triangular area formed by the upper edge of the pancreas, the left edge of the gastroduodenal artery, the right edge of the common hepatic artery and the beginning of the splenic artery (Figure 2). This triangle was the fixed projection of the beginning of the portal vein behind the common hepatic artery. It contained the dorsal pancreatic artery, initial segment of the portal vein, left gastric vein, station 8p lymph nodes, lymphatic vessels, and inferior vena cava (IVC).

Dissecting the portal triangle
The posterior part of the common hepatic artery was used as the approach to expose and protect the portal vein, and complete dissection of lymph nodes in stations 7, 8a, 8p, 9 and 11p of the superior pancreatic region. The specific surgical steps were as follows: (1) Judging the boundary of the portal triangular base of the portal vein (the upper edge of the pancreas): the assistant grabbed the bare area of the posterior wall of the stomach corresponding to the left gastric artery with their left hand and lifted it forward and upward to form the main tension of the posterior wall of the stomach. The right hand was always pulled upward with the corresponding point of the left hand to form an appropriate tension. The left hand of the main surgeon pulled or pressed the pancreas downward, and the right hand used the ultrasonic scalpel or electric hook to dissect along the upper edge of the pancreas; (2) Separation of the posterior pancreatic space: the ultrasonic scalpel or electric hook was used to separate the posterior pancreatic space parallel to the upper edge of the pancreas, from shallow to deep, from bottom to top, and from left to right. If the left gastric vein converged into the portal vein or splenic vein from the front of common hepatic artery, it should be separated, clipped and cut off; (3) Exposure of the dorsal pancreatic artery for protection or disconnection: in some patients, one or two branches of the dorsal pancreatic artery originated from the common hepatic artery, and the two ends of the artery could be dissected by the electric hook, and then clipped and disconnected, or preserved; (4) Exposure and protection of the portal vein: the tissue gap became loose after the dorsal pancreatic artery was cut off, and the light blue portal vein was faintly visible at this time. The anterior space of the portal vein was obtusely separated, and the portal vein was exposed by the dissection technique of the electric hook. The left hand continued to obtusely separate towards the hepatic hilar. In a small number of patients, the left gastric vein converged to the portal vein from the posterior direction of the common hepatic artery, and the left gastric vein was clipped close to the portal vein; (5) Along the space above the uncinate of the pancreas (this space continues with the Toldt space in front of the Gerota fascia), some patients could show metastatic and swollen lymph nodes and thick abdominal lymph vessels flowing into the intestinal trunk, which were clipped and cut off; (6) Continued separation back toward the IVC. The tissue in front of the site was loose, and there was no return vein branch or swollen lymph nodes; (7) The left adrenal gland was exposed by dissecting the starting segment of splenic artery and the left celiac artery along the anterior Toldt space of Gerota fascia above the splenic artery; and (8) The left gastric artery was dissected along the anterior space of the common hepatic artery and cut off. We continued to separate the proper hepatic artery for final confluence with the posterior space of the common hepatic artery. The lymph nodes in groups 7, 8a, 8p, 9 and 11p of the superior pancreatic region were removed completely (Figure 3).

RESULTS
A total of 51 patients were included; 34 were male (66.7%) and 28 (54.9%) were aged < 65 years. Most of the patients had a BMI < 24 (n = 34, 66.7%). In addition, according to the 8th edition of AJCC TNM staging, there were four (7.8%) patients in stage I, 13 (25.5%) in stage II, 33 (64.7%) in stage III and one (2.0%) in stage IV (Table 1). The average time duration for LND was about 1 h (67.7 ± 6.9 min), and the volume of intraoperative blood loss was < 100 mL (78.8 ± 17.8 mL). In addition, the average duration for postoperative exhaust was about 3 d. After surgery, four patients developed morbidities, including two with anastomotic leakage, one with the lung infection, and one with abdominal cavity infection; all of whom were treated successfully with percutaneous drainage and/or antibacterial treatments, with no need for reoperation, or in-hospital mortality (Table 1).
Table 1 Baseline characteristics and surgical factors

<table>
<thead>
<tr>
<th>Basic data</th>
<th>n = 51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (66.7)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (33.3)</td>
</tr>
<tr>
<td>Age (%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 65 yr</td>
<td>28 (54.9)</td>
</tr>
<tr>
<td>≥ 65 yr</td>
<td>23 (45.1)</td>
</tr>
<tr>
<td>BMI (%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 24</td>
<td>34 (66.7)</td>
</tr>
<tr>
<td>24-27</td>
<td>11 (21.6)</td>
</tr>
<tr>
<td>&gt; 27</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>TNM staging (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>II</td>
<td>13 (25.5)</td>
</tr>
<tr>
<td>III</td>
<td>33 (64.7)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Duration of LND in the upper pancreas (min)</td>
<td>67.7 ± 6.9</td>
</tr>
<tr>
<td>Intraoperative blood loss (mL)</td>
<td>78.8 ± 17.8</td>
</tr>
<tr>
<td>Postoperative exhaust time (d)</td>
<td>3.1 ± 0.9</td>
</tr>
<tr>
<td>Postoperative complications (%)</td>
<td>4 (7.8)</td>
</tr>
</tbody>
</table>

BMI: Body mass index; T: Primary tumor; N: Regional lymph nodes; M: Distant metastasis; LND: Lymphadenectomy.

Figure 1 The position of the patients, the operators and distribution of the trocars during laparoscopic radical gastrectomy.

Nodal status after SPLD-PPPH
Among the 51 patients, the percentage who had LNM at stations 5, 7, 8a, 8p, 9, 11p, 12a and 12p was 23.5%, 15.7%, 17.7%, 9.8%, 13.7%, 7.8%, 7.8% and 3.9%, respectively. Station 8p had 14 lymph nodes examined, and the incidence of LNM was 14.3% (Table 2). In contrast, the incidence of LNM at stations 5, 7, 8a, 9, 11p, 12a and 12p was 21.8%, 11.6%, 13.1%, 7.9%, 5.6%, 6.8% and 4.2%, respectively (Table 2).

DISCUSSION
LNM is an independent risk factor for long-term outcome of gastric cancer after curative resection, and the station and number of lymph nodes removed definitely affect the tumor staging, guidance of
postoperative adjuvant therapies, as well as long-term survival of patients[4,14,15]. Nowadays, the National Comprehensive Cancer Network (NCCN) Guidelines for Gastric Cancer in the United States and the Guidelines for the Treatment of Gastric Cancer in Japan and China have recommended D2 LND as the standard procedure during radical resection for advanced gastric cancer[16-18]. Typical D2 LND always exceeds 30 lymph nodes[19,20]. In contrast, the national database identified that fewer than 15 lymph nodes were examined in a majority of American cases[21,22]. As such, it is likely that the majority of American patients did not undergo D2 LND. In fact, adequate D2 LND has been strongly recommended by the guidelines, as well as consideration of adjuvant therapies following standard

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**Table 2 Nodal status after superior pancreatic lymphadenectomy with portal vein priority via posterior common hepatic artery approach**

<table>
<thead>
<tr>
<th>Nodal station</th>
<th>No. of patients with LNM</th>
<th>Rate of patients with LNM (%)</th>
<th>TNLE</th>
<th>No. of positive LNs</th>
<th>Rate of LNM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>12</td>
<td>23.5</td>
<td>55</td>
<td>12</td>
<td>21.8</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>15.7</td>
<td>164</td>
<td>19</td>
<td>11.6</td>
</tr>
<tr>
<td>8a</td>
<td>9</td>
<td>17.7</td>
<td>122</td>
<td>16</td>
<td>13.1</td>
</tr>
<tr>
<td>8p</td>
<td>5</td>
<td>9.8</td>
<td>14</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>13.7</td>
<td>127</td>
<td>10</td>
<td>7.9</td>
</tr>
<tr>
<td>11p</td>
<td>4</td>
<td>7.8</td>
<td>54</td>
<td>3</td>
<td>5.6</td>
</tr>
<tr>
<td>12a</td>
<td>4</td>
<td>7.8</td>
<td>44</td>
<td>3</td>
<td>6.8</td>
</tr>
<tr>
<td>12p</td>
<td>2</td>
<td>3.9</td>
<td>24</td>
<td>1</td>
<td>4.2</td>
</tr>
</tbody>
</table>

LNM: Lymph node metastasis; TNLE: Total number of lymph node examined; LN: Lymph node.

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**Figure 2 The boundary of the portal triangle.** PV: Portal vein; CHA: Common hepatic artery; GDA: Gastroduodenal artery; DPA: Dorsal pancreatic artery; PHA: Proper hepatic artery; SPA: Spleen artery; SPV: Spleen vein; IVC: Inferior vena cava.

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**Figure 3 Portal triangle dissection.** PV: Portal vein; CHA: Common hepatic artery; GDA: Gastroduodenal artery; PHA: Proper hepatic artery; SPA: Spleen artery.
gastrectomy (D2) for gastric cancer D2[23]. The 4th edition of the Japanese Guidelines for the Treatment of Gastric Cancer classified the station 8p lymph nodes outside the scope of D2 LND[8]. Whether it is necessary to expand the LND in station 8p is of debate[11,24]. Studies have reported that for advanced gastric cancer, removal of station 8p lymph nodes may improve the prognosis of patients with advanced gastric cancer[11]. In the current study, the incidence of station 8p LNM was 14.3%, which was similar to 12%-16% as reported previously, and the prognosis of patients with station 8p LNM was significantly worse[11,13]. As such, removal of station 8p lymph nodes might improve the prognosis of patients with gastrectomy, as well as inform adjuvant therapy strategies.

Given the difficult anatomic sites of station 8p lymph nodes (e.g., behind the common hepatic artery, adjacent to the portal vein and splenic vein), removal of them is technically challenging with high risk of portal vein injury, lymphatic fistula, and pancreatic injury. The current study is important as we introduced a new approach of SPLD-PPPH based on the concept of the portal triangle. The clinical significance of SPLD-PPPH approach included: (1) Complete clearance of the lymphatic tissues above the pancreas, including regional lymph nodes in station 8p, and avoidance of lymphatic residual or iatrogenic metastasis caused by lymph node transection via the front of the common hepatic artery; (2) The projection of the portal vein locates in this triangle, and its exposure can be actively performed for direct and effective protection of the vessel; (3) The left gastric vein can be dissected at the root of the portal vein to prevent retraction and bleeding; and (4) Lymphatic vessels can be clamped under direct vision to prevent postoperative lymphatic leakage.

In addition, intra- and postoperative complications related to the procedure should be cautioned against and can be avoided technically. First, intraoperative hemorrhage in the upper edge of pancreas: microvessels are common in the upper edge of the pancreas. Imprecise operation is the major reason for bleeding. Slow dissection with an ultrasonic knife and gauze compression can prevent bleeding. Portal vein injury: during the procedure of portal vein separation, fine dissection of loose tissue with an electric hook might be a better choice to avoid thermal injury of the vascular wall. Traumatic pancreatitis is mostly related to pancreatic membrane dissection during eradication of gastric cancer at the posterior wall of the stomach. Accurate judgement of the pancreatic tissue and the upper edge of the pancreas is critical to avoid pancreatic injury.

There were several limitations to the current study. First, all 51 patients underwent D2+ LND for advanced gastric cancer via SPLD-PPPH. As such, no control groups were available to define the advantage of this new approach. Nevertheless, we demonstrated that this new approach of SPLD-PPPH for D2 LND is easy and feasible in our patient cohort. However, validation of this new approach in other institutions is necessary. Second, the long-term survival of these patients was not reported due to the short period of follow-up, which needs to be further evaluated in the future.

**CONCLUSION**

About one in 10 patients with advanced gastric cancer had LNM at station 8p. Dissection of station 8p lymph nodes should be considered in patients with advanced gastric cancer. The current study introduced a new approach of SPLD-PPPH for D2+ LND during curative resection of advanced gastric cancer. With verification of this new approach in 51 patients, the SPLD-PPPH approach was safely and effectively performed with minimal morbidity of 7.8%. As such, this new approach can be adopted for station 8p LND in selected patients with gastric cancer.

**ARTICLE HIGHLIGHTS**

**Research background**
D2 lymph node dissection of station 8p lymph nodes in gastric cancer is technically difficult.

**Research motivation**
How to safely and effectively dissect the lymph nodes superior to the pancreas during gastrectomy...
remains a clinical challenge for surgeons.

**Research objectives**
The current study introduced a new procedure for dissection of the lymph nodes superior to the pancreas.

**Research methods**
Fifty-one patients who underwent laparoscopic gastrectomy for gastric cancer were retrospectively included with utilization of a new procedure for superior pancreatic lymphadenectomy (LND) with portal vein priority via the posterior common hepatic artery approach (SPLD-PPPH) based on a newly defined portal triangle.

**Research results**
All the procedures were safely performed. Among the 51 patients, 9.8% had lymph node metastasis at station 8p. Fourteen lymph nodes were harvested at station 8p, with an incidence of nodal metastasis of 14.3%.

**Research conclusions**
The new procedure of SPLD-PPPH is safe and effective for D2+ LND during laparoscopic radical gastrectomy.

**Research perspectives**
This new approach should be further evaluated with larger patient numbers.

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**FOOTNOTES**

**Author contributions:** Zhang YJ drafted the manuscript, and assisted with data analysis; Xiang RC participated in design and oversight of the study, and was involved with data collection; Li J participated in design of the study, and was involved with data collection; Liu Y was involved with data collection, and assisted with data analysis; Xie SM drafted the manuscript, and assisted with data analysis; An L and Li HL participated in study design and performed statistical analysis; Mai G participated in design of the study, was involved with data collection; all authors read and approved the final manuscript.

**Institutional review board statement:** The study has been approved by the ethics committee of the Deyang City People’s Hospital.

**Clinical trial registration statement:** The current study has not been registered, as the procedures of laparoscopic gastrectomy is a routine treatment of gastric cancers.

**Informed consent statement:** A waiver of informed consent was obtained, since the data were analyzed from the electronic medical record and reported without personal identifiers.

**Conflict-of-interest statement:** The authors declare that they have no competing interests.

**Data sharing statement:** Can be requested via contacting with the corresponding author.

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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REFERENCES


Randomized Controlled Trial

Systematic nursing interventions in gastric cancer: A randomized controlled study

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Abstract

BACKGROUND
Scientific and effective nursing methods can effectively mitigate negative emotions in patients. Related studies have shown that systematic nursing interventions are beneficial in enhancing the self-efficacy and self-care abilities of patients and improving their physical and mental state, thereby alleviating their fatigue and improving their quality of life.

AIM
To explore the effects of systematic nursing intervention on cancer-related fatigue, self-efficacy, self-nursing ability, and quality of life in gastric cancer (GC) patients during the perioperative period.

METHODS
In this study, sample size was based on the multivariable scale. The sample size was 10 times the acceptable variable, with an additional 20% added to account for an expected loss of patients in follow-up for a final sample size of 168 patients. Conventional nursing measures were used in the control group, while the systematic nursing intervention Adopted Cancer Fatigue Scale (CFS), General Self-Efficacy Scale-Schwarzer (GSES), Self-Care Agency Scale (ESCA), and simple health scale (SF-36) were used in the observation group. The questionnaires were administered on admission and discharge.

RESULTS
At admission, there was no statistically significant difference in the scores on each scale between the groups. At discharge, the CFS and GSES scores in the observation group were 21.56 ± 2.24 and 51.16 ± 11.71, while those in the control group were 29.61 ± 3.48 and 41.58 ± 8.54, respectively, with statistically significant differences. The ESCA score in the observation and control groups was 112.09 ±
11.72 and 97.87 ± 9.26, respectively. Moreover, the scores in all dimensions (self-concept, self-responsibility, health knowledge level, and self-care skills) in the observation group were higher than those in the control group, with statistically significant differences. The SF-36 score in the observation and control groups was 75.51 ± 3.63 and 63.24 ± 3.41, respectively, with statistically significant differences. The scores in all dimensions (mental health, vitality, physical function, physical pain, social function, emotional function, and overall health level) in the observation group were higher than those in the control group, with statistically significant differences.

CONCLUSION
Systemic nursing intervention for GC patients during the perioperative period could alleviate cancer-related fatigue, improve self-efficacy and self-nursing ability, and improve quality of life, which all have clinical value.

Key Words: Nursing intervention; Self-efficacy; Self-care ability; Cancer-related fatigue; Quality of life

INTRODUCTION
Gastric cancer (GC) ranks fifth for incidence and fourth for mortality globally. There are approximately one million new cases in 2020 and an estimated 769000 deaths[1]. Radical resection is the main treatment for GC, while subtotal gastrectomy with standard D2 lymph node dissection is the main surgical treatment, which is characterized by extensive surgical trauma and slow postoperative recovery[2]. Feeding difficulties are commonly seen in patients with GC, combined with physiological function changes after surgery, which seriously affects the patient’s quality of cancer-related fatigue (CRF). CRF is a persistent and subjective sense of fatigue and activity intolerance caused by cancer itself and surgery, which cannot be alleviated by sleep and rest, and is the most intolerable adverse reaction in patients with cancer[3]. The National Comprehensive Cancer Network believes that anemia, depression, pain, sleep disorders, and nutrition may all be related to CRF based on research on CRF symptoms[4]. Thus, CRF has a significantly negative impact on patients’ quality of life, and comprehensive research has found that the influencing factors of CRF mainly include the following aspects: cancer type and treatment pathways, psychological factors, socioeconomic factors, and cancer complications[4]. CRF is an ever-changing subjective feeling. The recognition and cognition of fatigue during the nursing process will also affect the patients’ expression of CRF. Most patients believe that fatigue is something that must be endured during treatment, and most of them will not actively complain about this symptom. However, fatigue can also be used to predict the occurrence of cancer[5].

GC surgery causes significant surgical trauma and slow postoperative healing. Therefore, effective implementation of nursing interventions is also a key issue in clinical research. Clinically, it is necessary to adopt an active nursing method for patients with GC to eliminate CRF, which will improve the self-efficacy of the patients, which in turn will improve patient prognosis. Scientific and effective nursing methods can effectively mitigate negative emotions in patients. Related studies[6] have shown that systematic nursing interventions are beneficial in enhancing the self-efficacy and self-care abilities of patients and improving their physical and mental state, thereby alleviating their fatigue and improving their quality of life. In this study, systematic nursing interventions were administered to patients with GC during the perioperative period, and their effects on CRF, self-efficacy, self-nursing ability, and quality of life were analyzed. This study also explored the application value of nursing interventions in patients with GC during the perioperative period.
MATERIALS AND METHODS

General information
In this study, sample size was based on the multivariable scale. Expecting approximately 20% loss of patients to follow-up, and with 10 times the acceptable variable (which had an expected 140 patients), the final sample size was 168 people. The inclusion criteria were as follows: (1) Clinical or pathological diagnosis of GC; (2) Age ≥ 18 and initial hospitalization; (3) Tumor-node-metastasis (TNM) stages I, II, IIIa, and IIIb without complications; (4) Patients were aware of their condition and were willing to participate in the study; (5) Patients who could communicate normally; and (6) Patients with no history of mental illness or emotional instability. The exclusion criteria were as follows: (1) Patients who withdrew and transferred for treatment due to personal reasons; (2) Patients who underwent palliative surgery in stage IV; (3) Patients with mental disorders or cognitive impairment; (4) Patients who could not communicate properly; and (5) Patients whose condition was critical and life-threatening. The research subjects were randomly divided into the observation and control groups according to a generated random number table, with 84 cases in each group. This study was approved by the hospital’s medical ethics committee, and the patients and their families understood the content and methods of the study before providing informed consent.

Intervention methods
The control group received conventional nursing interventions, were provided guidance on hospital admission, cooperated with the corresponding nursing measures during the perioperative period, and were actively provided life nursing and psychological nursing.

The observation group was treated according to NCCN guidelines for cancer-related fatigue. Based on the patients’ characteristics, systematic nursing interventions were performed. The main contents are as follows: First, on admission, nurses explained the ward environment and system to the patients to eliminate anxiety caused by the unfamiliar environment; second, for establishing a good relationship of trust with the patient, nurses needed to understand the patients’ experience of cancer-related fatigue and related symptoms, including the timing, frequency, severity of fatigue, and distress brought to the patient by fatigue symptoms; third, nurses assisted patients to assess their own available resources and developed personalized, targeted management plans for them, and on the day before the operation, nurses provided the patient with a brochure which included the key points of postoperative care, changes in the patients’ habits, and common complications. At the same time, nurses combined with the form of powerpoint to teach the patients how to correctly use the Fatigue Digital Rating Scale to express their degree of fatigue. Targeted health education was conducted according to the patients’ individual situations to correctly understand the dialectical relationship between their disease, treatment, and psychological conditions. The period after surgery was when nurses had the most contact with patients. Effective nurse–patient communication helped nurses identify patients’ nursing problems and emotional changes over time. When nurses found that the fatigue-related symptoms of the patient worsened, they made the patients listen to music, chatted with family members, and looked for ways to distract the patients’ attention from the fatigue. Nurses urged the patients to move on the bed for early venting. Moderate activities during the day can help ensure that patients sleep better at night. After the patients’ gastric tubes were removed and their diets gradually resumed, nurses used the food model to guide the family members on the issues that need attention while purchasing and cooking food materials. The patients were also encouraged to express their feelings to enhance communication with their families. Nurses listened to the patients’ chief complaints and intervene in the bedside setting. On the third postoperative day, nurses issued a “self-management manual,” and instructed the patients to fill in a daily fatigue diary. Nurses adjusted the nursing measures based on the patients’ fatigue assessment on the previous day and provided patients with a manual on the causes of fatigue and home care tips.

Observation indexes
CRF, self-efficacy, self-care ability, and quality of life of the patients were assessed on the day of admission and discharge. Questionnaires were issued by trained nurses, and on-site guidance was provided. The Cancer Fatigue Scale (CFS) evaluated the symptoms related to CRF from three aspects—physical, emotional, and cognitive. The Likert 5 (0–4 points) scoring method was used, with a total score of 0–60 points. The higher the score, the more serious the CRF[7]. The General Self-Efficacy Scale-Schwarzer was used to evaluate the self-efficacy changes of patients in the two groups after nursing using a 4-level scoring method, with each item scoring from 1 to 4[8]. The higher the score was, the better the self-efficacy of patients. Self-care ability was evaluated using the Self-Care Agency Scale, which included 4 dimensions and 43 items, including self-care skills, self-care responsibility, self-concept, and health knowledge level[9]. High scores in all dimensions indicated high self-care ability, and quality of life was evaluated using a simple health scale. The scale comprehensively assessed patients’ quality of life in terms of physiological function, physical pain, general health, physiological ability, social function, emotional function, and mental health, among others, with a total score of 100 points[10]. A higher score indicates a better quality of life.
**Statistical analysis**
The data were processed using SPSS 19.0 version, and the measurement data are expressed as mean ± SD, while the count data are expressed as percentage (%). Pairwise comparisons adopted an analysis of variance. The threshold for significance was set at $P < 0.05$.

**RESULTS**

**General information**
In the observation group, 3 patients dropped out and 5 were transferred. Fifty-three cases were male and 23 cases were female. The average age was $(55.14 ± 4.67)$ years. The TNM stages in 28, 33, and 15 cases were I, II, and III, respectively. The highest educational levels for 1343, 8, and 12 patients were primary school, junior high school, senior high school, and university, respectively. In the control group, 4 patients dropped out and 1 was transferred. Forty-four patients were male and 35 patients were female (Figure 1). The average age was $56.09 ± 4.19$ years. The TNM stages in 25, 40, and 14 cases were I, II, and III, respectively. The highest educational levels of 12, 39, 15, and 13 patients were primary school, junior high school, senior high school, and university, respectively. There were no significant differences in age, sex, TNM stage, and educational level between the groups; both groups were comparable ($P > 0.05$).

**CFS scores**
Table 1 shows that there was no significant difference in CFS scores between the groups before the intervention ($P > 0.05$). However, after the nursing intervention, the CFS scores in the two groups were reduced, indicating that the nursing intervention effects were relatively good, but the effects of systematic nursing intervention in the observation group were more obvious than those of conventional intervention in the control group, with a significant difference ($P < 0.05$).

**Self-care ability**
Table 2 shows that there was no significant difference in self-care ability scores between the two groups before the intervention ($P > 0.05$). After receiving the nursing interventions, the self-care ability scores of the two groups were increased, indicating that the effects of nursing intervention were relatively good. However, the effects of systemic nursing interventions in the observation group were more obvious than those in the control group, with a significant difference ($P < 0.05$).

**Self-efficacy**
Table 3 shows that there was no significant difference in self-efficacy scores between the two groups before the intervention ($P > 0.05$). After nursing interventions, the self-efficacy scores of the two groups were increased, indicating that the nursing intervention effects were relatively good. However, the effects of systemic nursing interventions in the observation group were more obvious than those in the control group, with a significant difference ($P < 0.05$).

**Quality of life**
Table 4 shows the comparison results of the quality of life of the two groups before and after the intervention. The specific indices set were mental health, vitality, physical function, physical pain, social function, health status, and overall health level. After nursing interventions, the scores of all dimensions of quality of life in the observation group were significantly higher than those in the control group, and the difference was significant ($P < 0.05$).

**DISCUSSION**

*Systematic nursing intervention could alleviate symptoms related to CRF in patients with GC during the perioperative period*

Systemic nursing intervention was centered on patients based on their negative emotions, wherein nurses implemented multiple interventions, such as knowledge education, psychological and social support, and CRF nursing, and constantly adjusted the care they gave to patients according to their individual situations. The results of this study showed that after intervention, the degree of CRF in the observation group was lower than that in the control group. This was consistent with the results of a previous study[11], which reported that systematic nursing intervention could improve the fatigue state and quality of life of patients with cancer. In this study, nurses and patients established a good relationship of trust. Nurses actively guided patients to correctly face the symptoms and treatment of the disease and improved patients’ cognition of the disease. Patients better followed the nursing measures that could relieve bodily fatigue. In the face of fatigue-related symptoms, nurses guided
patients to seek help from family members and friends and, thus, helped the patients get more social support. These measures alleviated patients’ anxiety and depression and relieved patients’ emotional fatigue. From the second day after surgery, nurses instructed patients to move while on the bed to promote venous circulation in the lower extremities. According to the NCCN guidelines, exercise is an effective intervention for CRF\[12\]. Patients recorded their daily activity levels in a “self-management manual” to encourage them to continue exercising and performed individual movement appropriately to increase muscle strength and stimulate airframe lively sex, which would reduce the feeling of fatigue.

**Systematic nursing interventions could improve the self-efficacy and self-care abilities of patients with GC during the perioperative period**

CRF is a series of subjective feelings resulting from patients’ long-term tension and pain caused by GC, such as weakness, activity intolerance, inattention, and reduced motivation or interest, with fatigue being the most distressing of all the related symptoms\[13\]. Some studies have shown that self-efficacy is negatively correlated with the total score for cancer-related fatigue\[14\]. The self-efficacy of patients can be improved by alleviating symptoms of cancer-related fatigue. In this study, after instituting the nursing interventions, the self-care ability and self-efficacy scores of the two groups improved, and the systemic nursing intervention in the observation group demonstrated more obvious effects than the conventional nursing intervention in the control group, with the difference being significant (P < 0.05).

The reasons are as follows: the researchers used the NCCN guidelines for the management of symptoms of cancer-related fatigue and developed a “self-management manual” for nursing measures for patients, which included general management of fatigue and non-pharmacological measures. Common management practices included monitoring of fatigue levels and the use of diverting attention, including increased exercise, psychological regulation, regulation of sleep disorders, pain self-

| Table 1 Comparison of Cancer Fatigue Scale scores between the two groups before and after intervention |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Group                                             | Before intervention                              | After intervention                                | t value | P value | t value | P value | t value | P value |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Body fatigue                                     | Observation group 19.02 ± 1.51                    | 19.23 ± 1.63                                     | 0.242  | 0.835  | 10.85 ± 1.22 | 14.63 ± 1.34 | 5.499  | < 0.001 |
| Cognitive fatigue                                | 9.63 ± 0.85                                       | 9.71 ± 0.80                                      | 0.429  | 0.684  | 5.16 ± 0.50  | 7.38 ± 0.57  | 7.181  | < 0.001 |
| Emotional fatigue                                | 10.70 ± 0.90                                      | 10.64 ± 0.9                                      | 0.257  | 0.814  | 6.42 ± 0.43  | 7.92 ± 0.51  | 8.927  | < 0.001 |
| Total score                                       | 40.24 ± 6.47                                      | 41.47 ± 6.59                                     | 0.896  | 0.794  | 21.56 ± 2.24 | 29.61 ± 3.48 | 9.983  | < 0.001 |

Data are mean ± SD.

| Table 2 Comparison of self-care ability between the two groups before and after intervention |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Group                                             | Before intervention                              | After intervention                                | t value | P value | t value | P value | t value | P value |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Self-concept                                     | 22.17 ± 4.10                                     | 21.83 ± 3.41                                     | 1.897  | 0.825  | 27.91 ± 3.77 | 21.15 ± 3.31 | 9.875  | < 0.001 |
| Self-responsibility                              | 18.75 ± 7.07                                     | 18.91 ± 7.38                                     | 1.612  | 0.795  | 30.22 ± 5.84 | 19.61 ± 6.69 | 10.851 | < 0.001 |
| Health knowledge level                           | 32.92 ± 5.08                                     | 33.74 ± 4.64                                     | 1.472  | 0.814  | 37.08 ± 3.88 | 18.69 ± 2.54 | 9.411  | < 0.001 |
| Self-care skills                                 | 26.56 ± 4.20                                     | 27.73 ± 3.76                                     | 1.392  | 0.763  | 40.47 ± 4.14 | 29.50 ± 4.27 | 11.245 | < 0.001 |
| Total score                                       | 87.00 ± 12.52                                     | 85.83 ± 13.06                                     | 1.412  | 0.821  | 112.09 ± 11.72 | 97.87 ± 9.26 | 13.417 | < 0.001 |

Data are mean ± SD.

| Table 3 Comparison of self-efficacy between the two groups before and after intervention |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Group                                             | Before intervention                              | After intervention                                | t value | P value | t value | P value |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Before intervention                              | 34.39 ± 10.45                                     | 35.11 ± 9.60                                     | 1.335  | 0.813  | 5.53  | < 0.001 |
| After intervention                               | 51.16 ± 11.71                                     | 41.58 ± 8.54                                     | 5.53  | < 0.001 |
management, and relaxation therapy. Patients used the nursing measures in the manual for self-regulation, and their self-care ability continued to improve. Self-efficacy refers to a person’s subjective judgment of whether he can successfully conduct a certain achievement behavior[15] and is a degree of confidence that can be gradually developed through learning and cultivation. Positive psychological regulation can improve patients’ cognition of the disease and allow them to calmly face difficulties and adopt positive self-management methods[16]. This increased patients’ confidence in beating cancer and increased their sense of self-efficacy. This was in line with the results reported by Krok et al[17], who reported that the use of a systematic nursing method can greatly alleviate the psychological discomfort of patients with GC and found that after such intervention, the psychological status of the patients improved.

**Table 4 Comparison of quality of life between the two groups before and after intervention**

<table>
<thead>
<tr>
<th>Group</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observation group</td>
<td>Control group</td>
<td>t value</td>
<td>t value</td>
</tr>
<tr>
<td>Mental health</td>
<td>56.57 ± 6.80</td>
<td>56.95 ± 6.86</td>
<td>0.349</td>
<td>77.30 ± 4.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.416</td>
</tr>
<tr>
<td>Vitality</td>
<td>58.28 ± 9.64</td>
<td>58.69 ± 9.43</td>
<td>0.412</td>
<td>71.80 ± 8.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.295</td>
</tr>
<tr>
<td>Physical function</td>
<td>60.39 ± 7.12</td>
<td>60.95 ± 7.25</td>
<td>0.499</td>
<td>74.92 ± 5.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.421</td>
</tr>
<tr>
<td>Physical pain</td>
<td>55.70 ± 5.05</td>
<td>56.14 ± 4.92</td>
<td>1.649</td>
<td>67.16 ± 4.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.292</td>
</tr>
<tr>
<td>Social function</td>
<td>51.13 ± 3.07</td>
<td>51.39 ± 3.13</td>
<td>0.301</td>
<td>65.57 ± 2.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.226</td>
</tr>
<tr>
<td>Emotional function</td>
<td>42.30 ± 2.66</td>
<td>42.59 ± 2.86</td>
<td>0.351</td>
<td>51.68 ± 2.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.261</td>
</tr>
<tr>
<td>Overall health level</td>
<td>50.38 ± 2.33</td>
<td>50.48 ± 2.19</td>
<td>0.287</td>
<td>63.24 ± 3.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.214</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

**Figure 1 The flow diagram of the study.**

As a major negative life event, cancer causes a significant emotional toll on the family. Sandler et al[18] improved the quality of life of patients with cancer through a combination of cognitive behavioral intervention and physical exercise. The day before the operation, nurses explained patients the function of the stomach and the matters needing attention during the operation to eliminate any unknown facts regarding the disease and the fear of the operation. Before discharge, nurses taught patients how to adapt to changes in diet after gastrectomy. With the advancement of treatment, the patients’ concern gradually shifted to concerns related to radiotherapy and chemotherapy. Nurses dynamically adjusted nursing measures based on the recorded daily in the patients’ “self-management manual.” Nurses fully considered the needs of patients and helped them achieve their subjective initiative. Targeted nursing measures improved patients’ treatment compliance and effectively reduced their symptoms of dysphagia, stomach pain, hiccup, restricted diet, and so on. Therefore, the physical and psychological functions of patients were improved, and the quality of life of patients thereafter also improved. Table 4 shows that the comparison of quality of life between the two groups before and after treatment was statistically significant (P < 0.05).
This study showed that the implementation of systematic nursing interventions in patients with GC during the perioperative period could significantly improve their fatigue state, mental health status, self-nursing ability, self-efficacy, and quality of life, all of which have a positive clinical value. However, the patients included in this study were all from the same specialized oncology hospital, and patients in stage IV who underwent palliative surgery and those with more serious disease were not included. Further studies are needed to clarify whether systematic nursing intervention can be used to improve the CRF and quality of life of patients to elucidate the etiology and pathogenesis of CRF. This would involve other disciplines, such as pharmacy, psychology, and nursing. The creation of a multidisciplinary team, including clinicians, nurses, psychotherapists, and dietitians to comprehensively fulfill organizational and coordinating roles will be optimal in clinical practice.

CONCLUSION
Systemic nursing intervention for GC patients during the perioperative period could alleviate cancer-related fatigue, improve self-efficacy and self-nursing ability, and improve quality of life, which all have clinical value.

ARTICLE HIGHLIGHTS
Research background
Systematic nursing interventions are beneficial in enhancing the self-efficacy and self-care abilities of patients and improving their physical and mental state, thereby alleviating their fatigue and improving their quality of life.

Research motivation
To explore the effects of systematic nursing intervention.

Research objectives
Gastric cancer (GC) surgery causes significant surgical trauma and slow postoperative healing. Systematic nursing interventions were administered to patients with GC during the perioperative period.

Research methods
This is a randomized controlled study, sample size was based on the multivariable scale. Ten times of the acceptable variable was determined to be 140 patients, and accounting for 20% loss of patients due to follow-up, the sample size was 168 people. Conventional nursing measures were used in the control group, while the systematic nursing intervention Adopted Cancer Fatigue Scale (CFS), General Self-Efficacy Scale-Schwarzer (GSES), Self-Care Agency Scale (ESCA), and simple health scale (SF-36) were used in the observation group. The questionnaires were administered on admission and discharge.

Research results
The scores in all dimensions (mental health, vitality, physical function, physical pain, social function, emotional function, and overall health level) in the observation group were higher than those in the control group, with statistically significant differences.

Research conclusions
Systemic nursing intervention for GC patients during the perioperative period could alleviate cancer-related fatigue, improve self-efficacy and self-nursing ability, and improve quality of life, which all have clinical value.

Research perspectives
Systemic nursing intervention for GC patients during the perioperative period are beneficial. More large scale randomized controlled studies are needed.

FOOTNOTES
Author contributions: He F and He RX were responsible for the study conception and design, data analysis, and manuscript drafting; He RX critically revised the article for important intellectual content; All authors reviewed and approved the final version to be published.
REFERENCES


Impact of adding opioids to paravertebral blocks in breast cancer surgery patients: A systematic review and meta-analysis

Meng-Hua Chen, Zheng Chen, Da Zhao

**Abstract**

**BACKGROUND**

Several breast cancer studies have reported the use of adjuvant opioids with the paravertebral block (PVB) to improve outcomes. However, there is no level-1 evidence justifying its use.

**AIM**

To elucidate if the addition of opioids to PVB improves pain control in breast cancer surgery patients.

**METHODS**

We conducted an electronic literature search across PubMed, Embase, Scopus, and Google Scholar databases up to October 20, 2020. Only randomized controlled trials (RCTs) comparing the addition of opioids to PVB with placebo for breast cancer surgery patients were included.

**RESULTS**

Six RCTs were included. Our meta-analysis indicated significantly reduced 24-h total analgesic consumption with the addition of opioids to PVB as compared to placebo [standardized mean difference (SMD) -1.57, 95% confidence interval (CI): -2.93, -0.21, \( P = 94\% \)]. However, on subgroup analysis, the results were non-significant for studies using single PVB (SMD: -1.76, 95%CI: -3.65, 0.13 \( P = 95.09\% \)) and studies using PVB infusion (SMD: -1.30, 95%CI: -4.26, 1.65, \( P = 95.49\% \)). Analysis of single PVB studies indicated no significant difference in the time to first analgesic request between opioid and placebo groups (mean difference -11.28, 95%CI: -42.00, 19.43, \( P = 99.39\% \)). Pain scores at 24 h were marginally lower...
in the opioid group (mean difference -1.10, 95%CI: -2.20, 0.00, \(I^2 = 0\%\)). There was no difference in the incidence of postoperative nausea and vomiting between the two groups.

**CONCLUSION**

Current evidence suggests a limited role of adjuvant opioids with PVB for breast cancer surgery patients. Further homogenous RCTs with a large sample size are needed to clarify the beneficial role of opioids with PVB.

**Key Words:** Opioids; Pain; Surgery; Breast cancer; Nerve block; Paravertebral block

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**URL:** https://www.wjgnet.com/2307-8960/full/v10/i6/1852.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i6.1852

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**INTRODUCTION**

Breast cancer is the most common malignancy in females worldwide, and surgical intervention is the primary mode of management even in advanced cases (basically palliative in selected populations)[1]. Studies have shown improved survival with mastectomy in patients with breast cancer[1,2]. While general anesthesia is the standard-setting used for surgical interventions for these patients, a substantial number of individuals encounter significant postoperative pain[3,4]. Inadequate analgesia in the immediate postoperative period can lead to a prolonged hospital stay, increased healthcare cost, and reduced patient satisfaction[5]. Optimal management of acute pain in breast cancer survivors can also reduce the development of chronic post-surgical pain[6].

Over the last decade, several quality-improvement protocols have been described to improve perioperative management and optimize pain control in breast cancer patients[7]. One such method is the use of locoregional anesthetic techniques like the paravertebral block (PVB), intercostal nerve block, erector spinae plane block, and pectoral block[5,8,9]. Of these, the PVB has been widely used to provide better analgesia after surgery in breast cancer patients. The clinical efficacy of PVB has also been demonstrated by several studies[10,11]. Terkawi et al[12] in a meta-analysis of 24 studies demonstrated that the use of PVB decreased opioid consumption and postoperative pain scores at 2, 24, 48, and 72 h after surgery. However, the effects of PVB were found to be modest with a limited beneficial effect on postoperative recovery. In this context, several researchers have evaluated the addition of adjuvants to PVB to improve its efficacy. It is hypothesized that the addition of drugs like opioids, clonidine, and dexmedetomidine would lead to better analgesic efficacy of PVB[13,14]. Opioids have been used in combination with local anesthetics for several locoregional anesthetic techniques leading to better pain control in the immediate postoperative period[15,16]. However, it is not known if the addition of opioids to PVB would lead to better outcomes in breast cancer patients. Despite several studies reporting the use of adjuvant opioids with PVB, there is a lack of pooled evidence to guide clinical practice. Thus, this systematic review and meta-analysis aimed to answer the following clinical question: Does the addition of opioids to PVB lead to improved pain control in the immediate postoperative period in patients undergoing surgery for breast cancer?

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**MATERIALS AND METHODS**

**Search strategy**

The authors planned and executed this study conforming to the recommendations of the PRISMA...
statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[17] and the Cochrane Handbook for Systematic Reviews of Intervention[18]. Protocol registration was, however, not carried out. We conducted an electronic literature search across PubMed, Embase, Scopus, and Google Scholar databases. Two reviewers independently carried out the literature search. Search limits were from the inception of databases to October 20, 2020. The search terms included “breast surgery”, “mastectomy”, “paravertebral block”, “opioid”, “morphine”, “fentanyl”, “buprenorphine”, and “tramadol”. Supplementary Table 1 presents the search strategy and the result of the PubMed database. At first, the search records were reviewed by their titles and abstracts. Relevant articles to the review were identified, and full texts of the articles were extracted. Both the reviewers assessed individual articles based on the inclusion and exclusion criteria. Any disagreements were resolved by discussion. The bibliography of studies meeting the inclusion criteria was also hand-searched for any missed references.

Inclusion criteria
We defined the inclusion and exclusion criteria of the review based on the PICOS (Population, Intervention, Comparison, Outcome, Study type) framework a priori. Population: Studies conducted on patients undergoing breast cancer surgery and receiving PVB before general anesthesia. The intervention was to be the addition of an opioid to the PVB. The comparison was the addition of placebo or no drug to the PVB. Studies were to report at least one of the following outcomes: 24 h total analgesic consumption, pain scores, time to the first analgesic, and/or incidence of Postoperative nausea and vomiting (PONV). Only randomized controlled trials (RCTs) were eligible to be included in the review. No language restriction was placed. Studies comparing opioids with any other active drugs were excluded. We also excluded studies using opioids not as an addition to PVB but via other routes like intravenous, subcutaneous, etc. Furthermore, non-RCTs, retrospective studies, single-arm studies, and studies not reporting relevant data were also excluded.

Data extraction and quality assessment
Data were extracted using a data extraction form by two reviewers independently. Name of the first author, publication year, study type, study location, age of patients, surgery type, sample size, intervention drug and dose, PVB protocol, use of other analgesics, and study outcomes were extracted. The primary outcome of the interest of our analysis was 24-h total analgesic consumption. The secondary outcomes were to report at least one of the following outcomes: 24 h total analgesic consumption, pain scores, time to the first analgesic, and incidence of PONV. Furthermore, a descriptive analysis of other outcomes reported by the included studies was also performed.

Two reviewers assessed the quality of each RCT using the Cochrane Collaboration risk assessment tool[18]. Each study was assessed for bias in random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The study was judged to have a "high", "unclear", or "low" risk of bias for each domain. Any disagreements were resolved by discussion.

Statistical analysis
The software “Open MetaAnalyst” was used for the meta-analysis[19]. Meta-analysis was conducted only if at least three trials reported similar outcomes. Owing to the methodological heterogeneity of the included studies, we used a random-effects model to calculate the pooled effect size for all analyses. Continuous data not reported on the same scale were summarized using standardized mean difference (SMD) with 95% confidence interval (CI) or else mean difference (MD) was used. Specifically, different analgesics were used by the individual studies for the outcome of ‘total analgesic consumption’, hence we used SMD to pool this variable. For studies not reporting mean and standard deviation (SD) scores of continuous variables, the method described by Wan et al[20] was used to calculate data from the median and interquartile range. For the incidence of PONV, we calculated odds ratios (OR) with 95%CI. Sub-group analysis was conducted for single and continuous PVB. Heterogeneity was assessed using the I² statistic. I² values of 25%-50% represented low, values of 50%-75% represented medium, and more than 75% represented substantial heterogeneity. As < 10 studies were included per meta-analysis, funnel plots were not used to assess publication bias.

RESULTS
The PRISMA flowchart of the review is presented in Figure 1. Of the 11 studies assessed by the full-texts, five were excluded with reasons, and a total of six RCTs fulfilled the inclusion criteria[21-26]. Characteristics of studies included in the review are presented in Table 1. Three trials[22,23,25] were conducted exclusively on modified radical mastectomy patients, while the remaining three included other breast cancer surgeries as well. The sample size of the included studies was small, ranging from 12-20 patients per group. The opioids used as an adjunct to PVB were fentanyl in three trials, while morphine, tramadol, and buprenorphine were used in one study each. Two trials[22,26] used continuous PVB infusions, while the remaining used single PVB.
Table 1 Details of included studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Yr</th>
<th>Study location</th>
<th>Surgery type</th>
<th>Sample size</th>
<th>Age (yr)</th>
<th>Common protocol for PVB</th>
<th>Opioid added to PVB in intervention group</th>
<th>Drug added to PVB in control group</th>
<th>Post-operative analgesics used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostafa et al[21]</td>
<td>2018</td>
<td>Egypt</td>
<td>MRM or breast conservation surgery with axillary node dissection</td>
<td>20</td>
<td>18-78</td>
<td>Nalbuphine 10 mg</td>
<td>PVB at the level of T4 with bupivacaine 0.5% 0.3 mL/kg</td>
<td>No drug</td>
<td>Tramadol as PCA</td>
</tr>
<tr>
<td>Pushparajan et al [22]</td>
<td>2017</td>
<td>India</td>
<td>MRM</td>
<td>20</td>
<td>18-60</td>
<td>Fentanyl 2 μg/mL at 0.1 mL/kg/h for 24 h</td>
<td>Continuous PVB at the level of T4 with 0.2% ropivacaine for 24 h</td>
<td>No drug</td>
<td>Fentanyl as PCA. Paracetamol or tramadol or fentanyl for breakthrough pain</td>
</tr>
<tr>
<td>Morsy et al[23]</td>
<td>2017</td>
<td>Egypt</td>
<td>MRM</td>
<td>15</td>
<td>NR</td>
<td>Morphine 2 mg</td>
<td>PVB at the level of T3 with 20 mL of bupivacaine 0.25%</td>
<td>No drug</td>
<td>Meperidine for breakthrough pain</td>
</tr>
<tr>
<td>Bhuvaneshwari et al[24]</td>
<td>2012</td>
<td>India</td>
<td>Total mastectomy and axillary lymph node dissection</td>
<td>12</td>
<td>Study: 49.1 ± 7.1; Control: 50.7 ± 11</td>
<td>Fentanyl 2 μg/mL</td>
<td>PVB at the level of T3 with bupivacaine 0.25% and epinephrine 5 μg/mL</td>
<td>No drug</td>
<td>Morphine for breakthrough pain</td>
</tr>
<tr>
<td>Omar et al[25]</td>
<td>2011</td>
<td>Egypt</td>
<td>MRM</td>
<td>19</td>
<td>Study: 47.5 ± 9.3; Control: 49.3 ± 10.5</td>
<td>Tramadol 1.5 mg/kg (maximum of 150 mg)</td>
<td>PVB at the level of T1 (1/3rd of the dose) and T4 (2/3rd of the dose) with bupivacaine 0.5% 2 mg/kg</td>
<td>No drug</td>
<td>Fentanyl as PCA. Paracetamol 1 g thrice daily and ibuprofen 400-600 mg thrice daily</td>
</tr>
<tr>
<td>Burlacu et al[26]</td>
<td>2006</td>
<td>Ireland</td>
<td>Wide local excisions (at least one breast quadrant), mastectomies, and mastectomies with reconstruction</td>
<td>13</td>
<td>Study: 54 ± NR; Control: 51 ± NR</td>
<td>Fentanyl 50 μg with bolus followed by 4 μg/mL infusion</td>
<td>Continuous PVB at the level of T3 with initial bolus of 19 mL levobupivacaine 0.25% followed by continuous infusion of 0.1% solution for 24 h</td>
<td>Saline</td>
<td>Morphine as PCA</td>
</tr>
</tbody>
</table>

PVB: Paravertebral block; MRM: Modified radical mastectomy; PCA: Patient controlled analgesia; T: Thoracic vertebral level.

Outcomes

Table 2 presents the results of the outcomes reported by the included studies. For the primary outcome, data were reported by all six studies. Our meta-analysis indicated significantly reduced 24-h total analgesic consumption with the addition of opioids to PVB as compared to placebo (SMD: -1.57, 95% CI: -2.93, -0.21, P = 94%) (Figure 2). However, on subgroup analysis, the results were non-significant for studies using single PVB (SMD: -1.76, 95% CI: -3.65, 0.13, P = 95.09%) and studies using PVB infusion (SMD: -1.30, 95% CI: -4.26, 1.65, P = 95.49%). Data on time to first analgesic request were reported by four studies using a single PVB. Our analysis demonstrated no significant difference in the time to first analgesic request between opioid and placebo groups in hours (MD -11.28, 95% CI: -42.00, 19.43, P = 99.39%) (Figure 3).

Data for a meta-analysis on pain scores on the Visual Analog Scale were available only from three studies. The study of Bhuvaneshwari et al[24] reported cumulative 24-h pain scores, while SD values of pain scores were not reported by Mostafa et al[21]. Both these studies reported significantly lower pain scores in the opioid group. For the remaining studies, our pooled analysis indicated pain scores at 24 h were marginally lower in the opioid group (MD -1.10, 95% CI: -2.20, 0.00, P = 0%) (Figure 4). Sub-group
Table 2 Outcomes reported by included studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Outcome</th>
<th>Results</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostafa et al[21]</td>
<td>Time to first analgesic request</td>
<td>Significantly longer in the opioid group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-operative analgesic time</td>
<td>Significantly longer in the opioid group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 h total analgesic consumption</td>
<td>Significantly lower in the opioid group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain scores up to 24 h</td>
<td>Significantly lower in the opioid group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR, SBP, DBP</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ramsay sedation scores</td>
<td>Patients in the control group were more agitated then opioid group in the first four hours after the operation. No difference between the two groups after four hours</td>
<td></td>
</tr>
<tr>
<td>Pushparajan et al[22]</td>
<td>Pain scores up to discharge</td>
<td>Significantly lower scores in the opioid group only at 24 h and not at other time periods</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 h total analgesic consumption</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PONV</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary retention, pruritus</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient satisfaction</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td>Morsy et al[23]</td>
<td>24 h total analgesic consumption</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to first analgesic request</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ramsay sedation scores</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PONV</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR, SBP, DBP</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td>Bhuvanendswari et al[24]</td>
<td>Time to first analgesic request</td>
<td>Significantly longer in the opioid group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 h total analgesic consumption</td>
<td>Significantly lower in the opioid group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cumulative pain scores at 24 h</td>
<td>Significantly lower in the opioid group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PONV</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient satisfaction</td>
<td>Significantly higher in the opioid group</td>
<td></td>
</tr>
<tr>
<td>Omar et al[25]</td>
<td>Time to first analgesic request</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 h total analgesic consumption</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain scores up to 24 h</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PONV</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td>Burlacu et al[26]</td>
<td>Total analgesic consumption</td>
<td>Significantly lower in the opioid group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain scores up to 24 h</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea scores</td>
<td>Significantly higher in the opioid group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SBP</td>
<td>No difference between the two groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient satisfaction</td>
<td>Significantly higher in the opioid group</td>
<td></td>
</tr>
</tbody>
</table>

PONV: Postoperative nausea and vomiting; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.
analysis demonstrated marginal difference favoring the opioid group in the studies using PVB infusion (MD -1.30, 95% CI: -2.61, 0.00, \( P = 0\% \)); however, for the study using single PVB no difference was noted (MD -0.60, 95% CI: -2.65, 1.45). Data on the incidence of PONV were reported by four studies. Our analysis indicated no statistically significant difference between opioid and placebo groups (OR 0.87, 95% CI: 0.39, 1.93, \( P = 0\% \)) (Figure 5). Results were non-significant on subgroup analysis as well.

**Risk of bias analysis**

Table 3 presents the risk of bias assessment of included studies. The majority of studies (5/6) were of good quality with a low risk of bias across six of the seven domains. Only the trial of Morsy et al\[^{[23]}\] did not provide adequate information on randomization, allocation concealment, and blinding.
Table 3 Risk of bias in included studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostafa et al[21]</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Pushparajan et al[22]</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Morsy et al[23]</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Bhuvaneshwari et al[24]</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Omar et al[25]</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Burlacu et al[26]</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

Figure 3 Forest plot of time to first analgesic request in hours.

Figure 4 Forest plot of 24-h visual analog scale pain score with sub-group analysis based on type of paravertebral block.

DISCUSSION

The results of our review assessing the role of adjuvant opioids to PVB for breast cancer surgery patients indicate that: (1) Total analgesic consumption in the immediate postoperative period may not be reduced with the addition of opioids to a single PVB or PVB infusion; (2) Time to first analgesic request is not increased with the addition of opioids to a single PVB; (3) There is only a marginal difference in pain score at 24 h with the addition of opioids; and (4) Adjuvant opioids do not increase the incidence of PONV.

PVB as a technique of regional anesthesia has gained popularity for pain control in patients undergoing breast surgery. The procedure involves the deposition of local anesthetic just lateral to the spinous process of the vertebrae in the area where spinal nerves emerge out of the intervertebral foramina. The local anesthetic blocks the somatic and sympathetic nerve supply of the dermatome of interest thereby providing postsurgical analgesia[27]. Its efficacy has been tested in a randomized setting by numerous authors not only for breast surgery but also for thoracic surgeries[12,28]. However, one important limitation of nerve blocks, in general, is the short duration of action of the local anesthetic. Even with agents with a longer duration of action, like bupivacaine and ropivacaine, the duration of analgesia is often inadequately sustained in the postoperative period[29]. Prolonging the
duration of analgesia by increasing the dose of local anesthetic entails the risk of adverse events involving the cardiovascular and central nervous systems[30]. To overcome this issue, several adjuvants have been used with local anesthetics to prolong the analgesic effect while maintaining the safety of regional anesthesia.

One of the earliest adjuvants used with local anesthetics was opioids. Their use with local anesthetics has accelerated since studies reported the presence of peripheral opioid receptors in the primary afferent neurons and peripheral sensory nerves[31]. It is thought that opioids exhibit a local anesthetic-like action causing hyperpolarization of the afferent sensory neuron through G protein-coupled receptor mechanism[32]. Nishikawa et al[33] have suggested that adjuvant opioids with local anesthetics can lead to the increased duration and improved quality of local anesthetic blockade. However, the results of our review indicate that this mechanism may have a limited role especially for PVB in breast cancer surgery patients. For the primary outcome of 24-h total analgesic consumption, our analysis demonstrated a statistically significant difference in favor of the opioid group, but no such difference was noted on sub-group analysis of single PVB and PVB infusions studies. It is important to note that the lower end of 95% CI of the meta-analysis was on the higher side (-3.65 for single PVB sub-group and -4.26 for PVB infusion group) and the upper end of the 95% CI close to zero (for single PVB sub-group) in the meta-analysis. Similar was the case in the analysis of 24-h pain scores with the upper end of 95% CI at 0, albeit with a very limited number of studies. The addition of opioids was found to be safe with no increase in the incidence of PONV. Therefore, while our results do not demonstrate a clear advantage of adding opioids to PVB they are suggestive of a probable role of adjuvant opioids in PVB for breast cancer surgery patients, which needs further research.

Such inconclusive result was also evident on descriptive analysis of the included studies with three RCTs[22,23,25] reporting no benefit of adding opioids to PVB, while the remaining three[21,24,26] reporting significant advantage in favor of adjuvant opioids. Such varied results with local anesthetic adjuvants have been reported with other nerve blocks as well. Souliotis et al[34] in an RCT reported improved outcomes with the addition of 100 mg of tramadol to brachial plexus block with ropivacaine. In contrast, no such benefit was noted by Kesimi et al[35] using a similar dose of tramadol with ropivacaine. Several other RCTs have reported the limited benefit of adding opioids to peripheral nerve blocks. In a recently published trial, Kim et al[36] failed to prove any beneficial effect of adding fentanyl to continuous femoral nerve blocks for knee arthroplasty patients. Two RCTs have shown that the addition of fentanyl to transverse abdominis plane block did not improve postoperative outcomes in patients undergoing cesarean section and gynecological surgeries[37,38]. The contrasting results on the role of adjuvant opioids in literature as well as in our review can be attributed to several factors, like the type of surgery, type of nerve block, type and dosage of local anesthetic, type and dose of opioid, pain threshold of patients, the post-operative pain control protocol, etc. In our review, while the type of surgery and nerve block were the same, four different opioids were used with varying doses in the included studies. Postoperative pain control protocol was different across studies, which could also have contributed to the heterogeneous results. However, such heterogeneity is expected in clinical trials conducted in different geographical settings. Several other meta-analyses in literature have also pooled outcomes of different opioids in a single analysis[39-41].

In addition to the inter-study heterogeneity, other limitations of our review should also be taken into account while interpreting the results. Firstly, only six RCTs were available for analysis in this review, all with limited sample size. Thus, our review may not have been statistically powered to detect significant differences between the groups. Secondly, data on pain scores at different periods were not available from included studies for a meta-analysis. Furthermore, data as mean and SD were not presented by all studies, further restricting our analysis. Thirdly, pain score and analgesic consumption after surgery can depend on several surgical and patient-dependent factors, like duration and complexity of the surgical procedure, the pain threshold of the patient, etc. Such uncontrolled factors could have also influenced the outcomes of the included trials. Lastly, we were unable to register the review protocol on any online database, and this is a significant limitation of our review. Nevertheless, our study has certain novelities. We have presented the first systematic review and meta-analysis assessing the role of adjuvant opioids in PVB for breast cancer surgery patients. The overall quality of
the included RCTs was high, and this lends credibility to the overall review.

CONCLUSION
To conclude, there is a limited role of adjuvant opioids with PVB for breast cancer surgery patients. The addition of opioids had no significant effect on 24-h total analgesic consumption, time to first analgesic, and 24-h pain score. Further homogenous RCTs with a large sample size are needed to clarify the beneficial role of opioids with PVB.

ARTICLE HIGHLIGHTS

Research background
Opioids have been used in combination with local anesthetics for several locoregional anesthetic techniques, leading to better pain control in the immediate postoperative period. However, it is not known if the addition of opioids to paravertebral block (PVB) would lead to better outcomes in breast cancer patients.

Research motivation
No meta-analysis has summarized evidence to assess the value of adding opioids to PVB in breast cancer patients undergoing surgical intervention.

Research objectives
To compare total analgesic consumption, time to first analgesic request, and pain scores with and without the addition of opioids to PVB in breast cancer surgery patients.

Research methods
We conducted an electronic literature search across PubMed, Embase, Scopus, and Google Scholar databases up to October 20, 2020 for randomized controlled trials (RCTs) comparing the addition of opioids to PVB with placebo for breast cancer surgery patients.

Research results
Analysis of six RCTs demonstrated that the addition of opioids to PVB significantly reduced 24-h total analgesic consumption but had no impact on the time to first analgesic request. Pain scores at 24 h were marginally lower with the addition of opioids.

Research conclusions
Current evidence suggests a limited role of adjuvant opioids with PVB for breast cancer surgery patients.

Research perspectives
Further homogenous RCTs with a large sample size are needed to clarify the beneficial role of opioids with PVB.

FOOTNOTES

Author contributions: Chen MH conceived and designed the study, analyzed the data, and wrote the paper; Chen Z and Zhao D were involved in literature search and data collection and reviewed and edited the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors deny any conflict of interest.

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

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34 Soulioti E, Tsaroucha A, Makris A, Koutsaki M, Sklika E, Mela A, Megaloikonomos PD, Favoussalaki A. Addition of 100 mg of Tramadol to 40 mL of 0.5% Ropivacaine for Interscalene Brachial Plexus Block Improves Postoperative Analgesia in Patients Undergoing Shoulder Surgeries as Compared to Ropivacaine Alone-A Randomized Controlled Study. *Medicina (Kaunas)* 2019; 55 [PMID: 31340565 DOI: 10.3390/medicina55070399]


Multiple different remote epidural hematomas after craniotomy: A case report

Qiang He, Chuan-Yuan Tao, Rui-Hong Fu, Chao You

**Abstract**

**BACKGROUND**

Epidural hematoma is one of the common postoperative complications after craniotomy. However, multiple remote epidural hematomas in different sites, including supratentorial and infratentorial regions, are exceedingly rare.

**CASE SUMMARY**

We present a rare case in which three remote epidural hematomas occurred after craniotomy. A 21-year-old woman was admitted with a headache for 1 mo, vomiting, and rapid vision loss for 1 wk. Brain magnetic resonance imaging indicated a right thalamic tumor. The intraoperative diagnosis was a cystic tumor, posterior cerebral artery aneurysm, and vascular malformation. The operation was successful. Unfortunately, the patient developed three extradural hematomas within 48 h. Family members consented to the first two hematoma evacuations but refused the third.

**CONCLUSION**

More attention should be paid to this kind of rare complication. Adequate preoperative evaluation is important, especially for acute patients. Monitoring neural function and early computed tomography scanning of the brain after surgery should be highlighted.

**Key Words:** Postoperative complication; Multiple epidural hematomas; Supratentorial and infratentorial regions; Remote epidural hematoma; Case report

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Core Tip: We report a 21-year-old emergency woman who developed three remote epidural hematomas in different sites after craniotomy.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i6.1863

INTRODUCTION
Postoperative hemorrhage includes intracerebral hematoma (ICH), subdural hematoma, and extradural hematoma (EDH), which are serious complications after craniotomy. EDH is one of the most frequent and devastating complications. It may occur in supratentorial, infratentorial, ipsilateral, and even contralateral sites of the operative area[1,2]. As a specific subset of EDH after craniotomy, multiple remote EDHs are very rare. In this study, we present a 21-year-old woman who developed three remote EDHs in different sites after craniotomy.

CASE PRESENTATION

Chief complaints
A 21-year-old woman visited the emergency department and was admitted to the Neurosurgery Department. She complained of headache and vomiting for 1 mo, and rapid vision loss for 1 wk.

History of present illness
The patient had a headache and recurrent vomiting, along with rapid vision loss.

History of past illness
The patient had no significant medical history.

Personal and family history
Neither the patient nor her family members had special medical history.

Physical examination
The patient was conscious. The extremities were moved as instructed. General sensory was normal. The positive sign was blurred binocular vision.

Laboratory examinations
The blood test results were within normal limits before surgery. The laboratory examination results in the whole treatment process are shown in Figure 1 and Table 1.

Imaging examinations
Computerized tomography (CT) revealed a solid cystic tumor in the right thalamus (Figure 2A). Brian magnetic resonance imaging (MRI) showed a solid cystic tumor in the right thalamus and midbrain (Figure 2B-D).

MULTIDISCIPLINARY EXPERT CONSULTATION
The patient was diagnosed with a right thalamic tumor before surgery.

FINAL DIAGNOSIS
The final diagnosis was a solid cystic tumor, right posterior cerebral artery aneurysm, vascular malformation in the thalamus, and multiple remote EDHs.
Table 1 The change of platelet count and the fluctuation of prothrombin time and activated partial thromboplastin time

<table>
<thead>
<tr>
<th>Item</th>
<th>PLT (10^9/L)</th>
<th>PT (s)</th>
<th>APTT (s)</th>
<th>D-dimer (mg/L)</th>
<th>Fibrinogen (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal value</td>
<td>100-300</td>
<td>9.6-12.8</td>
<td>24.8-33.8</td>
<td>&lt; 0.55</td>
<td>2.0-4.0</td>
</tr>
<tr>
<td>Preoperation</td>
<td>19.8</td>
<td>10.9</td>
<td>27.5</td>
<td>-</td>
<td>2.19</td>
</tr>
<tr>
<td>Before first EDH evacuation (3 h postoperatively)</td>
<td>17.3</td>
<td>13.2</td>
<td>29.1</td>
<td>32.24</td>
<td>1.18</td>
</tr>
<tr>
<td>After second EDH evacuation (22 h after operation)</td>
<td>1.6</td>
<td>18.2</td>
<td>58.2</td>
<td>1.96</td>
<td>0.69</td>
</tr>
<tr>
<td>After third EDH (41 h postoperatively)</td>
<td>1.9</td>
<td>15.2</td>
<td>34.5</td>
<td>6.23</td>
<td>2.62</td>
</tr>
<tr>
<td>Before discharge</td>
<td>8.3</td>
<td>13</td>
<td>28.7</td>
<td>1.92</td>
<td>4.33</td>
</tr>
</tbody>
</table>

PLT: Platelets; PT: Prothrombin time, APTT: Activated partial thromboplastin time; EDH: Epidural hematoma.

Figure 1 The change of platelet count and the fluctuation of prothrombin time and activated partial thromboplastin time were observed after the second extradural hematoma evacuation. PLT: Platelets; PT: Prothrombin time, APTT: Activated partial thromboplastin time; EDH: Epidural hematoma.

TREATMENT

Under the neuro-electrophysiological monitoring, a triangular approach was performed. The cystic mass was dissected, and then yellow fluid was released from the cyst. However, a small artery was observed below the cyst cavity. In addition, a red bulge was observed and considered an aneurysm, which had a drainage vein (Figure 3). Therefore, aneurysm clipping and vascular malformation resection were performed. Neuro-electrophysiological monitoring revealed a decline in the left lower limb. The entire procedure lasted 6.5 h.

Because the patient did not wake up from anesthesia after 3 h, CT confirmed the first EDH of about 130 mL in the occipital (Figure 4A). Hematoma evacuation was performed. However, the second EDH after 22 h and the third EDH after 41 h developed in the left frontotemporal and the frontal regions (Figure 4B and C). Familial members consented to the second hematoma evacuation but refused the third.
Figure 2 Computed tomography image and magnetic resonance imaging images of the mass before surgery. A: Computerized tomography image revealing a solid cystic mass in the right thalamus; B, C: T1 and T2 imaging showing heterogeneous signals and cystic and solid components; D: Inhomogeneous enhancement in the solid part was observed after administration of a contrast agent.

Figure 3 Intraoperative picture showing an aneurysm (blue arrow) and the draining vein (yellow arrow).

Figure 4 Three extradural hematomas in the occipital, the left frontotemporal, and the left frontal region, respectively (A-C).

OUTCOME AND FOLLOW-UP
The patient’s family members refused further treatment and asked for discharging. The patient died.

DISCUSSION
Remote EDH is defined as EDH at a site away from the primary surgical site. Although EDH accounts for 20%[1] among remote site bleeding[3,4], only 12% required surgical intervention[2]. According to published articles, only three cases of multiple postoperative EDHs were reported. Wolfsberger et al[5] presented a patient with four EDHs in the supratentorial area after surgery for the fourth ventricular...
choroid plexus papilloma. Lim et al[6] and Gaurav Tyagi et al[7] reported two EDHs in the supratentorial area after posterior fossa surgery. However, our patient had three remote EDHs in different locations, including supratentorial and infratentorial regions.

The drastic fluctuation of ICP is a trigger point of postoperative remote ICH[4,8,9]. The fluctuation may result from tumor resection and/or rapid release of cerebrospinal fluid (CSF) and sac fluid. Patients with ventricular drainage systems have a higher incidence of remote ICH than those without[10]. The fast decline of ICP results in negative pressure in a distant area. This fluctuation causes the rupture of blood vessels. With the increasing hematoma caused by vessel rupture, the dura and skull are separated. The phenomenon aggravates hematoma expansion. The above points are a vicious cycle. In our case, the lesion was in the thalamus and midbrain with a posterior cerebral artery. Angiographic assessment should be necessary but was not performed. Because the acute onset occurred and the lesion compressed the aqueduct, the patient had acute obstructive hydrocephalus. Those are special factors for the first occipital EDH.

The pins of a Mayfield head holder may be a reason[11], which may damage the transverse sinus. However, no evidence of fracture was found at the pin sites. Therefore, the cause was ruled out. Age may be a factor for the first EDH because the not-tight adhesion between the dura and skull is more frequent in young people[12,13]. Our patient was a 21-year-old woman. EDH may also result from jugular vein compression because of the extended neck position and intraoperative rotation[14,15]. The patient was positioned in a supine gesture with the head rotation about 65 degrees during surgery, which could lead to obstruction of cerebral venous return.

Coagulopathy is a possible explanation. Our patient had a normal coagulation function before surgery. For the second EDH, consumptive coagulopathy after tumor resection and first EDH might disturb coagulation. The disturbance presented increasing prothrombin time, activated partial thromboplastin time, and international normalized ratio and decreasing fibrinogen, combining with drastically declining platelets. The volume of the first EDH was 130 mL. After the first EDH hematoma evacuation, changes in ICP between the supratentorial and infratentorial regions led to the second left supratentorial EDH. The third EDH could also be attributed to those hypotheses. Thrombocytopenia may play an important role in the third bleeding. Platelet counts in our patients decreased drastically, although the patient was infused with platelets. Unfortunately, a thromboelastogram test was not performed. Decreased factor XIII activity and factor X deficiency may result in EDH[16-18], but the patient and her family did not have this medical history.

We noticed that no definitive source of ooze could be identified during the two hematoma evacuations. There was no visible bleeding on the edge of the dura mater. In the first EDH, the pupil change was noted in time. CT confirmed the EDH. In the third and second EDH, the assessment of CT scan was also a matter of time. Accordingly, early computed tomography scanning of the brain after surgery should be highlighted. Postoperative pupil changes and not waking up from anesthesia are indications for early CT scanning.

CONCLUSION

Although multiple remote EDH is an uncommon complication, attention should be paid to it. Understanding the mechanism of the complication, sufficient preparation and evaluation before an operation, and meticulous operation during surgery are the keys to preventing postoperative EDH, especially for acute onset. Intraoperative administration of ICP should be meticulous. It is important to monitor the ICP and nerve function after the operation. When the pupil change and the patient cannot recover from anesthesia in time, early CT scanning of the brain should be a priority.

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FOOTNOTES

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He Q et al. Multiple remote epidural hematomas after craniotomy

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Tuberculous pericarditis-a silent and challenging disease: A case report

Oscar David Lucero, Marlon Mauricio Bustos, Darwin Jhoan Ariza Rodríguez, Juan Camilo Perez

BACKGROUND
Tuberculous pericarditis (TP) remains a challenge for endemic countries. In developing countries, one to two percent of patients with pulmonary tuberculosis develops TP.

CASE SUMMARY
A 49-year-old woman presented with dyspnea, chest pain and dry cough. On physical examination, veiled heart sounds were found. The electrocardiogram showed low-voltage complexes and the transthoracic echocardiography revealed a large and free-looking pericardial effusion. The patient was taken for an open pericardiotomy. The pericardial fluid revealed high levels of adenosine deaminase and Ziehl-Neelsen stain showed acid-fast bacilli. Polymerase chain reaction study for Mycobacterium tuberculosis in pericardial fluid was positive. The patient received tetra conjugate management with adequate clinical response after the first week of treatment and resolution of fever and chest pain.

CONCLUSION
In cases of TP, obtaining pericardial fluid and/or pericardial biopsy is the most efficient strategy to confirm the diagnosis. Early diagnosis of this entity will allow physicians to initiate timely treatment, avoid complications and improve the patient's clinical outcome, so we consider the description of this case pertinent and its review in the literature.

Key Words: Tuberculosis; Pericardial disease; Tuberculous pericarditis; Pericardial effusion; Mycobacterium tuberculosis; Case report

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Core Tip: Tuberculous pericarditis should be suspected in the evaluation of all cases of pericarditis that do not have a self-limited course. The present case identifies the usefulness of the study of Adenosine deaminase in the pericardial fluid and the performance of polymerase chain reaction for *Mycobacterium tuberculosis* in the biopsy, thanks to which the diagnosis could be confirmed. Management is based on the use of rifampin, isoniazid, ethambutol, and pyrazinamide.

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INTRODUCTION

Tuberculosis (TB) is a transmissible disease and it is the main cause of morbimortality and one of the ten leading causes of death worldwide. It is also the leading cause of death from a single infectious agent [ahead of human immunodeficiency virus (HIV)/AIDS]. A quarter of the world’s population is infected with *Mycobacterium tuberculosis* and thus is at risk of developing the disease[1]. In developing countries, coinfection with the HIV is associated with a higher mortality[2]. Although the lung is the target organ for TB, any other organ can be affected. Extrapulmonary TB accounts for 10%-20% of the clinical presentation suffered by immunocompetent patients[3]. Approximately 1% to 2% of patients with pulmonary TB have tuberculous pericarditis (TP) and this carries a high mortality rate (17% to 40% over 6 mo)[4].

Pericarditis can be caused by infectious agents (e.g., viral and bacterial) or can be non-infectious in origin (e.g., systemic inflammatory diseases, cancer, and post-cardiac injury syndromes). TB is a major cause of pericarditis in developing countries, but accounts for less than 5% of cases in developed countries, where viral causes are responsible for 80% to 90% of the cases[5]. TP accounts for approximately 4% of acute pericarditis, 7% of cardiac tamponade and 6% of constrictive pericarditis cases[6]. *Mycobacterium tuberculosis* usually affects the pericardium by retrograde lymphatic spread from the peritracheal, peribronchial, or mediastinal lymph nodes or by hematogenous spread of a primary TB infection and is rarely affected by contiguous spread of a tuberculous lesion in the lung or hematogenous spread of a distant focus[7].

CASE PRESENTATION

Chief complaints
A 49-year-old woman came to the emergency room for unquantified fever peaks and intermittent chest pain lasting 2 mo.

History of present illness
Unquantified fever peaks and intermittent chest pain lasting 2 mo which increased in intensity.

History of past illness
During the 2 wk prior to admission, the patient experienced dyspnea, cough and hyaline expectoration.

Personal and family history
The patient had a surgical history of liposuction and augmentation mammoplasty.

Physical examination
The patient was febrile with a temperature of 39.5 °C. Her heart rate 117 beats per minute, blood pressure 100/60 mmHg, respiratory rate of 24 breaths per minute and her oxygen saturation was 80%. The patient’s neck veins were distended and heart sounds were muffled.

Laboratory examinations
Electrocardiogram was done (Figure 1) and showed sinus tachycardia and low-voltage complexes in the limb and precordial leads. There were no alterations in PQ interval or ST-segment. Deaminase level in the pericardial fluid of 36.50 U/L (reference range, 0 to 9 U/L). The cytology of the pericardial fluid was of lymphocytic predominance and examination of the pericardial fluid revealed acid-fast bacilli. Polymerase chain reaction (PCR) study of pericardial fluid was positive for *Mycobacterium tuberculosis*. 
Figure 1 Low-voltage electrocardiogram (defined as QRS < 5 mm in limb shunts).

**Imaging examinations**
Chest x-ray was done (Figure 2) showing a generalized increase of the mediastinal cardiac silhouette, suggestive of pericardial effusion. There was an adequate pulmonary vascularization pattern. Pleuropulmonary lesions were not seen. Transthoracic echocardiography revealed a large and free-looking pericardial effusion, with an anterior interface of 17 mm and a posterior interface of 27 mm. The right cavities had a partial diastolic collapse, between 20%-30% (Figure 3). High-resolution chest tomography revealed a heart of normal size and there was evidence of pericardial effusion without alteration of the ventricular walls with a thickness of up to 25 mm (Figure 4).

**MULTIDISCIPLINARY EXPERT CONSULTATION**
TP was made. HIV was negative.

**FINAL DIAGNOSIS**
Tuberculous pericarditis.

**TREATMENT**
The patient received treatment each day with isoniazid 300 mg, rifampin 600 mg, pyrazinamide 1600 mg, and ethambutol 1100 mg for 2 mo. This was followed by rifampin and isoniazid for an additional 4 mo along with prednisolone for 6 wk.

**OUTCOME AND FOLLOW-UP**
In the days following pericardiocentesis and initiation of tetracconjunctive management for TB, the patient progressed satisfactorily with improved hemodynamic parameters and fever resolution.

**DISCUSSION**
TP has a diverse clinical picture and should be considered in the evaluation of non-self-limiting pericarditis cases. Despite the fact that the prevalence of TB has been reduced in general, the cases of extrapulmonary TB remains stable; approximately 1050000 new cases were reported in the world in 2018[8]. In developing countries, one to two percent of pulmonary TB patients develop TP. However, it can also appear as an isolated extrapulmonary form[9]. There are few studies that evaluate the prevalence of TP in Colombia, and generally, it is considered that there is an underdiagnosis of the disease. 13626 new cases of TB were reported during 2020, of which 83% corresponded to pulmonary TB and 17% to extrapulmonary TB, while 1.6% of these corresponded to TP[9]. Furthermore, in Colombia, a
progressive increase in the extrapulmonary TB rate has been observed: 2.1 cases/100000 inhabitants in 1997; 3.7/100000 in 2006 and 4.4/100000 in 2018. Less than 1% of these cases correspond to TP, and generally, it occurs in patients coinfected with HIV who constitute about 85% of cases [10].

TP usually develops insidiously and with nonspecific systemic symptoms such as fever, night sweats, fatigue and weight loss. Although chest pain, cough, and dyspnea are common, the severe acute-onset pericardial pain characteristic of idiopathic pericarditis is rare [10]. Large pericardial effusion should be suspected when micro voltage is observed on the electrocardiogram. This is seen in complexes < 5 mm in the limb leads and < 10 mm in the precordial leads [11]. Chest radiography generally shows a widening of the cardiac silhouette in more than 90% of cases, with a globular image described as “Bottle of water” configuration. Generally, these findings are observed in conjunction with active lung TB and pleural effusion in 30% and 60% of cases, respectively [12]. On the echocardiogram, TP usually comes accompanied by pericardial effusion with thickening of the visceral pericardium and it is possible to identify fibrin bands or fibrosis that heals the pericardium [13].

TP diagnosis is confirmed if one of the following criteria is present: Positive culture for the bacillus of Koch in pericardial fluid, positive direct examination for Koch bacillus, or value greater than 50 IU/L on the Adenosine deaminase (ADA) test [14]. Furthermore, the diagnosis can be confirmed if the pericardial biopsy shows the following findings: Positive culture for the Koch bacillus and granulomas with caseous necrosis, or presence of Langhans-type multinucleated giant cells, or presence of tubercle bacilli in the sample [15].
The diagnosis of TP remains difficult due to the absence of a simple, rapid and accessible diagnostic test despite its associated morbidity and mortality. A protein-rich lymphocytic exudate that is often grossly hemorrhagic is a typical finding in the pericardial fluid. However, the TP fluid is paucibacillary and the estimated diagnostic accuracy based on the smear is only 5%\cite{16}. The sensitivity of pericardial fluid culture ranges from 53% to 75\%\cite{17}. However, results are obtained in an average of 3 wk. PCR test for *Mycobacterium tuberculosis* DNA or RNA in pericardial fluid is more accessible and faster, and it has a lower cost than pericardial tissue PCR, but it also has a lower sensitivity (15\% vs 80\% respectively), and can yield up to 20\% false positives\cite{18}. PCR has been very useful since it is capable of identifying different nucleic acid sequences in samples with low bacilli concentrations and in addition, it identifies resistance to rifampicin encoded in the *rpoB* gene, which can be useful in settings where there is a high prevalence of multidrug-resistant TB. Finally, in recent years, the performance of the immunoassay has been studied which quantifies the release of interferon gamma (IFN-γ) (QuantiFERON®, ELISpot) for the diagnosis of pulmonary TB, extrapulmonary TB and latent TB. The sensitivity of pericardial biopsy varies from 10\% to 64\%\cite{19}.

Pericardial ADA levels ≥ 35 U/L are diagnostic of TP with a sensitivity and specificity of 90\% and 74\%, respectively\cite{20}. On the other hand, it has been shown that IFN-γ, which is produced by CD-4 + and CD-8 + T lymphocytes in the context of TP, could be a precise diagnostic biomarker\cite{21}.

Treatment of TP is based on the use of rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 mo, followed by isoniazid and rifampicin (a total of 6 mo of treatment)\cite{22}. The effectiveness of treatment with corticosteroids in TP remains controversial. Steroids have not yet been found to have overwhelming beneficial effects on reabsorption of pericardial effusion or in the progression to constrictive pericarditis\cite{23}.

**CONCLUSION**

TP occurs in 1%-2% of patients with pulmonary TB and carries a high mortality rate. The diagnosis of TP remains difficult due to the absence of a simple, rapid and accessible diagnostic test despite its associated morbidity and mortality. Treatment of TP consists of rifampicin, isoniazid, pyrazinamide,
and ethambutol for 2 mo, followed by isoniazid and rifampicin (total of 6 mo of therapy). Early diagnosis of this entity will allow physicians to initiate timely treatment, avoid complications and improve the patient’s clinical outcome.

FOOTNOTES

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Transileocolic endovascular treatment by a hybrid approach for severe acute portal vein thrombosis with bowel necrosis: Two case reports

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Abstract

BACKGROUND
Acute portal vein thrombosis (PVT) with bowel necrosis is a fatal condition with a 50%-75% mortality rate. This report describes the successful endovascular treatment (EVT) of two patients with severe PVT.

CASE SUMMARY
The first patient was a 22-year-old man who presented with abdominal pain lasting 3 d. The second patient was a 48-year-old man who presented with acute abdominal pain. Following contrast-enhanced computed tomography, both patients were diagnosed with massive PVT extending to the splenic and superior mesenteric veins. Hybrid treatment (simultaneous necrotic bowel resection and EVT) was performed in a hybrid operating room (OR). EVTs, including aspiration thrombectomy, catheter-directed thrombolysis (CDT), and continuous CDT, were performed via the ileocolic vein under laparotomy. The portal veins were patent 4 and 6 mo posttreatment in the 22-year-old and 48-year-old patients, respectively.
CONCLUSION
Hybrid necrotic bowel resection and transileocolic EVT performed in a hybrid OR is effective and safe.

Key Words: Bowel necrosis; Endovascular treatment; Hybrid operating room; Hybrid treatment; Portal vein thrombosis; Transileocolic approach; Case report

INTRODUCTION
Acute portal vein thrombosis (PVT) is a rare condition involving thrombus formation in the portal vein (PV) and its branches. Extension of the thrombus to the splenic vein (SV) and superior mesenteric vein (SMV) may lead to bowel necrosis, which has a reported mortality rate of 50%-75%[1-3]. Although systemic anticoagulation is the standard treatment for PVT, most thrombi (both intra- and extrahepatic) are not sufficiently dissolved using this therapeutic approach[4,5]. Recently, in addition to systemic anticoagulation, endovascular treatments (EVTs), including aspiration thrombectomy (AT) and catheter-directed thrombolysis (CDT), have been reported to be useful for PVT[6]. However, they have yet to be established as recommended treatment strategies for this condition. Additionally, in previous reports of EVT used for PVT, transjugular, transhepatic, or transsplenic approaches to the PV are relatively common, whereas the transileocolic approach under laparotomy is rarely reported[7]. Hybrid treatment [performed in a hybrid operating room (OR)], which consists of simultaneous surgical necrotic bowel resection and thrombus removal by transileocolic EVT, is an ideal treatment for PVT with bowel necrosis. Herein, we report the cases of two patients with PVT extending to the SV and SMV complicated with bowel necrosis. The patients were successfully treated using transileocolic EVT, including AT and CDT, performed in a hybrid OR.

CASE PRESENTATION

Chief complaints
Case 1: A 22-year-old man presented with abdominal pain lasting 3 d.
Case 2: A 48-year-old man presented with acute abdominal pain lasting 1 wk.

History of present illness
Case 1: This man had abdominal pain and visited another hospital but was diagnosed with gastroenteritis and returned home. After that, his symptoms worsened, and he was taken to the emergency room again. He was diagnosed with gastroenteritis by computed tomography and was hospitalized. Melena was observed at night on the same day, and intestinal ischemia was suspected based on contrast-enhanced computed tomography (CECT).

Case 2: This man was admitted to another hospital because of epigastric pain. He was diagnosed with reflux esophagitis and was prescribed an analgesic. He returned home and was followed up. Afterwards, the patient’s abdominal pain and nausea worsened, and he again went to his local hospital. He was referred to our hospital on suspicion of acute peritonitis.
History of past illness
Case 1: The patient had a history of acute pancreatitis.
Case 2: There was no significant past illness.

Personal and family history
There was no significant personal or family history in two patients.

Physical examination
Case 1: The abdomen had diffuse tenderness, with rebound tenderness in the entire area.
Case 2: The abdomen had diffuse distention and tenderness, with rebound tenderness in the entire area.

Laboratory examinations
Case 1: Blood test results were as follows: white blood cell count, 17.7 × 10³/μL; neutrophil count, 86.0%; C-reactive protein (CRP), 9.03 mg/dL; aspartate aminotransferase, 499 U/L; alanine aminotransferase, 575 U/L; creatinine phosphokinase, 2888 U/L; lactate dehydrogenase, 1025 U/L; and lactate, 19 mg/dL.
Case 2: Blood test results were as follows: white blood cell, 18.5 × 10³/μL and CRP, 20.56 mg/dL. Liver function and lactate analyses revealed no abnormal changes.

Imaging examinations
Case 1: CECT showed massive PVT extending to the SV and SMV with non-enhancement of the bowel wall. The intestinal wall was edematous and thickened, accompanied by bloody ascites.
Case 2: CECT showed complete PVT extending to the SMV and SV without contrast medium enhancement in the jejunum walls. The wall of the small intestine was edematous and thickened, and the contrast effect was also diminished. The intestinal wall was edematous and thickened, accompanied by a large amount of ascites.

FINAL DIAGNOSIS
Case 1
The patient’s condition was diagnosed as acute PVT extending to the splenic and SMVs with bowel necrosis.
Case 2
The patient’s condition was diagnosed as severe PVT extending to the splenic and SMVs with bowel necrosis.

TREATMENT
Case 1
A decision was made to perform an emergency hybrid treatment including simultaneous surgical necrotic bowel resection and EVT in a hybrid OR. Under general anesthesia, approximately 340 cm of necrotic bowel, which appeared as irreversible bowel ischemia at the time of laparotomy, was resected from the region between the distal ileum and the proximal jejunum. EVT via the ileocolic vein was performed immediately after the surgery (Figure 1A) over three sessions within a period of 4 d. The blood flow from the main PV to the right PV was completely recovered by the end of the final EVT (Figure 1B).

Case 2
Hybrid treatment was performed in a hybrid OR with the patient under general anesthesia over a total of four sessions of EVT. In the first session, considering that bowel ischemia could be improved by EVT, open abdomen management without resection was adopted. However, the next day, there was no improvement in the ischemic bowel, indicating that the change was irreversible. In the subsequent session, approximately 210 cm of necrotic bowel was resected in total, and the thrombus was removed using the same method as that used in case 1 (Figure 1C). A total of four EVT sessions took place over a period of 5 d. The final angiogram showed good PV flow at the end of the fourth EVT session (Figure 1D).
EVT procedure

During the laparotomy, the ileocolic vein was divided, isolated, and punctured with an 18-G needle (Catheter Introducer; Medikit, Tokyo, Japan). After ligation of the proximal end of the ileocolic vein, a 0.035-in guidewire (Radifocus Guide Wire M; Terumo, Tokyo, Japan) was inserted, and an 8-Fr sheath (Supersheath; Medikit) was inserted. At this point, heparin (5000 U) was administered. A further 1000 U was then administered every hour to keep the activated clotting time within the range of 200-300 s. Next, the 0.035-in guidewire and a 4-Fr guide catheter (GLIDECATH; Terumo) were advanced into the PV, SMV, and SV via the sheath. The 4-Fr guide catheter was then replaced with a 6-Fr catheter (Aspiraircass; Medikit) and an 8-Fr guiding catheter (Launcher; Medtronic, Dublin, Ireland) for the patient in case 1 and the patient in case 2, respectively. Manual AT using these catheters was repeatedly performed. Additionally, to remove the residual thrombus found after AT, CDT using 30000 U of urokinase (Mochida, Tokyo, Japan) for the patient in case 1 and 24000 U for the patient in case 2 was performed via a 5-Fr multiple-side-hole infusion catheter (Fountain Infusion System; Merit Medical, South Jordan, UT) within the same session. This was repeated almost every day for 3 d in the patient in case 1 and for 4 d in the patient in case 2 until peripheral PV circulation was completely restored. During the interval between each session, a 5-Fr sheath (Medikit) and a heparin-coated catheter (Anthron; Toray Medical, Tokyo, Japan) were kept in place within the SMV and PV. Continuous CDT using urokinase was performed via the sheath (120000 U/d) and catheter (240000 U/d) with an open abdomen and continuous negative pressure.

OUTCOME AND FOLLOW-UP

Case 1

After the treatments, an intravenous injection of systemic heparin (20000-50000 U; Mochida) was administered daily for 45 d, while the activated partial thromboplastin time was maintained at 50-60 s.
Heparin was switched to warfarin (Eisai, Tokyo, Japan) 3 mg/d on postfinal EVT Day 40. Although the patient experienced short bowel syndrome, he was discharged 4 mo after the treatment. CECT showed that the patient’s main and right PVs were patent 4 mo after the treatment.

**Case 2**

Heparin (15000 U) was replaced with edoxaban (Daichi-Sankyo, Tokyo, Japan) 60 mg/d on postfinal EVT Day 24. The patient was discharged 33 d after the final EVT. CECT showed that the PV was patent 9 mo after the treatment.

**DISCUSSION**

PVT is a rare condition, with an incidence of approximately 0.7 per 100000 people per year[1]. Acute PVT is even more infrequent and is difficult to diagnose. In this case report, acute PVT was diagnosed as gastroenteritis in one patient and peritonitis in another patient. Thus, infections might have induced three factors of Virchow’s triad, including intravascular vessel wall damage, stasis of flow, and the presence of a hypercoagulable state, and caused PVT[4]. Focusing on risk factors, such as thrombophilia and portal hypertension, may be effective for diagnosing PVT; however, it is difficult to distinguish PVT from enteritis and other ischemic intestinal diseases, such as arterial thrombosis or nonocclusive mesenteric ischemia, based on clinical symptoms without imaging evaluation[4]. Nevertheless, early diagnosis is important because PVT can be quite severe and is associated with a high mortality rate[1-3]. In severe PVT, such as in these cases, venous congestion is initially induced owing to various etiologies. Hemorrhagic infarction then occurs, and arteriovenous obstruction finally leads to bowel necrosis. Yerdel et al[8] classified PVT into four grades of severity (1 to 4), with Grade 4 being the most severe stage, defined as “complete PV and entire SMV thrombosis.” According to their study, the in-hospital mortality of Grade 4 PVT was 50%. In the present case report, both patients had Grade 4 PVT; nonetheless, despite the severity of their conditions and the high associated mortality rate, positive outcomes were achieved using hybrid treatment including necrotic bowel resection and multiple EVT sessions for thrombi until the intrahepatic blood flow became stable.

Although there are no reports that clearly define the treatment endpoint for PVT, we believe that it is important to improve the inflow and outflow systems of the liver. Sharma et al[4] revealed that different treatments were shown according to the etiologies. It is reasonable to monitor conservatively, without anticoagulation, for reversible risk factors such as pancreatitis or abdominal infections in patients with minimal thrombus in PV. In cases of noncirrhotic, nonmalignant, and symptomatic PVT, anticoagulation is recommended. For asymptomatic PVT, especially with extension to the mesenteric veins, nonreversible risk factors, and hypercoagulable states, anticoagulation is reasonable for preventing or reducing symptoms such as abdominal pain, nausea or vomiting, or ischemic complications, including bowel necrosis and portal hypertension-related symptoms. In patients with PVT accompanied by malignancy, anticoagulation is also recommended in the majority of cases. Thrombolysis can be considered in those with thrombus extension or worsening pain while on anticoagulation and in patients with impending or ongoing bowel necrosis owing to thrombosis. For these, anticoagulation is often recommended.

According to the guidelines for PVT treatment[9], systemic anticoagulation is considered the first-line therapy for this condition. However, collective data from retrospective studies show that anticoagulation alone might be insufficient. A report showed that in cases of extensive PVT in which anticoagulation was initiated early and maintained for 6 mo, 50% of patients recanalized completely, 40% did so partially, and 10% did not recanalize at all[6]. This result supports the idea that combining systemic anticoagulation with EVT might be beneficial, especially in cases of imminent bowel infarction. Furthermore, EVT may become the sole effective therapy for PVT in patients with a contraindication to anticoagulation.

Recently, several EVT techniques, including CDT and AT, have been described for acute PVT[6]. Wang et al[10] reported the successful treatment of 12 patients with acute PVT by aspiration combined with CDT. Eight patients achieved complete recanalization, and four patients achieved partial recanalization, which shows that AT combined with CDT was more effective than monotherapy. Kenkoki et al[7] reported a case of successful recanalization of acute extensive PVT by AT and continuous CDT. The present case report involved EVT’s, including AT, CDT, and continuous CDT. Although CDT is effective for acute thrombosis and enhances the efficacy of thrombolitics, it generally takes time and may cause clot migration and hemorrhagic complications[11]. In contrast, high recanalization rates have been achieved using AT, which has frequently allowed for the removal of large sections of thrombus all at once. This reduces the time required for recanalization, is not associated with hemorrhagic risk, and may prevent distal embolization, which is not the case in CDT[11]. Nevertheless, a large sheath is generally required to avoid vessel injury, and this cannot be applied to tortuous vessels.

In terms of the approach to the PV, the percutaneous transeptic, percutaneous transsplenic, and transjugular approaches, including transjugular intrahepatic portosystemic shunt (TIPS), are known, along with the transileocolic approach under laparotomy. The percutaneous approach is the least...
invasive. However, it may increase the risk of bleeding. In one report, out of 46 patients who underwent the percutaneous transsplenic approach, 3 (6.5%) had severe bleeding, and 6 (13%) had mild bleeding [7]. Moreover, although TIPS using covered stents is a common procedure in Europe and the United States when approaching the PV, TIPS has not been allowed by the health insurance system in Japan and is only performed in a limited number of institutions. In the present cases, there were a few reasons for the choice of the transileocolic approach. First, the percutaneous approach would have been difficult to perform because of the large amount of ascites, especially in case 1, and the complete occlusion of the intrahepatic PV. Second, considering that both patients required necrotic bowel resection, it was reasonable to perform EVT under laparotomy. Third, the transileocolic approach is associated with a low risk of bleeding compared with other approaches because the ileocolic vein is punctured under direct observation [12]. Finally, this approach enables the use of larger devices for AT. Therefore, the transileocolic approach is considered a useful method that does not cause serious complications in the short term; however, further research and evaluation of the complications and long-term prognosis of patients is required.

As shown in the present cases, surgery and EVT should be performed in a hybrid OR to optimize the treatment of PVT with bowel necrosis. Indeed, the hybrid OR enabled us to reduce the transfer time from the intervention room to the OR and, consequently, the risks related to this transfer. Moreover, these patients’ abdomens were left open with negative pressure applied during the intervals between EVT sessions. The open abdomen allowed for the bowel condition to be monitored and permitted a sheath to be left with a catheter in the PV during the intervals between EVT sessions. Multiple EVT procedures in combination with an open abdomen enabled us to perform minimal bowel resection while visually observing the condition of the bowel.

CONCLUSION

Herein, two patients with severe acute PVT extending to the SV and SMV with bowel necrosis were successfully treated with EVTs. Overall, hybrid necrotic bowel resection and transileocolic EVT with AT and CDT performed in a hybrid OR were found to be effective and safe.

FOOTNOTES

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Efficacy of EGFR-TKI sequential therapy in patients with EGFR exon 19 insertion-positive non-small-cell lung cancer: A case report

Bin-Bin Shan, Yuan Li, Chang Zhao, Xiao-Qin An, Quan-Mao Zhang

Abstract

BACKGROUND
Insertions in exon 19 in the epidermal growth factor receptor gene (EGFR) is a rarely seen mutation in non-small cell lung cancer. These patients have been effectively treated with sequential EGFR tyrosine kinase inhibitors (TKIs).

CASE SUMMARY
Here, we presented a case of non-small cell lung cancer, stage IIIB, with EGFR exon 19 insertion mutation as detected in the right lower lobe by next-generation sequencing. The patient was sequentially treated with first, second, and third-generation EGFR TKIs after the surgical operation. The overall survival of the patient was 21.3 mo. There was no dynamic analysis of drug resistance mechanisms in targeted therapy.

CONCLUSION
This case emphasized the importance of following the guidelines. In patients with EGFR mutations, repeated and dynamic next-generation sequencing monitoring is necessary to prescribe a personalized treatment plan.

Key Words: Non-small cell lung cancer; Next-generation sequencing; EGFR exon 19 insertion; Afatinib; Case report
Core Tip: We presented a case of non-small cell lung cancer carrying the rare EGFR exon 19 insertion mutation. The patient had a good and durable response to afatinib, which provided clinical evidence for the use of afatinib in these patients.

INTRODUCTION

The epidermal growth factor receptor (EGFR), a kind of receptor tyrosine kinase, plays critical roles in the initiation, promotion, and progression of malignant tumors by modulating downstream signaling pathways[1]. It has been documented that EGFR is overexpressed and mutated in several tumors, including non-small cell lung cancer (NSCLC)[2]. Apparently, EGFR serves as an important regulator of lung cancer growth, and overexpression of EGFR symbolizes the advancement of lung cancer, which is correlated with poor prognosis[3]. These characteristics suggest EGFR as a promising molecular target for tumor-specific therapy. EGFR mutations occur primarily in the EGFR tyrosine kinase (EGFR-TK) coding region, the target of EGFR tyrosine kinase inhibitors (TKIs)[4]. In NSCLC, especially lung adenocarcinoma, EGFR mutation is an important indicator for the use of EGFR TKIs. Therefore, the detection of EGFR mutation can facilitate the optimal use of these TKIs. The United States Food and Drug Administration has successively approved several EGFR TKIs as standard treatment regimens for NSCLC in first-line treatment. Different EGFR mutants showed different sensitivity to EGFR TKIs.

The most common EGFR mutations are short, in-frame deletions in exon 19 (usually 15 or 18 base pairs) and the exon 21 point mutation L858R and sensitive to the EGFR TKIs[5]. Other EGFR mutations are rare and respond differently to EGFR TKIs. Among these, EGFR exon 20 insertion mutation and T790M mutation are related to drug resistance. G719X, E709K, S768I are reported as moderate sensitive mutations[6]. The EGFR exon19 insertion mutation is also rare and accounts for only 0.11% of all lung cancer patients and 0.23% of EGFR mutation patients in the East Asian population[7]. Studies and case reports have shown that first-generation EGFR TKIs are effective in lung adenocarcinoma patients with EGFR exon 19 insertion. In contrast, second-generation afatinib has limited reports concerning this mutation[8].

Herein, we presented a NSCLC case carrying the rare EGFR exon 19 insertion mutation. The patient had a good and durable response to afatinib, which provides clinical evidence for the use of afatinib in these patients.

CASE PRESENTATION

Chief complaints
In this study, a 63-year-old Chinese male (45 pack year history) presented with chest pain for several days.

History of present illness
Patients a had history of chest pain.

History of past illness
Healthy.

Personal and family history
Patient had a long history of heavy smoking.

Physical examination
One month later, the patient underwent right lower lobectomy, right upper lobe wedge resection, and mediastinal lymphadenectomy under general anesthesia. Postoperative pathology suggested that patient had a T4N2M0 (stage IIIB) right lung adenocarcinoma with a positive surgical margin.
Laboratory examinations
Next-generation sequencing (NGS) was performed to identify the targeted mutations and identified an EGFR exon 19 insertion mutation.

Imaging examinations
Chest computed tomography (CT) revealed a ground-glass nodule in the right upper lobe (about 2 cm × 1.5 cm), a nodular soft tissue density (about 2.02 cm × 2.7 cm) in the right lower lobe, and the presence of multiple lymph nodes in mediastinal space (Figure 1).

FINAL DIAGNOSIS
After 1 mo, the patient received Gefitinib, a first-generation EGFR-TKI at a dose rate of 250 mg per day. Four months later, the patient visited again with chest and back pain. The patient underwent preoperative examination, and results showed no distant metastasis, as diagnosed by magnetic resonance imaging, abdominal ultrasound, and full-body bone scan. However, chest CT showed a postoperative change in the right lung. Meanwhile, bone scan showed multiple metastasis bone lesions of the sternum and the left seventh rib (Figure 1). The patient presented with recurrent postoperative metastasis with disease-free survival of 4 mo.

TREATMENT
Since the diagnosis of the recurrent metastasis, afatinib 30 mg p.o. daily was started to achieve the symptomatic control of the chest pain. After 8 mo, patient showed slow progression of the right upper lobe lesion (Figure 1). Due to the elevated tumor marker, carcinoembryonic antigen, a second NGS-based genetic testing of 73 cancer-related genes was performed on the patient’s peripheral blood sample (Geneplus-Beijing Ltd., Beijing, China) to identify possible causes and potentially targeted mutations. The test revealed a somatic EGFR exon 19 insertion (NM_005228.3, c.2214_2231dupTAAAATTCCCGTCGCTAT, p.I740_K745dup) (Figure 2), which was identical to the mutation previously detected in the lung cancer samples. The NGS results suggest that afatinib was the best treatment to follow. Therefore, the patient continued to receive oral afatinib for 5 mo. Adverse reactions, such as skin rashes, nausea, vomiting, and diarrhea, were noted during the afatinib treatment course, which were treated symptomatically. Meanwhile, the patient reported the onset of acute sharp chest pain. Chest CT showed multiple bands in both lungs and a right pleural effusion (Figure 1). It is noteworthy that, initially, pleural effusion was slowly elevated without distinct clinical symptoms and pleural effusion puncture and drainage. After that, pleural effusion of the patient was augmented with chest depression, shortness of breath, and poor fluid quality, which was manifested as clinical progress. Later, the patient presented with dyspnea and cachexia, indicating clinical progression. The progression-free survival for the patient treated with afatinib was 13.4 mo. The patient, with no clinical improvement, was then switched to oral Osimertinib treatment, a third-generation EGFR-TKI. The three generations of drugs were taken orally instead of pleural effusion puncture and drainage.

OUTCOME AND FOLLOW-UP
The patient passed away after receiving 2 mo of treatment, with overall survival length of 21.3 mo.

DISCUSSION
The insertion mutation in exon 19 in EGFR gene is usually sensitive to targeted therapy[9]. Most patients with this mutation are females with adenocarcinoma who are non-smokers or light smokers. In patients with advanced NSCLC, first-generation EGFR TKIs are often used as the postoperative adjuvant or first-line treatment. The efficacy of TKIs fluctuates from 15.5%-24%[8]. A limited number of studies used the second-generation EGFR TKI, which achieved the best clinical results[9]. The case that we presented in this study is a male patient with a history of heavy smoking, who was treated with sequential EGFR-TKIs treatment. However, the efficacy of the first generation of TKI was only 30% and achieved 4 mo disease-free survival. The second-generation TKI afatinib treatment resulted in progression-free survival of 13.4 mo, which could be contributed to the fact that afatinib is a pan human epidermal growth factor receptor family inhibitor[9]. The last sequential use of Osimertinib treatment lasted 2 mo, and the overall survival was 21.3 mo. So far, this is the first time that Osimertinib was used to treat patient carrying EGFR19 insertion mutation. There are reports that the incidence of rare mutation T790M is low.
Shan BB et al. Efficacy of EGFR-TKI sequential treatment of lung cancer

Figure 1 Treatment course of non-small cell lung cancer with sequential epidermal growth factor receptor tyrosine kinase inhibitor regimen with serial chest computed tomography scanning. June 22, 2018, a nodular density shadow in the lower lobe of the right lung, approximately 2.0 cm × 2.7 cm in size, and a ground-glass shadow in the upper right lung lobe, approximately 2 cm × 1.5 cm in size; August 8, 2018, postoperative changes and pleural effusion in the right lung; December 3, 2018, pleural effusion absorbed in the right lung after targeted therapy; June 13, 2019, encapsulated effusion in the right pleural cavity; December 3, 2019, encapsulated effusion increasing in the right pleural cavity. EGFR: Epidermal growth factor receptor; TKI: Tyrosine kinase inhibitor; cfDNA: cell free DNA; NGS: Next-generation sequencing.

Figure 2 Next-generation sequencing showed EGFR exon 19 insertion.

after treatment with afatinib[10].

In the course of treatment, the surgical and peripheral blood samples were sent for second-generation sequencing to evaluate the mutations in 73 genes. The sequencing analysis to determine the mutations, including point mutations, small fragment insertions and/or deletions, copy number variations, and known fusion gene variations, are related to tumor occurrence and development. The results showed insertion mutation in exon 19 of EGFR gene. The nucleotide mutation was p.i740 K745dup, which results in the insertion of certain amino acids in the protein encoded by the EGFR gene. Previously, this mutation was not recorded in Catalogue of Somatic Mutations in Cancer and Memorial Sloan Kettering databases[11]. All patients with EGFR exon 19 insertion had amino acid change causing substitution of leucine at residue 747 by proline (L747P). The amino acid sequences of EGFR exon19 insertions reported in the literature include I740_P741insPVAIKI, I740_K745insIPVAIK, I744_K745insKIPVAI, K745_E746insIPVAIK, K745_E746insVPVAIK, and K745_E746insTPVAIK. Among these, the first four forms of mutation cause the same changes in the amino acid sequence. This amino acid change finally activates the tyrosine phosphorylation by binding with ligands. Autophosphorylation promotes downstream signal transduction pathways, including mitogen-activated protein kinase, phosphatidylinositol 3 kinase, and jun N-terminal kinase pathways, which induce cell proliferation and differentiation [12].

The patient reported in the current report had lesions in both right upper and lower lobes, as demonstrated on preoperative chest CT images, and there were ground-glass nodules in both lung lobes. The postoperative pathology of both nodules was adenocarcinoma. Mediastinal lymph nodes were positive. It is unclear whether they are both primary foci or one of them metastasized from the other. The earliest diagnostic criteria for multiple primary lung cancer (MPLC) was reported by Martini
which focused on different tissue types. With the development of molecular pathology, the American Association of Chest Physicians revised the diagnostic criteria of MPLC. The new criteria classified the simultaneous multiple cancers located in different lobes without N2 and N3 lymph node infiltration and without systemic metastasis as MPLC. It also added molecular genetic characteristics. The histological subtype of lung adenocarcinoma is recommended to distinguish MPLC from lung metastasis[14]. There is literature showing that second-generation sequencing can be used to increase the diagnostic accuracy. There is a general consensus among several countries on the treatment of MPLC. However, the surgical treatment is considered as the first choice. Stella et al[15] suggested that surgical treatment should be performed no matter whether the multiple lesions are MPLC or pulmonary metastasis, as long as the lung function is acceptable and there is no lymph node metastasis.

CONCLUSION

In conclusion, we presented a case of lung adenocarcinoma with rare EGFR exon 19 insertion benefitting from afatinib therapy. This case provides unequivocal clinical evidence for the afatinib effectiveness in lung adenocarcinoma patients harboring EGFR exon 19 insertion and also provides evidence that these patients may benefit from EGFR TKIs sequential therapy. The treatment of this case is worth further discussing the importance of following the guidelines and initiating the standardized treatment. On the other hand, in the case of two nodules in different lobes, more molecular diagnosis is required to confirm the origin of the two nodules, which would be helpful for the selection of suitable drugs.

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CASE REPORT

Novel compound heterozygous variants in the TAF6 gene in a patient with Alazami-Yuan syndrome: A case report

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Abstract

BACKGROUND
This case report describes a novel genotypic and phenotypic presentation of Alazami-Yuan syndrome, and contributes to the current knowledge on the condition.

CASE SUMMARY
We report an 11-year-old boy with Alazami-Yuan syndrome. The main clinical manifestations were rapid development of puberty, typical facial features of Cornelia de Lange syndrome, and normal intelligence. Peripheral blood DNA samples obtained from the patient and his parents were sequenced using high-throughput whole-exosome sequencing, which was verified by Sanger sequencing. The results showed that there was a compound heterozygous mutation of c.1052delT and c.76A>T in the TATA-Box Binding Protein Associated Factor 6 (TAF6) gene. The mutation of c.1052delT was from his mother and the mutation of c.76A>T was from his father.

CONCLUSION
This study extends the mutation spectrum of the TAF6 gene, and provides a molecular basis for the etiological diagnosis of Alazami-Yuan syndrome and genetic consultation for the family.

Key Words: Alazami-Yuan syndrome; TAF6; Children; Cornelia de Lange syndrome; Case
Core Tip: We report an 11-year-old boy with Alazami-Yuan syndrome. The main clinical manifestations were rapid development of puberty, typical facial features of Cornelia de Lange syndrome, and normal intelligence. DNA sequencing test showed that there was a compound heterozygous mutation of c.1052delT and c.76A>T in the TATA-Box Binding Protein Associated Factor 6 (TAF6) gene. This study extends the mutation spectrum of the TAF6 gene, and provides a molecular basis for the etiological diagnosis of Alazami-Yuan syndrome and genetic consultation for the family.

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INTRODUCTION
Alazami-Yuan syndrome is an autosomal recessive genetic disease caused by mutation of the TATA-Box Binding Protein Associated Factor 6 (TAF6) gene. Its clinical features are similar to those of Cornelia de Lange syndrome (CdLS). Typical features include short stature, mental retardation, arched eyebrows, conjoined eyebrows, protruding bridge of the nose, nose tilted forward, and a thin upper lip.[1,2] There are differences in the gene mutation site and genetic mode between Alazami-Yuan syndrome and CdLS. CdLS is caused by mutations in Nipped-B-like protein (NIPBL), structural maintenance of chromosomes 1A (SMC1A), SMC3, RAD21, and histone deacetylase 8, and the genetic mode is autosomal dominant inheritance and X-linked dominant inheritance[3].

In this case study, two new mutations of the TAF6 gene were found by high-throughput whole-exosome sequencing in an 11-year-old patient with rapid development of puberty and special facial features.

CASE PRESENTATION

Chief complaints
An 11-year-old male patient was referred to our clinic due to testicular enlargement and rapid growth in height.

History of present illness
The patient presented with testicular enlargement without obvious cause, no pubic hair, no spermatorrhea, and a small amount of beard hair for 6 mo. Peripheral blood DNA samples obtained from the patient and his parents were sequenced using high-throughput whole-exosome sequencing, which was verified by Sanger sequencing.

History of past illness
The patient was the 2.1 kg (< -3sd), 46 cm (< -1sd), and the product of a 36 wk pregnancy born by cesarean section to a gravida 1, para 0-1 mother without a history of asphyxiation and resuscitation. The patient exhibited catch-up growth after birth and no history of feeding difficulties. The physical and mental development of the child at 2-years-old was similar to that of children the same age.

Personal and family history
His non-consanguineous parents were clinically normal. His father and mother were 170 and 151 cm in height, respectively. There was no family history of genetic or infectious diseases.

Physical examination
On physical examination at his visit at 11 years of age, his weight was 52.5 kg and length was 146.1 cm. The patient had a clear mind, good spirit, normal hair, and no yellow coloring or bleeding spots on the skin. He had arched eyebrows, protruding bridge of the nose, forward leaning nostrils, a thin upper lip, a small amount of beard, normal jaw, and an inconspicuous laryngeal knot. Both pupils were equal in
size and were sensitive to light. Breath sounds in both lungs were clear, and dry and moist rales were not heard. Heart sounds were strong and regular, the heart rate was 90 bpm, and no pathological murmur was found in each valve area. The abdomen was soft, no tenderness and rebound pain was observed, the liver and spleen were unpalpable. The big toes on both feet were widened and the limbs were normal. Limb muscle tension was normal. Physiological reflexes were present, and pathological reflexes were not found. Bilateral testes were symmetrical, about 8-10 mL in size, without pubic hair.

**Laboratory examinations**

The patient’s liver function, kidney function, electrolytes, blood glucose and blood lipids were normal. Insulin-like growth factor was normal. Karyotype analysis of cultured cells revealed a karyotype of 46XY. Sex hormone levels were as follows: estradiol 25 pg/mL, (adult male reference value: < 20-47 pg/mL), follicle-stimulating hormone 6.62 mIU/mL (adult male reference value: 1.27-19.26 mIU/mL), luteinizing hormone 3.20 mIU/mL (adult male reference value: 1.24-8.62 mIU/mL), and testosterone 1.75 ng/mL (adult male reference value: 1.75-7.81 ng/mL). Total 25 hydroxy vitamin D was 13.79 ng/mL (reference value < 20 ng/mL vitamin D deficiency). Fasting insulin was 23.1 mU/L (reference value: 2.3-11.8 mU/L). Thyroid function was evaluated as follows: Triiodothyronine 6.84 pmol/L (reference value: 2.63-5.71 pmol/L), thyroxine 12.10 pmol/L (reference value: 9.01-19.05 pmol/L), and thyroid-stimulating hormone 1.9145 μIU/mL (reference value: 0.30-4.80 μIU/mL).

**Imaging examinations**

The patient underwent a skeletal examination, and the results showed that the bone age was 13 years. Magnetic resonance imaging of the pituitary gland was normal. Slight lateral curvature of the thoracic spine was observed.

**High throughput whole-exome sequencing and mitochondrial sequencing**

Informed consent was obtained from the parents on behalf of the proband for whole-exome sequencing, mitochondrial sequencing, and the publication of photographs. DNA was obtained from peripheral blood samples from the patient and his parents. Sequencing and analyses were performed by the Beijing Myogenetics (Beijing, China), which is a high-tech biotechnology company providing life science instruments, reagents and technical services. The second generation sequencer Illumina NextSeq™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, the splices and low-quality data in the sequencing data were removed. Using Burrows-Wheeler Aligner software to compare with the reference genome (hg19 version), the data on sequencing depth, homogeneity, and probe specificity were analyzed. Genome Analysis Toolkit software was used to detect the polymorphic sites in the comparison data of each sample, and statistical analyses of the data on single nucleotide polymorphisms (SNPs) and insertion deletion mutations (indels) were conducted. The SNPs and indels were screened using the database of SNPs, (http://www.ncbi.nlm.nih.gov/SNP), 1000 human genome (http://www.internationalgenome.org), and the Exome Aggregation Consortium database (http://exac.broadinstitute.org). Application of the human gene mutation database (HGMD, http://www.hgmd.cf.ac.uk) and the human Online Mendelian genetic database (OMIM, http://omim.org) confirmed the reported pathogenic gene locus. The effects of variation on protein structure and pathogenicity were predicted by Rev, Polyphen-2, and Sift. The American College of Medical Genetics and Genomics (ACMG) sequence variation interpretation standards and guidelines[4] were used for a comprehensive evaluation of the pathogenicity of mutation sites.

**Gene detection results and pathogenicity analysis**

Whole-exome sequencing showed that there was complex heterozygous variation of the TAF6 gene in this patient, one of which was an unreported frameshift mutation c.1052delT (p.I351Tfs*40), which may lead to the loss of gene function; the frequency of the variation in the normal population database is unknown, and is a low-frequency variation; the results of protein function prediction are unknown, and are not reported in the HGMD database. According to Sanger sequencing, the variation originated from the child’s mother, and the paternal gene was wild-type (Figure 1). According to ACMG guidelines, the mutation was suspected to be pathogenic.

The other was a missense mutation c.76A>T(p.M26L), which has not been reported. This missense mutation showed 76 nucleotide deficiency changes from adenine to thymine, resulting in the 26 amino acids changing from methionine to leucine. The frequency of the mutation in the normal population database is 0.0014, and is a low-frequency mutation; the results of protein function prediction are unknown, and are not reported in the HGMD database. According to Sanger sequencing, the variation originated from the child’s father, and the maternal gene was wild-type (Figure 1). According to ACMG guidelines, the clinical significance of the variation is unknown.
Lin SZ et al. TAF6 variant causes Alazami-Yuan syndrome

Figure 1 Sanger sequencing of the TATA-Box Binding Protein Associated Factor 6 gene in the patient and his parents. A: Compound heterozygote of c.1052delT and c.76A>T in the TATA-Box Binding Protein Associated Factor 6 gene in the patient; B: The mother of the patient is a c.1052delT mutation carrier; C: The father of the patient is a c.76A>T mutation carrier.

FINAL DIAGNOSIS
Sanger sequencing showed that there was a compound heterozygous mutation of c.1052delT and c.76A>T in the TAF6 gene.

TREATMENT
According to the clinical manifestations, laboratory tests, and gene sequencing results, the clinical phenotype of the patient was Alazami-Yuan syndrome. The boy’s weight was above the normal range, and he was given exercise and diet guidance. The patient’s total 25 hydroxy vitamin D level was low, and vitamin D 2000 U was administered once a day for 3 mo, and calcium carbonate 500 mg once a day for 3 mo. To improve the final height of the child, 3.75 mg of diphereline was injected once every 28 d, and 10 U recombinant human growth hormone was injected sub-cutaneously every night.

OUTCOME AND FOLLOW-UP
After 4 mo of treatment, the child’s height increased by 3.6 cm, his weight decreased by 0.7 kg, and the vitamin D level returned to normal. During treatment, skin at the injection site was good, fasting blood glucose and nail function were normal, and there was no eyelid edema, headache, or other adverse reactions.

DISCUSSION
The TAF6 gene is located on chromosome 7q22.1, which is involved in the initiation and activation of
RNA transcription and is closely related to human cell viability[5]. The mutation of TAF6 gene can lead to Alazami-Yuan syndrome. In published cases, 5 patients from two families have been reported. Their parents were consanguineous, and the mutation types were homozygous mutations, with mutation locations at c.136c>T and c.212t>C[1,2]. The clinical manifestations of these patients were similar, with short stature, mental retardation, and typical facial features of CdLS. We report a case of compound heterozygous mutation in which the parents were non-consanguineous and the mutation location was c.1052deT and c.76A>T. The main clinical manifestations were rapid puberty and special body surface characteristics, including arched eyebrows, protruding nose bridge, forward leaning nose, thin upper lip and widened big toes on both feet. The child had normal intelligence and was born small for gestational age, but had no history of feeding difficulties. Growth and development before puberty were basically normal.

CdLS (OMIM: 122470) is a type of multiple congenital dysplasia. Patients usually have physiological, cognitive and behavioral characteristics[6]. According to previous case reports, CdLS1 caused by gene mutation of NIPBL accounts for about 50% to 60% of CdLS cases[7]. A large number of individuals with typical CdLS carry a mosaic NIPBL variation[8]. Although individuals with typical CdLS phenotypes are likely to have mutations in NIPBL, individuals with one of the other pathogenic CdLS genes can also meet the standard for typical CdLS[9-14]. Typical CdLS has a unique craniofacial appearance and growth pattern, as well as limb deformities. However, not all CdLS patients show typical phenotypes, and there are differences in the manifestations of the disease itself, from mild to severe, and the degree of facial and limb involvement is also different[15]. In this report, although the patient had typical facial features of CdLS, he had a unique clinical phenotype and gene mutation sites, which has practical significance for in-depth research and clinical guidance.

The patient first attended hospital due to enlarged testicles for 6 mo. His bone age was 2 years older than his actual age, and puberty developed rapidly. In order to improve the final height of this patient, he was treated with the combination of diphereline and recombinant human growth hormone. The patient’s special facial features were similar to those of CdLS which attracted our attention at his first visit, but the patient had no mental retardation or language deficiency. In order to determine the cause of the disease, we used high-throughput whole-exome sequencing and identified a compound heterozygous mutation of the TAF6 gene. Most patients with CdLS have new mutations, and the risk of their parents having another CdLS child is low. In this case, the two mutated genes were from the father and mother, respectively. The probability of the parents having a child with Alazami-Yuan syndrome was 25%, and the probability of carrying the pathogenic gene in a subsequent child was 50%. It is suggested that prenatal consultation and diagnosis should be carried out if the child’s mother has subsequent pregnancies.

CONCLUSION

Herein, the rapid development of puberty and older bone age were defined for the first time in the TAF6-related phenotype. We suggest that TAF6 should be considered in individuals with rapid development of puberty and CdLS-overlapping features. Furthermore, our patient was found to be a compound heterozygote for two novel pathogenic variants in TAF6. Identification of a compound heterozygote should encourage clinicians to consider Alazami-Yuan syndrome in patients with similar clinical features and without a family history of consanguinity.

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FOOTNOTES

Author contributions: Lin SZ and Feng JH collected and analyzed all clinical data and wrote the manuscript; Sun LP participated in collation of the literature and the chart research; Ma HW was involved in the genetic diagnosis and treatment of the patients; Lin SZ, JF, Wang WQ, and Li JY substantially participated in drafting and revising the manuscript for important intellectual content; all authors involved have read and approved the final manuscript.

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Lin SZ et al. TAF6 variant causes Alazami-Yuan syndrome


Asymmetric limb weakness in Guillain-Barré syndrome: Three case reports

Ming Hu, Xiang Li, Hiu Yi Wong, Xun-Gang Feng, Yu-Zhong Wang, Guo-Rong Zhang

BACKGROUND
Guillain-Barré syndrome (GBS) is an autoimmune-mediated peripheral neuropathy characterized by symmetric weakness. Asymmetric weakness in GBS is uncommon and may be easily confused with other differential diagnoses. We herein present three cases of asymmetric GBS and review the literature on this atypical subtype of GBS in order to describe the characteristics of asymmetric GBS and to provide experience for clinicians.

CASE SUMMARY
Different from patients in the previous reports, our patients showed persistent asymmetric limb weakness from the onset to recovery phase. All three patients were serologically positive for antecedent infections. Two of the three cases had IgG antibodies against ganglioside GM1. Two patients received immunotherapy including intravenous immunoglobulin and plasma exchange, while one patient received only supportive treatment. Autoantibodies against gangliosides, asymmetry of congenital development of blood-nerve barrier and limb use may contribute to the development of asymmetric limb weakness in GBS.

CONCLUSION
Asymmetric GBS may be a rare clinical variant and should be considered when a patient develops acute and progressive asymmetric limb weakness. The differences in clinical features and prognosis between asymmetric GBS and classic...
GBS deserve further investigation in a large study.

**Key Words:** Guillain-Barré syndrome; Asymmetric limb weakness; Autoantibodies; Blood-nerve barrier; Case report

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**Core Tip:** Atypical Guillain-Barré syndrome (GBS) with asymmetric limb weakness was rarely reported, which is easily confusing the diagnosis by clinicians. We herein present three patients diagnosed as GBS who suffered persistent asymmetric limb weakness from onset to recovery phase, two of which received immunotherapy in timely and had a good prognosis. Asymmetric blood-nerve barrier, ganglioside distribution or limb use may cause asymmetric GBS. To differentiate asymmetric GBS is important for an early treatment, which can lead to a good patient outcome and early recovery.

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**INTRODUCTION**
Guillain-Barré syndrome (GBS) is one of the most common causes of acute flaccid paresis with significant clinical heterogeneity[1]. At disease onset, most patients present with typical features of GBS such as symmetric tetraparesis, while some patients only present with incomplete variants, such as paraparetic or pharyngeal-cervical-brachial forms[2,3]. Recently, some atypical forms, such as asymmetric cranial nerve palsies, have been reported in patients with GBS[4]. However, asymmetric limb weakness in GBS is uncommon and may be confused with other conditions such as stroke. We herein describe three patients diagnosed with GBS who suffered from asymmetric limb weakness, review the literature and hypothesize the possible underlying mechanisms.

**CASE PRESENTATION**

**Chief complaints**

**Case 1:** A 56-year-old male worker presented with distal weakness of right upper and lower limb for five days and distal weakness of left upper and lower limb for two days.

**Case 2:** A 59-year-old male farmer presented with right upper and lower limb weakness for five days and left upper and lower limb weakness for four days.

**Case 3:** A 36-year-old male farmer presented with right upper and lower limb weakness for two days and left upper and lower limb weakness for one day.

**History of present illness**

**Case 1:** The patient had a history of pneumonia two weeks previously. At disease onset, he complained of right distal upper and lower limb weakness, loss of pain and temperature sensation in the right hand and foot, and could not walk independently. Three days later, the limb weakness and numbness extended to the left distal upper and lower limb, which continued to worsen until day 5.

**Case 2:** The patient denied antecedent infections. His clinical symptoms started five days ago with right upper and lower limb weakness, which had been extended to the left upper and lower limb on day 2 after onset. He complained of significant loss of pain and temperature sensation in bilateral hands and feet.

**Case 3:** The patient had a history of gastroenteritis 10 d before the onset of limb weakness. Two days ago, he complained of right upper and lower limb weakness and numbness, which was initially diagnosed with cerebral infarction at another hospital. The following day, his clinical symptoms progressed and the limb weakness and numbness extended to the left right upper and lower limb.
**History of past illness**

The three patients had no particular past history.

**Personal and family history**

The three patients had no particular individual or family history.

**Physical examination**

**Case 1:** The neurological examination revealed normal cranial nerves, 5/5 Medical Research Council (MRC) grade on proximal four limbs, 3/5 MRC on the right distal limb and 4/5 on the left distal limb. The tendon reflex of the four limbs was absent.

**Case 2:** Neurological examination on admission revealed bilateral distal and proximal limb weakness (for the distal, 1/5 MRC on the right and 2/5 MRC on the left; for the proximal, 3/5 MRC on the right and 4/5 on the left). Sensory examinations showed significant loss of pain and temperature sensation in bilateral hands and feet. The tendon reflex of four limbs was absent.

**Case 3:** On admission, neurological examination revealed weakness of both proximal and distal limbs, 3/5 MRC on bilateral proximal, 2/5 MRC on distal upper limbs, 2/5 MRC on the left distal lower limb and 1/5 on the right distal lower limb, deep tendon reflexes were decreased and he had loss of pain and temperature sensation in bilateral hands and feet.

**Laboratory examinations**

**Case 1:** Cerebrospinal fluid (CSF) analysis on day 10 showed normal cell counts (normal range, 0 to 8/mL) and increased protein concentration of 1.421 g/L (normal range, 0 to 0.45 g/L). Serological analysis of IgG antibodies against GM1, GM1b, GalNAc-GD1a, GD1a, GD1b, GQ1b, and GT1a were negative. Serological testing for IgM antibodies against influenza A virus and *Mycoplasma pneumoniae* were positive.

**Case 2:** CSF analysis on day 6 showed normal cell counts and increased protein levels (0.987g/L). IgG antibodies against GM1 were positive. Serological testing for IgM antibodies against influenza A virus was positive.

**Case 3:** CSF analysis showed normal cell counts and increased protein concentration of 0.483 g/L on day 3 after onset. IgG antibodies against GM1 were positive. Serological testing for IgM antibodies against *Campylobacter jejuni* was positive.

**Imaging examinations**

**Case 1:** A nerve conduction study (NCS) on day 10 showed that the distal latencies of the median, ulnar and peroneal nerves were significantly increased, conduction velocities of the median, ulnar and tibial nerves were reduced and there was temporal dispersion of the median and tibial nerves. NCS results suggested demyelination. Magnetic resonance imaging (MRI) of the brain was normal. The spinal MRI was not performed.

**Case 2:** MRI of the spine was normal. He refused to undergo a NCS.

**Case 3:** A NCS on day 3 showed that the amplitudes of the median, ulnar, tibial and peroneal nerves were significantly reduced.

**FINAL DIAGNOSIS**

The three cases were diagnosed with GBS.

**TREATMENT**

**Case 1:** The patient received intravenous immunoglobulin which was initiated on day 10 at 2 g/kg/day for 5 d.

**Case 2:** The patient opted for supportive treatment due to cost.

**Case 3:** He was treated with plasma exchange (PE) every two days.
OUTCOME AND FOLLOW-UP

Case 1: On day 16, his limb weakness and numbness started to improve. On day 17, he was discharged. A follow-up at six months after onset showed 5/5 MRC on proximal four limbs, residual mild weakness of distal upper limbs (5/5 MRC on the left, 4/5 MRC on the right) and lower limbs (4/5 MRC bilateral).

Case 2: His clinical symptoms progressed and reached the nadir on day 9 after onset and he developed urinary retention. The MRC on four proximal limbs was 2/5, left distal limb muscle strength was 1/5 and right distal limb muscle strength was 0/5. The patient was discharged and returned to a local hospital on day 11. Six months later, a follow-up of this patient showed 2/5 MRC on four proximal limbs and 2/5 MRC on the left distal limb and 1 MRC on the right distal limb.

Case 3: His clinical signs showed no response to the first session of PE and symptoms progressed on day 4 after onset. The neurological examination showed 2/5 MRC on the left proximal limb and 3/5 on the right proximal limb, 1/5 MRC on the left and 2/5 MRC on the right distal lower limbs, and 1/5 on distal bilateral lower limbs. His sensory deficits in bilateral feet rose to bilateral legs. PE treatment proceeded as planned. On day 10 after onset, his weakness and numbness started to improve. Following PE, he was transferred to the rehabilitation ward for a course of electrical stimulation and physical rehabilitation. He was discharged on day 28. A follow-up at six months after onset showed asymmetric weakness on upper (4/5 MRC on the right and 3/5 on the left) and lower limbs (3/5 MRC on the right and 2/5 on the left).

DISCUSSION

Typical GBS is a mono-phasic polyneuropathy with acute onset symmetric cranial or limb weakness[5]. Asymmetric deficits, especially asymmetric limb weakness is easily confused with other neurological conditions such as stroke, demyelinating myelopathy, acute-onset chronic inflammatory demyelinating polyneuropathy[6], and beriberi neuropathy[7]. Although a study from Israel reported that asymmetric weakness accounted for 23% of atypical clinical findings of GBS in children[8], atypical GBS in adults with asymmetric limb weakness is rarely reported. Weakness or paresthesia in GBS may begin with symptoms in one limb, but most of the asymmetric symptoms at onset are transient and will progress to symmetric weakness at nadir[9,10]. Chi et al[11] reported a patient with axonal GBS who presented with acute onset of left hemiplegia and left sublingual nerve palsy mimicking stroke, of which the hemiplegia further progressed to tetraparesis within a few days. A Dutch study reported four patients who had asymmetric GBS[12], and three of these patients progressed to symmetric GBS within one week. Being different, both the case presented by Logullo et al[13] and our patients showed persistent asymmetric limb weakness starting from the acute phase until the recovery phase. In this report, we review the literature and summarize the clinical presentation of asymmetric GBS, including a case reported previously[13] and our cases reported in this paper (Table 1).

Although the exact mechanism of asymmetric deficits in GBS remains unclear, current evidence suggests a potential association between anti-ganglioside antibodies and asymmetric deficits in GBS. Stork et al[14] previously suggested that auto-antibodies against asialo-GM1 were associated with more pronounced motor deficits and asymmetry. Kim and Yuki[15] reported an unusual patient with hemiparetic GBS who had preceding gastroenteritis and anti-GD1a antibodies. In our patients, two out of three had autoantibodies against GM1. Anti-GM1 IgG antibodies binding to the nodal axolemma, which locates the GM1 and voltage-gated sodium channels, leads to the formation of membrane attack complex and disruption of sodium channels, which causes axonal impairment and nerve-conduction failure[16]. Binding of circulating antibodies onto the peripheral nerve myelin or axolemma relies on a rich blood supply and discontinuity of the blood-nerve barrier (BNB). Generally, the BNB along the nerve fiber is inhomogeneous and the distal and proximal are selectively more vulnerable to injury[17]. Manousakis et al[18] reported a patient with melanoma who developed multifocal and asymmetric polyradiculoneuropathy after ipilimumab treatment. The asymmetry of congenital development of BNB including the vascular endothelium permeability or asymmetric disruption of the BNB may be one of the underlying mechanisms leading to asymmetric limb weakness in GBS and antibodies-related peripheral neuropathy. Furthermore, the asymmetric distribution of the gangliosides may also cause the difference in limb involvement on both sides of patients with GBS. Finally, body position or limb use has also been suggested as a possible cause, which influences the initial distribution of weakness during crucial moments of influx of inflammatory factors into nerves[19]. All of our three patients were right-handed and their first clinical presentation at onset was all right-sided weakness. At nadir, the first two patients had more serious limb weakness on the right while the third patient had more serious limb weakness on the left. Our cases suggest a possible correlation between limb use and asymmetric GBS, which deserves further investigation.
Table 1 Clinical features of patients with asymmetric Guillain-Barré syndrome

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Case 1</td>
<td>Case 1</td>
</tr>
<tr>
<td><strong>Age (yr)/sex</strong></td>
<td>14/M</td>
<td>56/M</td>
</tr>
<tr>
<td><strong>Antecedent illness</strong></td>
<td>Gastroenteritis</td>
<td>Pneumonia</td>
</tr>
<tr>
<td><strong>At entry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GBS disability score</strong></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>MRC sum-score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left limb weakness</strong></td>
<td>NA</td>
<td>26</td>
</tr>
<tr>
<td><strong>Right limb weakness</strong></td>
<td>NA</td>
<td>22</td>
</tr>
<tr>
<td><strong>Sensory deficits</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Tendon reflex</strong></td>
<td>Normal</td>
<td>Areflexia</td>
</tr>
<tr>
<td><strong>Bulbar palsy</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Ataxia</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cranial nerve involvement</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Albuminocytological dissociation in CSF</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Cerebral magnetic resonance imaging</strong></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>IgG antibodies to</strong></td>
<td>GM1</td>
<td></td>
</tr>
<tr>
<td><strong>Nerve conduction studies</strong></td>
<td>Axonal</td>
<td>Demyelination</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>IVIg</td>
<td>IVIg</td>
</tr>
<tr>
<td><strong>At nadir</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Days between onset and nadir</strong></td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td><strong>GBS disability score</strong></td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>MRC sum-score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left limb weakness</strong></td>
<td>NA</td>
<td>26</td>
</tr>
<tr>
<td><strong>Right limb weakness</strong></td>
<td>NA</td>
<td>22</td>
</tr>
<tr>
<td><strong>Sensory deficits</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Tendon reflex</strong></td>
<td>Areflexia</td>
<td>Areflexia</td>
</tr>
<tr>
<td><strong>At six months after onset</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GBS disability score</strong></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>MRC sum-score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left limb weakness</strong></td>
<td>NA</td>
<td>29</td>
</tr>
<tr>
<td><strong>Right limb weakness</strong></td>
<td>NA</td>
<td>26</td>
</tr>
<tr>
<td><strong>Sensory deficits</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Tendon reflex</strong></td>
<td>NA</td>
<td>Hyporeflexia</td>
</tr>
</tbody>
</table>

GBS: Guillain-Barré syndrome; MRC: Medical Research Council; CSF: Cerebrospinal fluid; IVIg: Intravenous immunoglobulin; PE: Plasma exchange; ST: Supportive treatment; NA: Not available.

CONCLUSION

To sum up, asymmetric GBS is challenging the diagnosis criteria of GBS. To differentiate asymmetric GBS, especially the hemiplegia at onset with other similar conditions such as stroke, is important for an early treatment of IVIg or PE, which can lead to a good patient outcome and early recovery. Additionally, further study is necessary to investigate whether asymmetric GBS can be taken as a variant of GBS.
FOOTNOTES

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Modified treatment of knee osteoarthritis complicated with femoral varus deformity: A case report

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Abstract

BACKGROUND
Surgical treatment of knee osteoarthritis (KOA) complicated by extra-articular deformity has always been controversial regardless of whether it is simultaneous or staged. Simultaneous total knee arthroplasty (TKA) combined with supracondylar osteotomy without plate for treatment of KOA complicated by femoral varus deformity has not been reported in the literature.

CASE SUMMARY
A 53-year-old Chinese woman complained of left knee pain for 6 years that worsened for 4 mo during her visit on April 3, 2020, accompanied by instability in walking, which seriously affected quality of life. According to her medical history and preoperative imaging, the patient was diagnosed with left KOA with varus deformity. We used the angular center of rotation principle for osteotomy of the femur deformity and placed a poststabilized femur prosthesis into the knee joint. At the same time, a 13 mm × 130 mm femur extension rod was used instead of a steel plate to fix the end of the femur osteotomy, reducing the possible complications caused by steel plate implantation and reducing the economic burden on patients. The operation successfully solved two major problems of KOA and varus deformity, and the clinical and imaging evaluation of postoperative follow-up were satisfactory.

CONCLUSION
TKA and supracondylar femoral osteotomy can be used for simultaneous KOA treatment and deformity correction.

Key Words: Knee osteoarthritis; Varus deformity; Same-stage; Total knee arthroplasty; Osteotomy; Case report

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Core Tip: Knee osteoarthritis (KOA) with extra-articular deformities is a common disease, but the choice of surgical methods has always been controversial. The use of total knee arthroplasty alone to achieve the purpose of extra-articular osteotomy and treatment of KOA at the same stage has been rarely reported in the literature. After the operation, the varus deformity was well corrected and the force lines of lower extremities were basically aligned. The follow-up results showed that the prosthesis was firmly fixed and the unstable walking function was significantly improved. This method provides a feasible choice for the surgical treatment of KOA with extra-articular deformity.

INTRODUCTION

Knee osteoarthritis (KOA) is a common disease in middle-aged and aged people. The incidence of symptomatic KOA is approximately 8.1%[1]. Pain and walking instability are often the main reasons for patients seeing a doctor. Total knee arthroplasty (TKA) not only effectively relieves pain but also corrects the deformed lower limb line, greatly improving quality of life. However, KOA complicated by extra-articular knee deformity[2], regardless of whether from the femur or tibia, complicates treatment. When TKA is indicated, the extra-articular knee deformity must be taken into account to achieve satisfactory ligament balance. Therefore, osteotomy should be performed as a separate procedure before TKA or during TKA. To our knowledge, descriptions of simultaneous TKA combined with femoral supracondylar osteotomy without plate for the treatment of KOA complicated by femoral varus deformity are rare. This paper discusses such a case in detail.

CASE PRESENTATION

Chief complaints
A 53-year-old Chinese woman complained of left knee pain for 6 years that worsened for 4 mo before her visit on April 3, 2020.

History of present illness
Six years ago, she had left knee pain accompanied by varus deformity of the knee and walking instability, but she did not receive systematic treatment. Four months earlier, the patient’s left knee joint pain and walking instability worsened, seriously affecting her quality of life.

History of past illness
The patient denied any previous medical history of the left knee or surgery.

Personal and family history
The patient had no specific personal or family history.

Physical examination
The following physical metrics were examined: Claudius gait, varus deformity of the left knee, knee varus stress test (+), lateral stress test (-), anterior drawer test (-), hospital for special surgery knee score (HSS) score (46 points, 10 points for pain and 11 points for function).

Laboratory examinations
Laboratory examinations showed no obvious abnormalities.

Imaging examinations
Knee radiographs revealed KOA (Figure 1A). The angle of the lower limbs was measured by long-leg weight-bearing radiography before surgery (Figure 1B), in which the hip–knee–ankle angle was 163°, the mechanical lateral distal femoral angle was 103°, the mechanical proximal medial angle of the tibia was 89.5°, and the varus angle was 17°. The CORA of the left femur was at the level of the upper edge of the patella.
FINAL DIAGNOSIS

Based on the history and preoperative imaging examination, this patient was diagnosed with left KOA complicated by femoral varus deformity.

TREATMENT

Surgical plans were made to treat the KOA and correct the varus deformity by simultaneous TKA and femoral osteotomy to achieve an optimal surgical effect.

During surgery, the anterior median incision of the left knee joint was chosen to open the joint capsule, release the medial tissue to the upper part of the medial tibia foot insertion point, and release the posterior medial angle to the posterior joint capsule. Osteotomy was performed on the femoral condyle according to the preoperative plan. At the level of the upper edge of the patella on the femoral condyle, a 2.5-mm Kirschner wire was drilled from the inside out along the direction parallel to the articular surface of the distal femur. Next, another 2.5-mm Kirschner wire was drilled diagonally along the 15° valgus angle of the previous Kirschner wire. Finally, the two wires were intersected in the medial femoral bone cortex. The 15° wedge was removed along the direction of the Kirschner wire using a pendulum saw (Figure 2A). The bilateral osteotomy ends were reduced, and the other two Kirschner wires were inserted diagonally through the inner and outer parts of the femoral condyle for temporary fixation. The varus deformity of the knee joint was corrected, and the line of gravity of the lower limb was restored satisfactorily (Figure 2B). TKA was performed after completion of orthopedic surgery. An intramedullary fixation system was used for the distal femur. The medullary cavity was drilled from a position 0.5 cm anterior to the attachment point of the posterior cruciate ligament in the intercondylar fossa. A T-shaped rod was inserted, and an osteotomy device was installed setting at 5° valgus. The distal femur osteotomy thickness was approximately 9 mm. Anteroposterior condylar osteotomy (external rotation of 3°) and anteroposterior oblique osteotomy were performed, and the medullary cavity was re-expanded to ensure that the 13-mm extension rod could enter. The proximal tibia was fitted with an extramedullary positioning system, and the osteotomy was kept perpendicular to the tibial force line. The lowest point of the tibial plateau was taken as the reference. The osteotomy angle was tilted backward 5°, and the osteotomy thickness of the tibia was 2 mm. The knee joint was straightened, and then a 10-mm gap measuring block was inserted to measure the extension and flexion gaps. The medial and lateral collateral ligaments and the posteromedial angle were released to ensure the balance of the extension and flexion gaps, and the medullary cavity was also expanded to ensure the entry of the 13-mm extension rod. After reaming on both sides, cement was placed, and the joint prosthesis was implanted. Based on previous tests, a femoral extension rod of 130 mm was found to be the most effective for fixation of femoral osteotomy ends. A posterior stabilized femoral prosthesis (PFC), a 13 mm × 130 mm femoral extender rod, a 10-mm tibial spacer, a tibial platform (PFC) SZ 3, and a 13 mm × 60 mm tibial extender rod (DePuy Orthopaedics) were installed. After reduction, it was tested again to confirm that the line of gravity of the lower limb, the inner and outer soft tissue and the patellar movement trajectory were satisfactory, and femoral osteotomy ends at the orthodontic place were firmly fixed.
**OUTCOME AND FOLLOW-UP**

After the operation, the patient was in good condition without any discomfort. Postoperative radiographs showed that the prosthesis was in good position and that the varus deformity was corrected (Figure 3A and B). Eight months after the operation, re-examination showed that the prosthesis was firmly fixed and in good position, and the fracture line at the distal femoral osteotomy was blurred (Figure 3C). The patient’s walking instability was significantly improved. The HSS score was 86, including 25 points for pain and 22 for function.

**DISCUSSION**

For advanced KOA, surgery is the most effective treatment. However, for patients with KOA with extra-articular deformities, the choice of surgical approach, especially the corrective osteotomy and total knee replacement as a single-stage or two-stage procedure, remains controversial[3]. The following treatment modalities are usually chosen: (1) Plate fixation after a simple femoral or tibial osteotomy[4,5]; (2) Treatment with TKA (intra-articular compensatory osteotomy); (3) Staged corrective osteotomy and delayed TKA; and (4) Simultaneous total knee replacement combined with plate compression fixation after osteotomy. These four surgical procedures are aimed at a fixed population and all have good clinical outcomes, but there are also some deficiencies. The first modality is appropriate for delaying the patient’s years of joint replacement, but is appropriate for younger patients with less severe OA. The second modality requires asymmetric intra-articular osteotomy and ligament balancing to correct lower extremity force lines, but is limited by the site and severity of deformity, which is often ineffective for severe extra-articular deformities[6]. The third modality prolongs patient hospitalization and recovery time, increases the number of procedures, and also increases the odds of incisional infection and economic burden. The fourth procedure performed better than the previous several, especially for KOA with a deformity angle > 20°, which avoids excessive osteotomy within the joint and restores the lower limb force lines[7,8], but it increases the economic burden as well as the risk of possible consolidation with plate implantation.

From the perspective of patients, a single-stage operation should be a priority. In this case, the preoperative data showed that the patient had a femoral varus deformity[9], and the angle of the deformity was 17°. Although it has been reported that KOA with extra-articular deformities < 20° on the coronal plane can be compensated by increasing intra-articular osteotomy[10], compensatory osteotomy may cause iatrogenic ligament instability. Patients with medial collateral ligament contracture and lateral collateral ligament relaxation need soft tissue release during the operation, which further increases the probability of iatrogenic ligament injury or instability. Therefore, extra-articular osteotomy is considered to correct the deformity. Nha et al[11] pointed out that the incidence of postoperative hinge fracture in single-plane tibial wedge osteotomy is lower than that in double-plane tibial osteotomy. It has also been documented that patients with varus deformity tend to retain residual deformity within 0° ± 3° postoperatively, contributing to functional improvement and increased prosthetic life[12]. Therefore, the upper edge of the supracondylar patella of the femur was selected to maintain a 15° valgus angle for a single-plane wedge osteotomy.

As for the internal fixation method of osteotomy site, there is no significant difference between plate fixation and intramedullary fixation in reoperation rate[13]. However, it has been reported that the extension rod plays a role in the treatment of prosthesis loosening, bone mass difference and fracture morphology, and can improve the stability of periprosthetic fracture revision surgery. Stability provides...
better opportunities for early mobilization and long-term osseointegration\[14\]. The femoral side application of prosthesis extension rods in ensuring length belongs to intramedullary fixation, differing from the eccentric fixation of plates, which guarantees mechanical stability, and allows early functional exercise of patients.

Compared with the two-stage operation, single-stage surgical intervention can reduce the surgical damage to patients, accelerate recovery time, and avoid the risks that secondary anesthesia poses to patients. Meanwhile, using intramedullary fixation with extended rods also avoids a series of internal fixation complications caused by plate fixation applied after osteotomy, as the plates require larger incisions and greater soft tissue destruction, which are unfavorable for bone healing at the osteotomy end. The problem is solved for patients in terms of both clinical efficacy and economic cost. Using TKA alone, which achieves the two purposes of extra-articular osteotomy and KOA treatment, has rarely been reported in previous studies. However, the use of simultaneous TKA with extra-articular osteotomy is technically difficult. It requires the surgeon to be skilled in the techniques involved in knee revision arthroplasty.

This surgical approach has some limitations and cannot be applied to all knee deformities. Precise surgical protocols should be developed based on detailed evaluation of different individual cases. However, this surgical approach provides a feasible choice for the surgical treatment of KOA combined with extra-articular deformities. This is only a preliminary report, and studies with a higher level of evidence must be performed to validate our findings.

CONCLUSION

This is believed to be the first report of simultaneous TKA combined with supracondylar osteotomy without a plate for treatment of KOA complicated by femoral varus deformity. This method reduces the surgical trauma and economic burden of patients, and has a good clinical outcome. This procedure represents a promising option to treat KOA complicated by femoral varus deformity.

FOOTNOTES

Author contributions: Xu SM and Gu GS designed the work. Gu GS, Xu SM, Zhang DB, and Li W performed the surgery; Xu SM, Zhang DB, Li W, and Bi HY performed the data acquisition; Xu SM analyzed and interpreted the patient data; Xu SM was responsible for the primary manuscript generation; Gu GS substantively revised it; all authors read and approved the final manuscript.

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Novel HNF1A gene mutation in maturity-onset diabetes of the young: A case report

Qian Xu, Cheng-Xia Kan, Ning-Ning Hou, Xiao-Dong Sun

**Abstract**

**BACKGROUND**

Maturity-onset diabetes of the young 3 (MODY3), caused by mutations in the HNF1A gene, is the most common subtype of MODY. The diagnosis of MODY3 is critical because a low dose of sulfonylurea agents can achieve glucose control.

**CASE SUMMARY**

We describe a patient with MODY3 involving a novel splicing mutation, in whom low-dose gliclazide was sufficient to control clinically significant hyperglycemia. Sanger sequencing identified a splicing HNF1A mutation in intron 5 at position 24 of chromosome 12, where the base sequence was replaced from G to A, and the protein encoded was changed accordingly. Glycemic control has been maintained without insulin therapy for 28 mo after the diagnosis of diabetes.

**CONCLUSION**

This case report highlights a novel HNF1A gene mutation in MODY3 that is responsive to sulfonylurea therapy.

**Key Words:** Maturity-onset diabetes of the young; Diabetes; HNF1A; Genetics; Case report

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INTRODUCTION

Maturity-onset diabetes of the young (MODY) is the most common single-gene type of diabetes with an early age of onset. MODY often occurs in children or adolescents, beginning with mild symptoms that continue until middle age. The genetic heterogeneity of MODY is responsible for its clinical heterogeneity[1,2]. In total, 15 MODY subtypes have been identified. The most common are hepatocyte nuclear factor 4A (MODY1), glucokinase (MODY2), and HNF1A (MODY3). In patients with MODY3, mutations in HNF1A cause changes in proteins, such as glucose transporter 2, amylin, insulin, and L-pyruvate kinase. These changes are associated with insulin secretion and glucose metabolism[3]. Patients with MODY3 have clinical characteristics of hyperglycemia, including polyuria, polydipsia, and weight loss[4].

Therefore, accurate distinction between MODY3 and other types of diabetes is an important challenge in the diagnosis of MODY[5]. Patients with MODY3 are often initially misdiagnosed with other types of diabetes because the correct MODY3 molecular genetic diagnosis approach is not performed[6,7].

Therefore, early identification of MODY3 is critical for patient treatment.

In the treatment of MODY3, the response of pancreatic β cells to sulfonylurea drugs (SUs) is an important parameter[8-10]. Here, we report a Chinese patient with MODY3 involving a new splice mutation (12q24 NM_000545.5 Intron5 c.1108-1G>A) for whom low-dose gliclazide was sufficient to control clinically significant hyperglycemia[11]. The findings indicate that genetic factors are critical for early-onset diabetes. Our report provides insights regarding genetic diagnosis during the treatment of patients with MODY3.

CASE PRESENTATION

Chief complaints

A 22-year-old Chinese man presented to the Affiliated Hospital of Weifang Medical University for treatment of hyperglycemia. The patient had attended follow-up for 28 mo to undergo blood glucose monitoring.

History of present illness

The patient completed the relevant laboratory and imaging examination on admission. His fasting blood glucose and HbA1C levels were 8.08 mmol/L and 7.2%, respectively. Urine tests were positive for glucose. Insulin and C-peptide release test results were as follows: fasting blood glucose, 7.48 mmol/L; postprandial blood glucose (PBG), 15.94 mmol/L; fasting insulin, 7.16 µIU/mL; fasting C-peptide, 2.89 ng/mL; postprandial insulin (2 h later), 22.13 µIU/mL; C-peptide (2 h later), 4.65 ng/mL. The antibodies results were as follows: Glutamic acid decarboxylase antibody, 2.74U/mL; insulin autoantibody, 0.25 U/mL; tyrosine phosphatases antibody: 0.44 U/mL; zinc transporter 8- antibody was negative.

History of past illness

He had no history of previous illness or diabetic ketoacidosis.

Personal and family history

The patient’s father had been diagnosed with diabetes at the age of 45 years, and two of his aunts had been diagnosed at the ages of 48 and 52 years. Furthermore, his grandmother had been diagnosed with diabetes before her death. Gene sequencing analysis confirmed that the patient and his father had an identical mutation site. The gene mutation was not present in the patient’s mother (Figure 1).

Physical examination

The patient completed the relevant laboratory and imaging examination on admission.

Laboratory examinations

The patient’s characteristics were as follows: Age, 25 years; age at onset, 22 years; duration, 3 years; body mass index (BMI), 24.7 kg/m²; weight, 74 kg; waist circumference, 85 cm; systolic BP, 126 mmHg; total triglycerides, 0.78 mmol/L; LDL, 1.95 mmol/L; HDL, 1.07 mmol/L; VITD-T, 21.38 ng/mL; and TG, 0.78 mmol/L.
Figure 1 Sanger sequencing identified an HNF1A splicing mutation in 12q24 NM_000545.5 Intron5 c.1108-1G>A.

**Imaging examinations**
The ankle-brachial index and somatosensory potential findings were normal. Abdominal ultrasound showed fatty liver (light-medium).

**FINAL DIAGNOSIS**
Comprehensive laboratory and imaging examinations could not exclude the presence of a unique type of diabetes. To clarify the cause of the patient’s clinical manifestations, gene sequencing was performed. Sanger sequencing identified an HNF1A splicing mutation in 12q24 NM_000545.5 Intron5 c.1108-1G>A (Figure 1). This substantially affected mRNA splicing, thus causing the coded protein to become disordered and lose its normal function. To the best of our knowledge, there is no related literature reported in the Human Gene Mutation Database; moreover, this mutation is absent from the ESP6500siv2_ALL, dpSNP147, and Thousand Human Genome (1000g2015aug_ALL) databases.

**TREATMENT**
After admission, the patient was treated with insulin glargine; his blood glucose was controlled within 1 wk. Subsequently, treatment was changed to metformin (0.5 g/d) and saxagliptin (5 mg/d). Two months later, the patient’s Hb1Ac level was 5.5%. The genetic testing results supported a diagnosis of MODY3. Because MODY3 is reportedly sensitive to gliclazide, the patient’s treatment was changed to gliclazide (30 mg/d).

**OUTCOME AND FOLLOW-UP**
The patient’s glycemic control has been excellent (fasting blood glucose, 6 mmol/L; Hb1Ac level, 6%). No hypoglycemia episodes or complications have occurred during the past 28 mo of monitoring.

**DISCUSSION**
Patients with MODY3 require precise therapy. Animal experiments show that HNF-1A gene mutation results in defective insulin secretion through affecting glucose transport, glycolysis and glucose stimulated-ATP production in B cells[12]. SUs can effectively reduce blood glucose in MODY3 patients on ATP-sensitive potassium channels, while metformin is poor effectiveness[13]. This is the main reason why gliclazide can effectively control glucose. Clinical studies have also shown that the level of blood glucose control is significantly better in patients treated with SUs than in patients treated with insulin[2,
An appropriate SU dose is necessary to reduce the incidence of hypoglycemia. Current recommendations for the treatment of patients with MODY3 involve the use of SUs. Shepherd et al. [14] have reported that SUs is critical during MODY3 treatment. If SUs is withdrawn from the diagnosis and treatment plan, glucose deterioration is likely. Notably, our patient showed good blood glucose control when his dose of gliclazide was titrated to 30 mg/d. Diabetes treatment guidelines indicate that the common dose of gliclazide for diabetes treatment can reach 80 mg/d; patients receiving this treatment have a lower risk of hypoglycemia. A study from the United Kingdom showed that medication compliance is not the only influencing factor with respect to SU treatment success. Other important factors include lower glycosylated hemoglobin, lower BMI, and shorter diabetes course [14, 15]. Our patient exhibited typical abdominal obesity and had an irregular diet, which included substantial consumption of soft drinks. He was provided with medical guidance to address this lifestyle consideration. Furthermore, unaffected family members were advised to be vigilant for signs of diabetes. To provide appropriate treatment for affected members, a molecular diagnosis of the mutation is recommended. The prevalence of MODY3 among Asian ethnic groups is considered to be low, there is insufficient information available regarding MODY3.

In this report, we have described a new splice mutation and evaluated its effects. The findings indicate that symptoms in patients with non-autoimmune diabetes should be assessed for common genetic causes to clarify their pathogenesis; the assessment results can be used to guide appropriate genetic counseling and treatment indications. Further accumulation of information regarding MODY3 can aid in the identification of disease patterns, as well as timely diagnosis and treatment.

CONCLUSION

We have described a 25-year-old patient with MODY3, which involved an HNF1A splicing mutation at 12q24. The patient has maintained excellent diabetes control with low-dose SU treatment. To the best of our knowledge, this is the first report of a new gene mutation and exceptional response to SU treatment in a patient with MODY3. Our results highlight the need for genetic diagnosis, particularly in patients with early-onset diabetes.

FOOTNOTES

Author contributions: Xu Q and Kan CX contributed to the data curation, investigation, writing-original draft preparation; Hou NN contributed to the methodology, investigation, writing-reviewing and editing; Sun XD contributed to the supervision, writing-reviewing and editing, funding acquisition.

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Cerebral corridor creator for resection of trigone ventricular tumors: Two case reports

Xing-Wu Liu, Wei-Rong Lu, Tian-Yi Zhang, Xu-Sheng Hou, Zhi-Qiang Fa, Shi-Zhong Zhang

Abstract

BACKGROUND

Resection of deep intracranial tumors requires significant brain retraction, which frequently causes brain damage. In particular, tumor in the trigone of the lateral ventricular presents a surgical challenge due to its inaccessible location and intricate adjacent relationships with essential structures such as the optic radiation (OR) fibers. New brain retraction systems have been developed to minimize retraction-associated injury. To date, there is little evidence supporting the superiority of any retraction system in preserving the white matter tract integrity. This report illustrates the initial surgical excision in two patients using a new retraction system termed the cerebral corridor creator (CCC) and demonstrates its advantage in protecting OR fibers.

CASE SUMMARY

We report two patients with nonspecific symptoms, who had trigone ventricular lesions that involved the neighboring OR identified on preoperative diffusion tensor imaging (DTI). Both patients underwent successful surgical excision using the CCC. Total tumor removal was achieved without additional neurological...
deficit. DTI showed that the OR fibers were preserved along the surgical field. Preoperative symptoms were alleviated immediately after surgery. Clinical outcomes were improved according to the Glasgow-Outcome-Scale and Activity-of-Daily-Living Scale assessments.

CONCLUSION
In the two cases, the CCC was a safe and useful tool for creating access to the deep trigonal area while preserving the white matter tract integrity. The CCC is thus a promising alternative brain retractor.

Key Words: Cerebral corridor creators; Minimally invasive technique; Brain tumor; Optic radiation; Trigone of the lateral ventricle; Case report

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Core Tip: The cerebral corridor creator (CCC) is a specially designed surgical tool set containing a balloon catheter and a transparent tubular retractor. The balloon is made of natural latex and can gently open up the brain tissue with minimum fluctuations in intracranial pressure and creates a surgical corridor by gradually inflating and deflating, thereby reducing damage to the incised cortical tissue and deep white matter tracts. The transparent tubular retractor provides a clear view of the trigonal area and surrounding brain tissue, helps maintain the corridor, protects brain tissue from surgical instrument, and avoids brain tissue collapse during surgery. The CCC provides an innovative and minimally invasive surgical corridor especially for small to medium and deep-seated brain lesions.

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INTRODUCTION
The trigonal area of the lateral ventricle is the predilection site of intraventricular tumors, particularly primary meningiomas[1,2]. Due to the fluid cavity, tumors in this area are usually asymptomatic at the early stage and are considerably large upon diagnosis[3]. To date, complete resection is recommended for the majority of brain tumors. However, the surgical procedures can be challenging, especially for deep brain tumors[4,5]. The lateral ventricular trigone is situated deep within the cerebral hemisphere and is in close proximity to essential neural structures, such as the optic radiation (OR)[6]. The OR spans from the lateral geniculate body to the calcarine cortex and forms the apical wall of the lateral ventricular trigonal area. A common complication is postoperative visual field defect (VFD) due to OR damage[7]. Hence, one big challenge for the neurosurgery community is to create corridors to reach deep-seated tumors and achieve complete tumor resection without causing VFDs.

Conventional neurosurgery operations require brain spatulas to create a corridor for exposure. The brain spatulas are asymmetrically pressed on soft brain tissue, which frequently cause brain damage, especially when multiple brain spatulas are used in continuous retraction[8]. Additionally, brain spatulas may cause ischemia in local normal white matter due to contact pressure[9]. A longer retraction time causes greater risk of white matter injury. Minimally invasive surgery has been proposed to minimize operation-induced brain damage and is associated with lower surgical-related morbidity[10-12].

Minimally invasive techniques, such as tubular retractor systems, are effective and safe for the resection of deep-seated lesions and have shown satisfactory outcomes. Tubular retractors exert even pressure to the surrounding white matter tracts rather than focused retraction pressure, thus decreasing the likelihood of severe brain damage[10,13]. The cerebral corridor creator (CCC) (Shineyard Medical Corp., Shenzhen, Guangdong Province, China) is a tailored tubular retractor which represents an innovative minimally invasive method to create a surgical corridor (Figure 1). The CCC can be used for the removal of deep-seated tumors, blood clots associated with hemorrhages, and foreign matter. Diffusion tensor imaging (DTI) and intra-operative ultrasound enable identification of the best route to the trigonal region with minimal damage to white matter tracts compared with conventional surgical techniques, potentially diminishing morbidity.

We here report the successful resection of lateral ventricular trigonal tumors in two patients using the CCC. We presented our experience of surgical techniques and peri-operative management using this new brain retraction tool.
CASE PRESENTATION

Chief complaints
Case 1: Acute vomiting, headache, and dizziness for 3 d.
Case 2: Headache for 2 mo.

History of present illness
Case 1: The patient was a 63-year-old healthy woman with acute vomiting, and she had headache and dizziness for 3 d. A computed tomography scan at a local hospital revealed an intracranial mass lesion, and she was referred to our institution.
Case 2: The patient was a 53-year-old woman patient who had suffered from headaches for 2 m.

History of past illness
Case 1: The patient had no past medical problems.
Case 2: The patient had a 2-year history of stage IV colon adenocarcinoma, and all tumors were surgically removed.

Physical examination
In both patients, physical examination of the nervous system showed no obvious abnormalities, including visual deficits.

Laboratory examinations
Laboratory evaluation was performed before surgery, and no abnormalities were found in both patients.

Imaging examinations
Preoperative magnetic resonance imaging (MRI) and DTI were performed with a Philips 3.0 T scanner using a standard radio-frequency head coil. Pre-processing was performed using FMRIB Software Library v5.0 (http://www.fmrib.ox.ac.uk/fsl, created by the Analysis Group, FMRIB, Oxford, United Kingdom), as previously reported[14]. Then, diffusion metrics were calculated to obtain each diffusion tensor model and fractional anisotropy results. Following these steps, tract-graphic reconstruction was performed by using Diffusion Toolkit and Track-Vis software (http://www.trackvis.org/dtk/)[15]. The regions of interest of the OR were the lateral geniculate body and the calcarine cortex[16,17]. The reconstructed tracts were also overlaid onto T1-weighted images. Based on preoperative DTI images, surgical trajectories were planned to avoid crossing the OR in the lateral ventricular trigone.

Case 1: MRI revealed a well-defined lesion in the left lateral ventricular trigone with maximum diameter of 16 mm. A benign meningioma was initially suspected (Figure 2A). DTI depicted the close relations between the OR (green) and the lesion (pink, arrow head in Figure 2C). The OR under the tumor had shifted slightly.

Case 2: A heterogeneously ring-enhancing lesion (21 mm × 18 mm) in the left lateral ventricular trigone was found on the brain MRI (Figure 2E). The DTI-reconstructed OR tract was wrapped around the lesion and on its path through and intersecting the tumor (Figure 2G).
Liu XW et al. Cerebral corridor creator in brain tumors

Figure 2 Comparative magnetic resonance imaging and diffusion tensor imaging from the axial plane. A-D: Case 1: Preoperative T1-weighted image demonstrates a lesion in the left lateral ventricular trigone (A); Postoperative T1-weighted image demonstrates total tumor resection (B); Preoperative diffusion tensor imaging (DTI) shows the left optic radiation (OR) wrapped laterally around the tumor (C); Postoperative DTI shows the presence of intact OR adjacent to the tumor cavity was completely resected (D); E-H: Case 2: Preoperative T1-weighted image after Gadolinium contrast administration demonstrates a prominent ring-enhancing lesion in the left lateral ventricular trigone (E); Postoperative T1-weighted image demonstrates total tumor resection (F); Preoperative DTI reveals the left OR with subtle deformation due to tumor mass effect (G); Postoperative surgery: DTI shows the preserved left OR (H).

FINAL DIAGNOSIS

Case 1
Meningothelial meningiomas.

Case 2
Metastatic adenocarcinoma with immunohistochemistry positive staining of cytokeratin, CEA, SATB-2, and Ki-67 (80%).

TREATMENT

Operations were performed under general endotracheal anesthesia. The patient was placed in the prone position with the head fixed toward the opposite side of the tumor. First, a curvilinear skin incision was made, followed by a temporoparietal-occipital mini-craniotomy. The intra-operative ultrasound (ALOKA a7, Japan) was used to localize the lesion, to determine the entry point and to confirm that the entry route was parallel to the major white matter fibers over a non-eloquent gyrus (Figure 3A). The balloon catheter was used to gently puncture the lateral ventricular trigone based on the preoperative images (Figure 3B). After placement of the balloon catheter, saline was injected into the balloon to create an operative corridor from the cortical to the white matter by intermittent dilatation (Figure 3C).

When an adequate corridor was created, the outer tubular retractor was slowly pushed into the well-expanded corridor, and the inner balloon catheter was removed (Figure 3D). When the inner balloon was properly filled and contracted during the pushing process, the tubular plate was easier to insert. The tumor was resected using standard bimanual microsurgical methods under a microscope (Carl Zeiss Shanghai Co. Ltd., China) through the tubular retractor (Figure 3E).

The diameter (15 mm) of the retractor allows satisfactory visualization with sufficient lighting and a three-dimensional view. The direction of the tubular retractor can be gently adjusted to reach the margin areas of the tumor. Routine brain tumor resection techniques, including suction, tissue-biting, and bipolar cautery were used to remove the tumor until the intra-operative gross total resection was achieved. Following tumor resection, meticulous hemostasis was performed by standard bipolar coagulation. The tubular retractor was then gently withdrawn (Figure 3F). When withdrawing the transparent retractor, the surrounding regions were assessed for re-bleeding. The dura, skull, and skin were closed following the standard procedure.
Figure 3 Removal of trigone ventricular tumors using cerebral corridor creator. A: Check the tumor position; B: Puncture balloon catheter; C: Inflate and deflate the balloon; D: Secure the tubular retractor; E: Remove the tumor (details from the surgeon’s view); F: Withdraw the tubular retractor.

Case 1
Minimally invasive surgery with the CCC was performed in this patient. As mentioned earlier, resection was performed using the CCC following routine procedure (Figure 4A-F). The pale-white tumor was easily visualized through the tubular retractor, and the bottom part of the lesion was adherent to the choroidal vessels (Figure 4E and F). The tumor could not be sucked out, bipolar coagulation was used to cut off the blood supply on the surface of the tumor, and then the tumor was removed.

Case 2
The patient underwent surgery using the CCC. The procedure was performed in the same manner as in case 1. After placing the tubular retractor, the lesion was not found in the center of vision field. As the surrounding structures were visible through the transparent tubular wall, we adjusted the angle of the tubular retractor for lesion resection. The lesion was firm with moderate blood supply. After cauterizing the surrounding blood vessels, the lesion was excised.

OUTCOME AND FOLLOW-UP

Case 1
Headache and dizziness resolved after surgery. The patient was discharged at day 6 post-operation without additional deficits. The postoperative MRI scan confirmed no residual tumor except for a small amount of hematoma in the operative area (Figure 2B). Postoperative DTI showed the reconstructed OR (green) from the lateral geniculate body with no distinguishable loss of fibers (Figure 2D). The intact OR could be seen clearly spanning from the surgical field to the occipital lobe.

A neurosurgeon carried out a follow-up on the post-operation outcomes based on the activity-of-daily-living (ADL) scale and the Glasgow Outcome Scale (GOS). Follow-up findings showed that the patient’s ADL score was 85 and GOS grade 4 before discharge. At 1 mo, the ADL score and GOS grade improved to normal levels. At 3-mo follow-up, she was back to normal life. To date, the patient has been observed without further treatment.

Case 2
The patient’s headache resolved immediately after surgery. The 7-d postoperative MRI confirmed the total removal of the tumor and barely showed any sign of the surgical corridor (Figure 2F). Postoperative DTI showed that the OR fibers along the surgical corridor were successfully preserved (Figure 2H).

The patient recovered without additional neurological deficit according to follow-up neurologic examinations. She was discharged on day 7 after surgery with an ADL score of 90 and GOS grade 4. She further underwent standard chemotherapy with Capecitabine (1000 mg twice a day) for 2 wk. One
month after the operation, she resumed all previous activities with ADL score and GOS grade back to normal levels. The patient will be followed up with imaging to evaluate long-term outcome.

**DISCUSSION**

Deep-seated brain lesions (e.g., trigone ventricular tumors) require significant retraction to maintain the surgical corridor open. Traditional retractor systems such as brain spatulas frequently cause severe damage to adjacent normal brain tissue[18]. Exposure of deep-seated brain lesions by brain spatulas has been conducted for decades, although significant retraction-associated complications often occur[9].

Novel brain retraction systems have been developed to minimize brain damage. Based on an experimental study, Shahbabian *et al*[19] reported that a balloon catheter could access the subcortical lesions with minimal disruption of white matter fibers, which was easier and safer than blunt dissection with a metallic instrument. Kelly *et al*[12] proposed the concept of tubular retractor systems with stereotactic craniotomy in the 1980s. For the next 30 years, tubular retractors have been considered an effective technique and revolutionized minimally invasive surgery. Various commercial tubular retractor systems have been developed in recent years, including BrainPath (NICO, Indianapolis, IN, United States), VBAS (ViewSite Brain Access System, Vycor Medical, Boca Raton, FL, United States), and METRx (Minimal Exposure Tubular Retractor System, Medtronic, Memphis, TN, United States)[10, 13, 20-23]. The CCC extends the advantages of existing retractor systems by adding a balloon into the device. The balloon gradually dilates the brain tissue, whereby white fiber tracts are separated, and the dilation process protected by increasing the balloon diameter.

The CCC can be combined with intra-operative ultrasound and DTI to locate the optimal site of incision toward achieving a more precise and less damaging technique. The combination of techniques minimizes the injury during scalp incision and craniotomy, and reduces durotomy size. It has many advantages. For example, it reduces blood loss and operation time, obviates the need for prolonged intensive care unit stay, and reduces the risk of complications such as postoperative pain and postoperative wound infection. The cost of healthcare is reduced, and the patient’s outcome is improved.

Although previous studies have reported that tubular retractor systems provide optimal visualization and decrease the incidence of postoperative complications, no direct evidence has been reported on the preservation of fiber tracts[18]. In previous studies, fiber tracts with fewer functions were selected as invasion paths. However, insufficiency may be mapped to an area simply because of our current lack of anatomical knowledge. Therefore, in the present two cases, we identified the OR fibers in the lateral ventricular trigone using DTI in order to achieve an objective evaluation of the integrity of the white matter fibers. DTI is used for pre-operative evaluation and treatment guidance[20].

By identifying the spatial relationship between tumor and the exact course of the OR, we can significantly improve the preservation of the OR and reduce the risk of postoperative VFD.
Furthermore, DTI can predict the functional outcome by quantitatively assessing the integrity of white matter fibers. Our study demonstrated that the CCC can provide satisfactory protection to the surrounding white matter tracts as indicated by DTI.

Visualization of tumors can be achieved using a microscope or an endoscope. We found that the microscope is preferable to the endoscope in most circumstances. The microscope-assisted approach has several advantages. First, its wider and 3D field of view maintains higher quality visualization. Second and more importantly, the microscope shows the area outside the surgical cavity, whereas the endoscope decreases the scale of movement and results in a narrow work space. Moreover, microscopes facilitate the handling of intra-operative emergencies in a wider operation space. We believe that firmer tumors such as meningiomas and certain gliomas are easier to remove using a microscope. In contrast, soft lesions, such as hematoma, can be removed by suction with the aid of endoscope. Consequently, in our opinion, the firmness and presumed histology of the lesion are two important factors when selecting a suitable viewing device.

CONCLUSION

In this study, we described a novel brain retractor, the CCC, which creates a satisfactory surgical corridor with minimal brain injury. We also depicted the feasibility and advantages of combining the CCC with imaging techniques (intra-operative ultrasound and DTI). Resection in the two patients with lateral ventricle trigonometric tumors was presented as examples. However, evaluation of the CCC in other deep intracranial locations is warranted. Large multi-institutional, randomized clinical trials are needed for clinical implementation of the CCC. Based on our initial experience, patients with other deep intracranial tumors may also benefit from the CCC approach.

FOOTNOTES

Author contributions: Liu XW, Fa ZQ and Zhang SZ designed the study, wrote the manuscript and drew the diagrams; Lu WR contributed to the software and project administration; Zhang TY and Hou XS performed the data analysis and interpretation; and Fa ZQ performed the literature search and edited the manuscript; all authors issued final approval for the version to be submitted.

Informed consent statement: This study (No. 2020-KY-093-01) was approved by the Ethical Committee of the Zhujiang Hospital of Southern Medical University. Informed written consent was obtained from the patients for publication of this report and any accompanying images.

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1921
Left abdominal wall proliferative myositis resection and patch repair: A case report

Ren-Wei Xing, Han-Qiu Nie, Xian-Fei Zhou, Fang-Fang Zhang, Yong-Hua Mou

BACKGROUND
Proliferative myositis is a rare benign tumor that is typically self-limiting and does not become malignant. It can be cured by simple resection without reported recurrence. Due to its rapid growth, hard structure and ill-defined borders, it can however be mistaken for malignant tumors such as sarcomas.

CASE SUMMARY
We investigate the case of a 64-year-old male with proliferative myositis of the abdominal wall, who was preoperatively administered a needle aspiration biopsy and given a simple excision and patch repair. We then compared it with other similar cases to determine the effectiveness of this treatment method.

CONCLUSION
Resection with follow-up observation has shown to be an effective treatment method for proliferative myositis. To avoid unnecessarily extended or destructive resection, a thorough and conclusive diagnosis is crucial, which requires adequate imaging and pathological knowledge.

Key Words: Proliferative myositis; Sarcoma; Abdominal wall; Patch repair; Case report
Core Tip: Proliferative myositis is a rare and self-limiting benign tumor. Although preoperative imaging can identify certain characteristics, it is still difficult to achieve a conclusive diagnosis. Most cases are not diagnosed until after surgical resection. A needle biopsy is helpful in the diagnosis of proliferative myositis, and surgery involving local excision is sufficient. When the resected mass is located in the abdominal wall, local defects can be considered for patch repair. The key to treatment lies in avoiding misdiagnosis as a malignant tumor, resulting in excessive extended resection and corresponding trauma.

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INTRODUCTION
Proliferative myositis (PM) is a rare fibroblastic proliferative disease. It mainly occurs in adults, although cases have also been reported in children[1]. The pathogenesis of the disease is unknown and may be related to previous trauma of the corresponding part of the body. The clinical manifestations are local, rapidly growing masses, most of which have no clinical symptoms but can be painful in some cases. Imaging usually shows unclear capsular masses with fuzzy boundaries and infiltrative growth. The cut surface of surgical specimens reveals fish flesh, which can easily be misdiagnosed as sarcoma or another malignant tumor[2]. This may lead to unnecessary resection or radical surgery to treat these lesions.

PM is, however, a benign lesion with the potential for spontaneous contraction or complete regression. If it can be identified early, no treatment or only a simple resection is required. It is difficult to make a definitive diagnosis prior to surgery. Preoperative B-ultrasound, computed tomography (CT) scans, magnetic resonance imaging, and other imaging examinations as well as needle biopsies are helpful in the evaluation of the lesions, with surgical resection being the choice of treatment for many patients[3,4]. The most common sites of PM are the muscles of the head and neck, the chest wall, the scapula, and the limbs[4,5]. After a literature review, case reports of PM were retrieved from the PubMed and Web of Science databases using the search terms “proliferative myositis” and “abdominal wall,” from 2000 to 2020. There were no matching case reports. Here, we examine a case of a large PM in the left anterior abdominal wall, where patch repair was employed following its resection.

CASE PRESENTATION
Chief complaints
The patient, a 64-year-old male, was admitted to our hospital with a mass on the left anterior abdominal wall that had been present for more than 2 years.

History of present illness
The mass was painless, but it was gradually becoming larger, especially in the preceding 2 mo.

History of past illness
The patient had no previous medical history.

Personal and family history
The patient denied family history.

Physical examination
Physical examination revealed a 70 mm × 90 mm mass that was palpated at the costal margin of the quaternary rib region of the left abdominal wall (Figure 1). The skin above the mass was raised, without pigmentation or abnormal temperature. The mass was hard in texture, had a smooth surface, had no tenderness, poor mobility, and formed an unclear boundary with the surrounding tissues.

Laboratory examinations
Results of the laboratory examination (routine blood) were: white blood cell = 8.4 × 10⁹/L, nitrogen = 64.1%, C-reactive protein = 4.6 mg/L.
Imaging examinations
B-ultrasound examination revealed an 83 mm × 32 mm × 50 mm hypoechoic mass that was seen in the seasonal ribs of the left anterior abdominal wall, with an unclear boundary and uneven internal echo (Figure 2A). Several strong echoes with echo shadows were seen, and the color Doppler flow imaging revealed no definite blood flow. Abdominal, contrast-enhanced CT scans showed a mass in the left anterior abdominal wall: 56 mm (transverse diameter) × 30 mm (width). The CT scan values were 40 Hu, heterogeneous post enhancement, and 72-84 Hu, and the possibility of malignancy could not be excluded (Figure 2B and C).

FINAL DIAGNOSIS
Pathologic puncture findings
The puncture biopsy pathology showed that it was a spindle cell tumor within the left abdominal wall and was considered benign or borderline.

TREATMENT
Subsequently, the tumor was resected together with a small amount of muscle and myometrial tissue that infiltrated the peripheral part. Considering the absence of the muscle layer of the abdominal wall under the costal margin of the left-upper abdomen, patch repair and reinforcement was conducted to avoid an abdominal wall hernia (Figure 3). The gross pathological examination showed that the transverse section of the mass was gray-white and light yellow (Figure 4A). Microscopically, the tumor was composed of spindle cells and focally expressed ganglion-like cells (Figure 4B), which have a checkerboard-like structure (Figure 4C). Combining the morphological and immunohistochemical pathology resulted in it being considered PM. The results of the immunohistochemistry were as follows (Figure 4D-F): Vimentin (+), Smooth muscle actin (+), Desmin (partial +), S100 (partial +), cytokeratin (wide) (-), Ki67 (< 1% +), CD34 (-), CD68 (-/+), CD99 (-), and B-cell lymphoma-2 (-).

OUTCOME AND FOLLOW-UP
A follow-up was done with the patient after 31 mo. The incision healed well, with no local recurrence of the mass and no occurrence of an abdominal hernia.

DISCUSSION
PM was first described by Kern[6] in 1960. It is a rare benign tumor with unknown pathogenesis. While local trauma may be an important trigger[7], other theories include ischemia, paracrine myopathy, etc[8]. It mostly presents clinically as a mass that grows rapidly, may be accompanied by pain, and typically forms a sarcoma-like infiltrative border. It therefore results in a high misdiagnosis rate.
Figure 2 Imaging findings of the mass. A: The ultrasound showed that the tumor was a hypoechoic mass with an unclear boundary and an uneven internal echo (length 83 mm, and width 31 mm); B: Computed tomography (CT) scans showed inhomogeneous low contrast enhancement after injection of the contrast agent; C: The sagittal reconstruction of CT scans showed a solid space occupying the left anterior abdominal wall.

Figure 3 Resection of the mass (left position). A: The removed mass and defect of the abdominal wall; B: The defect repaired with a patch.

clinically, with malignant tumors often suggested as the initial diagnosis[2-5,9].

We summarized two articles on a total of 66 patients (Table 1), of which 33 PM patients were reported in earlier literature by Enzinger and Dulcey[5] and 33 from Trerattanavong et al[9], all from 2000 to 2018 retrieved from the PubMed and Web of Science databases. In these 66 cases, it can be seen that there are slightly more males than females, adults over 45-years-old account for the majority, the location of the mass is relatively common in the skeletal muscles of the upper extremities, the size of the mass is mostly less than 3 cm, and surgical resection was chosen in early-stage cases. Eleven earlier cases in the Enzinger and Dulcey[5] report underwent extended resection because they were misdiagnosed as rhabdomyosarcoma. After the year 2000, the advancement of techniques such as needle biopsy allowed patients to choose observation for follow-up; 11 of the 13 cases resolved spontaneously and 2 cases showed no obvious change No recurrence was reported in any case after elective resection.

Imaging is an essential step following appropriate medical history assessment and physical examination. B-scans show a mass that appears as a strip-like hypoechoic pattern between the inter- and intraphases of hyperechogenicity. Blood flow signals can be seen within, with relatively normal muscle fascicles. A transverse section shows the characteristic “glans dorsum or scitic soil like pattern”[10]. CT scans show a poorly demarcated intramuscular lesion that appears isointense or hypointense compared to surrounding muscle. Homogeneous or heterogeneous enhancement may be demonstrated after the injection of a contrast medium, but enhancement may not be detectable in some cases[11]. Magnetic resonance images with a low or isointense T1 signal compared with surrounding muscle tissue show a T2-weighted magnetic resonance that appears as a hyperintense soft tissue mass[3,11,12].

In most cases, PM is still difficult to clearly identify in laboratory tests and imaging studies, and a fine-needle aspiration biopsy may be helpful for further diagnosis[13,14]. Trerattanavong et al[9] reviewed 33 cases of PM where a definitive diagnosis was based on the occurrence of spindle-shaped fibrocytes admixed with giant ganglion-like cells on biopsy. Malhotra et al[15] considered the cytological diagnosis of PM based on the presence of a polymorphic population consisting of three cellular components: nonlesional skeletal muscle fibers, lesional myofibroblasts, and a ganglion cell-like component. The aspirate is similar to nodular fasciitis. However, PM differs from nodular fasciitis in...
### Table 1 A review of 66 cases of proliferative myositis

<table>
<thead>
<tr>
<th>Sex</th>
<th>Enzinger and Dulcey[5], 1967 (33 cases)</th>
<th>Trerattanavong et al[9], 2019 (33 case review)</th>
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<tbody>
<tr>
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<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Age (yr)</td>
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<tr>
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<td>2</td>
</tr>
<tr>
<td>18-45</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>45 +</td>
<td>26</td>
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<tr>
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<td></td>
</tr>
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<td>8</td>
</tr>
<tr>
<td>Trunk</td>
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<td>8</td>
</tr>
<tr>
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<td>17</td>
</tr>
<tr>
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</tr>
<tr>
<td>1 cm &lt; LD ≤ 3 cm</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>3 cm &lt; LD ≤ 5 cm</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>5 cm &lt; LD</td>
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<td>8</td>
</tr>
<tr>
<td>NA</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Excision</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>Wait and see</td>
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<td>13</td>
</tr>
<tr>
<td>NA</td>
<td>4</td>
<td></td>
</tr>
<tr>
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<td>0</td>
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<tr>
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<td>9/16</td>
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<tr>
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<td>3/30</td>
<td>7/16</td>
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<td></td>
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<tr>
<td>No further growth</td>
<td>2/13</td>
<td></td>
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<td>4</td>
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</table>

LD: Largest diameter; NA: Not available.

two ways: proliferating spindle cells are located in the skeletal muscle tissue and giant ganglion-like cells are more abundant[10]. At the same time, PM also had strong similarity to striated myoblasts, but no cytoplasmic cross striations were identified and the nuclear chromatin was fine with a smooth nuclear membrane. These features help exclude rhabdomyosarcoma as a diagnosis[15].

PM is a benign lesion, and some cases experience spontaneous regression[4,5,15,16]. For example, in one case “the local mass had disappeared after a 2 mo follow-up, which was considered PM as result of a fine needle aspiration biopsy of the neck mass”[15]. If a diagnosis can be clearly established preoperatively, close observation and follow-ups are therefore permitted. If the mass causes compression on peripheral organs or causes a large psychological burden affecting the daily life of the patient, surgical resection may be considered[4,7]. Radical resection can, however, be avoided if there are no reports of recurrence or malignant transformation following the initial resection[4,5,8].

During surgery, PM generally appears as a poorly circumscribed mass that forms grey white striated fascicles or scar-like masses between muscle fascicles or as a wedge-shaped, pointed insertion between fascicles, with the base lying within the fascia. The resected specimen can have a fish flesh-like aspect, microscopically resembling proliferative fasciitis except that the lesion mainly involves the striated muscle fascicles and muscle interstitium rather than the muscle fibers themselves. Cross-sections may...
Figure 4 Patient pathology and immunohistochemistry. A: A transverse section of the gross specimen showing fishy flesh; B: The tumor was composed of spindle cells and focally expressed ganglion-like cells (hematoxylin and eosin stained, 20 × magnification); C: The pathological examination showed that the lesion interspersed and grew between the rhabdomyo fibers, forming a checkerboard-like structure, not involving the rhabdomyo fibers themselves, while a large number of lymphocyte infiltrations could be seen locally (hematoxylin and eosin stained, 20 × magnification); D: Vimentin positive (20 × magnification); E: Smooth muscles actin positive (20 × magnification); F: Desmin positive (20 × magnification).

therefore show a checkerboard-like structure dominated by increased active fibroblasts and giant basophilic cells. These cellular and peculiar structural findings may be of value in the diagnosis of PM.

In our patient, preoperative enhanced CT scans suggested malignant lesions, while preoperative puncture pathology suggested benign or borderline possibilities. Therefore, further surgical treatment was provided. At the same time, the literature indicated that the most commonly affected sites were the muscles of the head and neck, chest wall, scapula and extremities, with only resection being performed. However, the case of the 64-year-old male was different because the mass was larger and the partial excision of the muscle layer of the abdominal wall was accompanied by local weakness. Further patch repair was therefore done to improve the strength of the abdominal wall and to avoid the formation of an abdominal wall hernia. There has been no local recurrence or abdominal wall hernia after more than 2 years of postoperative follow-ups.

CONCLUSION

PM is a rare and self-limiting benign tumor. Although preoperative imaging can identify certain characteristics, it is still difficult to achieve a conclusive diagnosis. Most cases are not diagnosed until after surgical resection. A needle biopsy is helpful in the diagnosis of PM, and surgery involving local excision is sufficient. When the resected mass is located in the abdominal wall, problem areas can be considered for patch repair. The key to treatment lies in avoiding misdiagnosis as a malignant tumor, resulting in excessive resection and related trauma.

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FOOTNOTES

Author contributions: Xing RW chaired the surgery and wrote the manuscript; Nie HQ guided the surgery; Zhou XF collected the data and collated the graphs; Zhang FF provided and discussed the pathological findings; Mou YH contributed to the discussion and revision; all authors gave final approval of the submitted version for publication.

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Concurrent ankylosing spondylitis and myelodysplastic syndrome: A case report

Guan-Hua Xu, Jin Lin, Wei-Qian Chen

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Abstract

BACKGROUND
Ankylosing spondylitis (AS) is an autoimmune disease characterized by sacroiliitis and spondylitis, with a few hematological abnormalities. Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell disorders with frequent autoimmune phenomena. The relationship between AS and MDS remains unknown.

CASE SUMMARY
We describe a rare case of concurrent AS and MDS. An 18-year-old man with low back pain and anemia was diagnosed with AS; however, the cause of anemia could not be determined by the first bone marrow examination. He recovered from anemia and the symptoms of AS resolved after treatment with etanercept, glucocorticoid, and blood transfusion, but he developed pancytopenia with an increased myeloblast count (from 2.5% to 9%). Chromosome analysis revealed del(7q) and trisomy 8. Refractory anemia with excess of blasts-1 (RAEB-1)/MDS was confirmed by repeating the bone marrow examination. He became blood transfusion-dependent and received decitabine-based chemotherapy but eventually died.

CONCLUSION
We suspect that AS may be an early autoimmune phenomenon related to MDS. However, a condition of coexistence cannot be excluded.

Key Words: Ankylosing spondylitis; Etanercept; Myelodysplastic syndromes; Sacroiliitis; Case report

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Core Tip: We report a case of simultaneous presentation of ankylosing spondylitis (AS) and myelodysplastic syndrome (MDS). Patients with MDS may have autoimmune manifestations. AS may be an early autoimmune phenomenon associated with MDS; however, the possibility of a coincidence cannot be excluded. Most importantly, AS may cause anemia, but it is usually mild. If a patient with AS presents with severe anemia, it must be diagnosed as a hematopoietic system pathology. Chemotherapy or bone marrow transplantation should be considered for acute leukemia.

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DOI: https://dx.doi.org/10.12998/wjcc.v10.i6.1929

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell disorders characterized by abnormal hematopoiesis and peripheral cytopenia. In some patients, MDS may ultimately transform into acute myeloid leukemia. Bone marrow failure results in transfusion dependence and infection. Autoimmune syndromes often develop in patients with MDS, and various autoimmune phenomena, including acute systemic vasculitis, chronic autoimmune disorders, connective tissue disorders, and asymptomatic immunologic abnormalities, have been reported [1,2]. Evidence shows immune dysregulation in patients with MDS, which may cause autoimmune myelosuppression and immune-mediated cytopenias [3,4].

Ankylosing spondylitis (AS), an autoimmune disease of unknown etiology, is characterized by sacroiliitis and spondylitis, along with few systemic complications and hematological or biochemical abnormalities. Mild anemia has been reported in some patients with AS. However, the concurrence of AS and MDS in the same patient has been rarely described in the literature. The relationship between the two diseases remains unknown, and the therapeutic strategy and prognosis are unclear. This case report of a simultaneous presentation of AS and MDS aims to describe and clarify the relationship between them.

CASE PRESENTATION

Chief complaints
An 18-year-old man complained of intermittent low back pain and fatigue.

History of present illness
In 2008, an 18-year-old man complained of intermittent low back pain with frequent relapses, relieved by non-steroidal anti-inflammatory drugs (NSAIDs). In July 2009, he was admitted to a local hospital due to severe low back pain and fatigue. Initial laboratory evaluation revealed severe anemia (Hb concentration, 40 g/L); increased mean corpuscular volume (MCV; 122.7 fl); mild leucopenia (WBC 3.8 × 10⁹/L); and normal platelet count. His blood folate and vitamin B12 concentrations were slightly decreased. However, he refused to undergo a bone marrow test. He was treated with red blood cell transfusion plus folic acid and vitamin B12; however, his symptoms were not relieved. Subsequently, in August 2009, he was referred to our hematology department for evaluation and further management of the severe anemia. He denied having traveled or being in contact with patients with tuberculosis or other infectious diseases recently. No sexual history was reported. His mother and father were healthy. There was no positive family history.

History of past illness
The patient had no previous disease history.

Personal and family history
No personal and family disease history.

Physical examination
Examination revealed pronounced skin pallor, a body temperature of 38.2 °C, and a pulse rate of 102 bpm. No dysmorphic features were observed.
Laboratory examinations
Hematological tests showed normocytic anemia (Hb 60.7 g/L), normal MCV, and leukocyte and platelet counts. Vitamin B12 and folate levels were increased. The blood reticulocyte count was 2.4%, serum ferritin concentration was 405.2 ng/mL, ESR was 160 mm/h, and C-reactive protein (CRP) concentration was 145.42 mg/L. The Rous test and the direct and indirect antiglobulin Coombs tests were negative. The CD55 and CD95 expression on red blood cells and granulocytes, and lactic dehydrogenase and bilirubin values were normal. Tests for human immunodeficiency virus, syphilis, hepatitis B, hepatitis C, and Parvovirus B19 were negative. Blood bacteria culture and the tuberculin purified protein derivative test were also negative. Bone marrow aspiration revealed hypocellular marrow with single erythroid dysplasia; however, ringed sideroblasts were absent in the sample obtained in August 2009 (Figure 1A). The cytogenetic test was normal. Therefore, a diagnosis of MDS could not be established. The patient received a blood transfusion, NSAIDs, analgesics, and antibiotics (cefuroxime, sulperazone, meropenem, imipenem/cilastatin, and azithromycin). However, the patient still experienced a low-grade fever and pain.

Imaging examinations
Abdominal ultrasonography showed splenomegaly (5.7 cm thickness). Computed tomography (CT) of the chest and the abdominal organs, and magnetic resonance imaging of the thoracic and lumbar vertebrae did not show any abnormalities. Tc-99m bone scintigraphy imaging showed active bone metabolism of the T9-11 and L4 vertebrae, the right sacroiliac joint, and both the knee joints (Figure 2).

MULTIDISCIPLINARY EXPERT CONSULTATION
On the advice of rheumatologists, the patient was referred to the rheumatology department for further evaluation. The patient had a 1-year history of low back pain, which was especially painful at night when turning over. He had morning stiffness of the back and hip, swelling, and tenderness in the right knee. Physical examination revealed that the range of motion of the lumbar spine was limited; however, no enthesitis or uveitis was noted. Patrick’s maneuver elicited pain in the right sacroiliac joint. HLA-B27 was positive, and pelvis X-ray showed bilateral asymmetric sacroilitis, grade 3 and grade 2 for the right side and left side, respectively, according to the modified New York criteria[5] (Figure 3A). Pelvis CT showed narrowing of the space of the sacroiliac joints, erosion, and subchondral sclerosis of the right iliac side with an irregular margin (Figure 3B). Hence, the diagnosis of AS was established. Anemia and fever were interpreted as manifestations of AS-related systemic inflammation. Although corticosteroids have a misleading effect on the bone marrow, he was treated with etanercept (25 mg twice a week) and methylprednisolone (40 mg daily) to suppress systemic inflammation. He also received a red blood cell transfusion. The patient reported no pain and fever, and his Hb level steadily increased to approximately 100 g/L. CRP concentration and ESR were nearly normal. Three months later, etanercept was reduced to 25 mg once a week with tapering of the glucocorticoid. Sulphasalazine (1500 mg daily) was introduced for a short time. However, this relatively safe Hb level was maintained for only 3 mo. Another month later, the Hb level was at 76 g/L.

At the same time, the patient self-discontinued etanercept and prednisone. His low back pain relapsed with fever; the Hb level decreased to 60.8 g/L. After another month, the Hb level was at 42 g/L, reticulocyte count was 3%, ESR increased to 124 mm/h, and CRP concentration increased to 63 mg/L. The patient was re-admitted to our rheumatology department in March 2010. Subsequently, the second bone marrow examination revealed trilineage dysplasia with 2.5% of blast cells. The bone marrow was hypercellular. Immunophenotyping showed that primitive myeloid cells were approximately 4.18%, and the suggested diagnosis was refractory cytopenia with multilineage dysplasia subtype of MDS[6].

FINAL DIAGNOSIS
We made a diagnosis of MDS based on the findings in bone marrow and cytogenetic abnormalities; and AS based on the clinical feature of low back pain and imaging finding of sacroiliitis.
TREATMENT

Following a hematology consultation, it was suggested that the MDS might be related to the AS; however, cytogenetic testing was not offered. The patient still had back pain with high ESR and CRP levels. He had a high AS disease activity score. Subsequently, the patient received a transfusion and was administered methylprednisolone (40 mg daily) again. There were significant improvements in the symptoms; the ESR and CRP concentrations decreased (16 mm/h and 15.6 mg/L, respectively). Subsequently, etanercept (25 mg weekly) was added with a tapering of the glucocorticoid. However, an Hb level of approximately 100 g/L could be maintained for only 1 mo.

After another 2 mo, the Hb level and platelet count decreased (34 g/L and 75 × 10^9/L, respectively), and ESR increased to 84 mm/h, and thus, the patient was admitted to the hospital for the third time in June 2010. He had no arthralgia. The etanercept and prednisone dosages were reduced to 25 mg once in 10 d and 25 mg per day, respectively. The third bone marrow examination showed hypercellular marrow with trilineage dysplasia, with an increased myeloblast count of 9%. Immunophenotyping showed primitive myeloid cells (10.26%) and abnormal mature or immature granulocytes (33.3%). The patient was diagnosed with refractory anemia with excess blasts-1 (RAEB-1)[6] (Figure 1B). Chromosome analysis revealed a karyotype of 47, XY, der(7)t(1;7)(q10;q10), +8 in all ten metaphases. Fluorescent in situ hybridization revealed del(7q) and trisomy 8 cytogenetic abnormalities in the bone marrow. The International Prognostic Scoring System (IPSS) score was 2, and it was categorized as intermediate-2 risk[7]. Even after more than six transfusions over 50 d (about three units of red blood cell each time), the Hb level remained approximately 50 g/L. Platelet count decreased to 24 × 10^9/L. The patient became transfusion-dependent and was referred to the hematology department for decitabine...
OUTCOME AND FOLLOW-UP

Unfortunately, 6 mo later, the patient died due to cerebral hemorrhage. The main cause of hemorrhage was a very low platelet count due to MDS progression.

DISCUSSION

Anemia in AS is not rare but is generally mild[8]. The exact prevalence of anemia in patients with AS is unknown. There are multiple potential causes of anemia in patients with AS, including chronic disease and the use of NSAIDs that can cause gastrointestinal bleeding[9]. In our patient, severe anemia could not be attributed to the aforementioned reasons. Furthermore, the anemia was accompanied by mild to severe thrombocytopenia. White blood cell and platelet counts are usually normal in AS, and the bone marrow is normal or hypercellular[10]. Radiotherapy, which was once adopted for treating AS patients, might produce extensive chromosomal damage, probably increasing the risk of leukemia in these patients; hence, its use has been discontinued[11]. When etanercept was administered to our patient, he had serious anemia. Phenybutazone used to treat AS may increase the incidence rate of acute myeloid leukemia (AML)[12]. However, our patient did not receive phenybutazone. There were no other related drugs, such as cyclophosphamide or radioactive agents, that could lead to anemia or MDS.

As the disease developed, single erythroid dysplasia progressed to trilineage dysplasia in our patient. The myeloblast counts rapidly increased from 2.5% to 9%. Del(7q) and trisomy 8 of the typical chromosome abnormalities were found in the bone marrow. The presence of del(7q) and trisomy 8 simultaneously suggested the diagnosis of de novo MDS.

Thus, there was no evidence that MDS was secondary to AS. However, autoimmune manifestations are often reported in MDS[2,13,14]. Sacroiliitis was described as a paraneoplastic phenomenon of de novo acute leukemia[15-17]. In our case, severe anemia appeared from the beginning. As noted, the anemia that occurs in patients with AS is generally mild. This may suggest a diagnosis of MDS from the beginning; however, the first bone marrow examination in our case did not confirm a diagnosis of MDS. We suspect that AS may be an early autoimmune phenomenon related to MDS. Recently, a paper reports that the mutation of an epigenetic regulator may increase the risk of autoimmune diseases, such as AS in patients with MDS[18].

One study reported that HLA-B27 carriers might have an increased risk of hematological malignancies[19]. Although they were uncertain about the relationship between AS and MDS, Lee et al [20] believed that HLA-B27 might provide a link between AS and MDS. However, HLA-B27 positivity did not affect the outcome of patients with leukemia who received an allogeneic transplant[21]. Thus, the possibility of a coincidental association of MDS and AS cannot be excluded.

Considering the patient’s young age, there is a high probability of an underlying germline cancer-predisposing syndrome[22]. However, our patient did not have any dysmorphic features. His mother and father were healthy. Regrettably, we did not finish a high throughput sequencing analysis to find any germline mutation.

Our patient had a good response to the combination therapy of etanercept, glucocorticoid, and transfusion in the early stage, but his Hb level remained unstable. The lifespan of red blood cells is about 120 da, and our patient experienced a transient improvement of anemia mainly due to the chemotherapy.
transfusion. Furthermore, his transfusion dependence increased with the disease progression. The efficacy of the etanercept and glucocorticoid therapy in MDS cannot be denied. Sufficient doses of the etanercept (25 mg twice a week for 3 mo) and glucocorticoid in the early phase may be useful in maintaining the Hb level. When etanercept was reduced to 25 mg once a week and then once every 10 d, the joint symptoms improved; however, the anemia status did not change (Figure 4). Braun et al[23] reported that infliximab treatment, compared with the placebo, significantly improved Hb levels in AS patients with anemia. Of note, there was an improvement in Hb levels when the levels of CRP and ESR decreased, suggesting that the positive effect of the glucocorticoid and etanercept on the anemia was due to their systemic anti-inflammatory properties.

Some patients with refractory anemia or refractory anemia with ring sideroblasts may benefit from glucocorticoid therapy; however, the result is not encouraging. A combination of anti-thymocyte globulin plus etanercept can offer effective therapy for some patients with MDS, with an overall response rate of 56%[24]. Striking hematological improvements and loss of transfusion dependence were found in the responding patients. The prognosis of MDS patients with autoimmune manifestations appeared to be closely related to the IPSS subcategory of the underlying hematological malignancy[25]. Thus, our patient with intermediate-2-risk MDS as defined by the IPSS category had a poor prognosis. Considering the patient’s young age and the presence of more than three cytogenetic aberrations, an allogeneic transplant would have been the gold standard for treatment[26]. The transplant plan was discussed with the patient and his family, but they did not accept it at that time. They wanted to see the effects of chemotherapy before deciding on the transplant. However, the severe thrombocytopenia resulted in bleeding and death, and the patient missed the opportunity for treatment with an allogeneic transplant.

**CONCLUSION**

In summary, we present a rare case of simultaneous presentation of AS and MDS in the same patient with positive HLA-B27. We suspect that the AS may be an early autoimmune phenomenon related to MDS; however, the possibility of a coincidence cannot be excluded. AS can cause anemia, but it is usually mild. Therefore, if a patient with AS presents with severe anemia, it must be diagnosed as a hematopoietic system pathology.

**FOOTNOTES**

**Author contributions:** Xu GH prepared and wrote the manuscript; Xu GH, Lin J, and Chen WQ performed the literature research and data analysis; Chen WQ edited and approved the manuscript.

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Life-threatening subclavian artery bleeding following percutaneous coronary intervention with stent implantation: A case report and review of literature

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Abstract

BACKGROUND
Vascular complications of transradial percutaneous coronary intervention (PCI) are rare and usually occur at the access site below the elbow. Life-threatening vascular complications during transradial PCI therapy, such as vessel perforation and dissection in the brachiocephalic, subclavian, internal mammary, and thyrocervical arteries, are rarely reported. Subclavian artery bleeding is a potentially serious complication of vascular interventional procedures leading to tracheal obstruction, hemothorax, respiratory failure, hemorrhagic shock, and death if not diagnosed early and treated promptly.

CASE SUMMARY
A male patient with typical angina pectoris underwent coronary angiography and stent implantation. During the procedure, the patient felt pharyngeal pain and tightness, which we mistook for myocardial ischemia. After PCI, swelling in the right neck and supraclavicular area was observed. The patient experienced dyspnea, emergency endotracheal intubation was performed, and then a sudden drop in blood pressure was observed. Ultrasound and contrast-enhanced computed tomography scans demonstrated a cervical hematoma severely compressing the trachea due to subclavian artery bleeding. Brachiocephalic angiography revealed a vascular injury site at the root of the right subclavian artery at the intersection of the right common carotid artery. A covered stent was deployed to the right subclavian artery with successful sealing of the perforation, and a bare stent was implanted in the junction of the right common carotid and brachiocephalic arteries to prevent obstruction of blood flow to the brain.

CONCLUSION
Subclavian artery bleeding is a lifethreatening complication of PCI. Early prevention, rapid recognition, and prompt treatment may improve the prognosis.

**Key Words:** Bleeding; Complication; Percutaneous coronary intervention; Subclavian artery; Stent; Case report

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**Core Tip:** Subclavian artery bleeding is a rare and serious complication of transradial percutaneous coronary intervention leading to tracheal obstruction, hemothorax, respiratory failure, hemorrhagic shock, and death if not diagnosed early and treated promptly. Bleeding at the root of the subclavian artery might manifest as pharyngeal pain and cervical hematoma, which requires the prompt decision to perform emergency endotracheal intubation. Computed tomography scans should be performed as early as possible for patients with suspected hematoma. Endovascular treatment with covered stents appears to be less time consuming and more effective, especially for large, life-threatening perforations, with great success rates and immediate control of bleeding.

**INTRODUCTION**

Percutaneous coronary intervention (PCI) is an extensively used medical therapy for acute and chronic coronary artery disease (CAD)[1,2]. Vascular complications of transradial PCI are rare and usually occur at the access site below the elbow[3-6]. A study population consisting of 1984998 PCI procedures performed at 1292 participating sites demonstrated that the median rate of bleeding at the access site was 0.2%-0.5%[7]. Life-threatening vascular complications during transradial PCI therapy, such as vessel perforation and dissection in the brachiocephalic, subclavian, internal mammary, and thyrocervical arteries, are rarely reported and can lead to mortality due to acute respiratory and circulatory dysfunction[8-10]. The present study reports a case of subclavian artery bleeding following PCI, which caused severe cervical hematoma, tracheal compression, and unstable hemodynamics.

**CASE PRESENTATION**

**Chief complaints**
A 59-year-old Chinese man presented to the outpatient department of our hospital with retrosternal chest pain.

**History of present illness**
Over the prior 12 years, the patient had experienced intermittent retrosternal pain on effort with palpitations, shortness of breath, and fatigue lasting from 5 to 10 min. Because of the manifestation of typical angina pectoris, he was admitted to our institution for coronary angiography (CAG) 10 years ago. CAG showed severe stenosis in the mid-segment of the left anterior descending coronary artery (LAD), and 3 stents were implanted. Since that time, he had been treated with aspirin, clopidogrel, statins, and nitrates. However, his chest pain had recently returned and occurred more frequently at 1 to 2 times a day.

**History of past illness**
The patient had a history of hypertension for 30 years and poor blood pressure control (blood pressure ranging from 150/100 mmHg to 205/120 mmHg), even after treatment with felodipine and enalapril. Secondary hypertension was excluded after an outpatient evaluation. He suffered a cerebral hemorrhage one year ago. Due to the small size of the cerebral hemorrhage, no sequelae were noted.
Personal and family history

He had been smoking approximately 60 cigarettes a day for 30 years. No significant family history was noted.

Physical examination

Physical examination demonstrated poorly controlled hypertension with a blood pressure of 180/105 mmHg. His body weight was 65 kg, and his height was 166 cm (body mass index 23.9 kg/m²). Jugular venous distention was not detected, and the thyroid gland was not enlarged. The breath sounds of the two lungs were normal, and no dry or moist rales were detected. Heart auscultation revealed a regular rhythm, normal heart sounds without murmur, and a heart rate of 63 bpm. The liver and spleen were normal, and no swelling was observed in the lower extremities.

Laboratory examinations

Electrocardiography indicated sinus rhythm and a high-voltage left ventricle but no significant change in the ST segment or T wave (Figure 1). Echocardiography demonstrated symmetrical left ventricular hypertrophy (wall thickness 13-14 mm, normal reference ≤ 11 mm), left atrial enlargement (42 mm, normal reference ≤ 35 mm), mild mitral regurgitation, and some reduction in left ventricular diastolic function[1]. Ultrasound of lower limb arteries revealed a rough intima and spotty calcified plaques without significant stenosis. All these observations suggested hypertensive heart disease and peripheral vascular atherosclerosis. No other abnormalities were present in other examinations, including routine blood tests (platelet count 211 × 10^9/L, normal reference 125-350 × 10^9/L), coagulogram, liver and kidney function, blood electrolyte levels, blood glucose, blood lipids, thyroid gland function, myocardial damage markers, and brain natriuretic peptide, a biomarker of heart failure.

Imaging examinations

The patient was preliminarily diagnosed with CAD, unstable angina, grade 3 hypertension, and hypertensive heart disease[12-14]. He was treated with aspirin (100 mg daily), clopidogrel (75 mg daily), atorvastatin (20 mg daily), isosorbide mononitrate (20 mg twice daily), amloidine (5 mg twice daily), and enalapril (5 mg twice daily). For the coronary anatomy evaluation, CAG was performed by puncturing the right brachial artery because the right radial pulse was absent due to the PCI 10 years prior. A 6 French (F) sheath, a 0.035 cm × 260 cm J-Tip guidewire (Cordis, Ireland), and a 5 F 100-cm Tig coronary catheter (Terumo, Japan) were used during CAG under fluoroscopic guidance. CAG showed total occlusion of the proximal left circumflex artery (LCX), subtotal occlusion at the opening of the first obtuse marginal branch (OM) and 60%-70% in-stent restenosis at the middle LAD. In addition, 60%-70% stenosis of the distal right coronary artery was observed (Figure 2). For PCI of the left coronary artery, the 5 F angiography catheter was replaced with a 6 F EBU 3.5 A LAUNCHER coronary catheter (Medtronic, United States) and a 0.014-cm × 180-cm ASAH SION coronary guidewire (ASAH INTECC, Japan), which were passed through the distal OM. Then, repeated attempts were made to pass through the proximal LCX using a 0.014-cm × 180-cm ASAH SION blue coronary guidewire (ASAH INTECC), a 0.014-cm × 190-cm Fielder XT-R coronary guidewire (ASAH INTECC), and a 1.8 F 0.018-cm × 130-cm FINECROSS coronary microcatheter (Terumo, Japan), but these attempts failed. We then decided to address the stenosis of the OM. During balloon angioplasty with a 2.5-mm × 12-mm TREK balloon (Abbott, United States), the patient began to feel pharyngeal pain and tightness, which we mistook for myocardial ischemia. Stenosis was eliminated by implanting a 2.75-mm × 16-mm PROMUS Element Plus stent (Boston Scientific, United States) in the proximal segment of the OM (Figure 2). PCI was terminated after high-pressure balloon angioplasty using a 2.75-mm × 12-mm NC Demax noncompliant balloon (Demax Medical Technology, Beijing, China). The procedure lasted 52 min, and 6000 units of heparin was administered through the artery. The activated clotting time measured immediately after the operation was 305 s (normal reference 80-120 s).

After the patient was returned to the critical care unit, swelling in the right neck and right supraclavicular area was observed and gradually increased, with bleeding spots under the skin. The patient felt dyspneic, and physical examination showed that the trachea was compressed to the left. Bedside ultrasound demonstrated a poorly defined hematoma behind the right internal jugular vein measuring 26.0 mm × 30.1 mm × 12.3 mm. A contrast-enhanced computed tomography (CT) scan performed immediately thereafter also showed contrast extravasation surrounding the proximal subclavian artery (Figure 3) and a cervical hematoma compressing the trachea (Figure 4), but no hemothorax, subclavian artery rupture or bleeding was diagnosed.

FINAL DIAGNOSIS

The final diagnosis was CAD, unstable angina, grade 3 hypertension, hypertensive heart disease, and subclavian artery bleeding.
Shi F et al. Iatrogenic subclavian artery bleeding

Figure 1 Electrocardiogram at hospital admission.

Figure 2 Coronary angiogram and stent implantation. A: Coronary angiogram showing 60%-70% in-stent restenosis at the middle left anterior descending artery (orange arrow); B: Coronary angiogram showing 60%-70% stenosis of the distal right coronary artery (orange arrow); C: Coronary angiogram showing total occlusion of the proximal left circumflex artery and subtotal occlusion at the opening of the first obtuse marginal branch (OM) (orange arrow); D: After deployment of a stent in the OM, stenosis was eliminated (orange arrow). LAD: Left anterior descending artery; LCX: Left circumflex artery; OM: Obtuse marginal branch; RCA: Right coronary artery.

**TREATMENT**

Emergency endotracheal intubation was successfully performed to avoid asphyxia. However, during rescue intubation, the patient’s blood pressure dropped sharply from 175/89 mmHg to 88/52 mmHg.
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Figure 3 Contrast-enhanced computed tomography and brachiocephalic angiography. A: Contrast-enhanced computed tomography showing contrast extravasation surrounding the proximal subclavian artery (SA) (orange arrow); B: Brachiocephalic angiography revealing the site of bleeding at the root of the right SA at the intersection of the right common carotid artery (orange arrow). SA: Subclavian artery; CCA: Common carotid artery; BCT: Brachiocephalic trunk.

Figure 4 Cervical computed tomography. A: Cervical computed tomography showing a normal trachea (orange arrow); B: Cervical computed tomography showing a cervical hematoma (3.43 cm × 1.65 cm) (orange cross) and tracheal compression (orange arrow).

and recovered to 128/66 mmHg by intravenous fluid hydration and vasopressor support with norepinephrine and dopamine. A concerning finding on the CT scan was that the trachea was tightly affixed to the tube, which would complicate later intubation. Hypotension was thought to be due to hemorrhage and aggravated by sedation, which was supported by subsequent routine blood monitoring showing a reduction in hemoglobin from 138 g/L to 91 g/L (normal reference 130-175 g/L). The carotid sinus baroreflex might have also been a cause of exacerbated hypotension based on the location of the hematoma. Subclavian artery injury occurred at the site where it was not compressable. Obtaining adequate proximal exposure of the subclavian artery is an intricate process, and antplatelet agents and heparin may complicate hemostasis during open surgical repair; thus, endovascular intervention was suggested. Brachiocephalic angiography from the right brachial access revealed a vascular injury site at the root of the right subclavian artery at the intersection of the right common carotid artery (Figure 3). An 11-mm × 50-mm covered stent was deployed to the right subclavian artery with successful sealing of the perforation via a femoral artery approach. Since the proximal segment of the covered stent was located at the brachiocephalic artery, a 10-mm × 40-mm bare stent was implanted in the junction of the right common carotid and brachiocephalic arteries to prevent obstruction of blood flow to the brain (Figure 5). Digital subtraction angiography after stent graft deployment showed that the rupture was repaired, and no contrast extravasation was observed.

OUTCOME AND FOLLOW-UP

The patient was moved to the intensive care unit for ventilator support and close hemodynamic monitoring. To avoid fatal tracheal compression, endotracheal intubation and ventilator care were maintained for 4 d while the cervical hematoma was gradually absorbed without discontinuation of aspirin and clopidogrel due to the coronary stent. The patient was discharged from the hospital on Day
10 after PCI. After discharge, he had good compliance with medication and smoking cessation. At the 1.5-mo follow-up, the patient had no complaints, and contrast-enhanced CT showed that the cervical hematoma was completely absorbed and that the two stent grafts in the right subclavian artery and common carotid artery were in a satisfactory position and unobstructed (Figure 5).

DISCUSSION

Transradial PCI is recommended as the preferred method by various guidelines due to its significant reduction in vascular bleeding complications[15-18]. However, if arterial injury from the transradial approach occurs at the access site, especially where it cannot be compressed, the injury could be fatal. Subclavian artery bleeding is a potentially serious complication of vascular interventional procedures leading to tracheal obstruction, hemothorax, respiratory failure, hemorrhagic shock, and death if not diagnosed early and treated promptly[19]. The total number of PCIs performed in our center is 1500 to 2000 per year, and the number of transradial PCIs performed by each clinician is approximately 200 per year. This is the first case of subclavian artery bleeding in our center in the past 5 years (Table 1).

Some of the reported predictors for vascular injury associated with interventional procedures are divided into potentially modifiable and nonmodifiable factors. Potentially modifiable factors include a larger sheath size, excessive guidewire manipulation, manual inflation, an oversized balloon, procedure time, anticoagulation or thrombolytics, and high intraoperative blood pressure. Nonmodifiable factors include diffuse vascular calcification, vascular tortuosity, vascular stenosis, female sex, advanced age, chronic kidney disease, a past history of hypertension and/or diabetes, prior stroke, connective tissue disease, and long-term steroid therapy[20-24]. In this case, the guidewire and coronary catheter were inserted under continuous fluoroscopy, and the guidewire was not observed to penetrate the blood vessel. We speculated that calcified plaques and even stenosis may have been present in the subclavian artery, as the presence of calcified plaques in the lower limb arteries and diffuse coronary artery stenosis suggested that the patient had a high possibility of systemic atherosclerosis. Subclavian artery hemorrhage might have been caused by plaque damage during the interventional procedure and aggravated by antithrombotic agents and hypertension. Another cause may have been spontaneous bleeding, and aneurysms cannot be excluded.

The patient felt pharyngeal pain and tightness during balloon angioplasty, which we mistook for myocardial ischemia. We ignored the fact that these symptoms were not relieved after stent implantation, which would be inconsistent with intraoperative myocardial ischemia. This case suggested that bleeding at the root of the subclavian artery might manifest as pharyngeal pain and cervical hematoma. The patient experienced dyspnea as the cervical hematoma progressed, compressing the trachea, which needed to be differentiated from a contrast-induced allergic reaction and required a prompt decision to proceed with emergency endotracheal intubation[25].

The management of this vascular bleeding complication includes open surgical repair and multiple percutaneous interventions, including repeatedly prolonged balloon tamponade, covered stent grafts, collagen plugs, and localized thrombin injection[26-29]. Some clinicians have used balloon tamponade for a few minutes as a treatment for vascular bleeding, but this method is thought to be unreliable, as bleeding may resume later, especially in the great vessels. Although multiple therapeutic modalities...
Table 1 Timeline

<table>
<thead>
<tr>
<th>Date</th>
<th>Events</th>
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<tbody>
<tr>
<td>June 1, 2011</td>
<td>Angina pectoris was reported</td>
</tr>
<tr>
<td>June 25, 2011</td>
<td>CAG showed severe stenosis in the left anterior descending artery, and 3 stents were implanted</td>
</tr>
<tr>
<td>February 11, 2019</td>
<td>Cerebral hemorrhage was identified</td>
</tr>
<tr>
<td>December 11, 2020;</td>
<td>Recurrent chest pain was reported; Unstable angina was diagnosed</td>
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<tr>
<td>January 11, 2021</td>
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<tr>
<td>January 15, 2021</td>
<td>CAG revealed severe coronary artery stenosis, and a stent was implanted; After PCI, subclavian artery bleeding was diagnosed; Emergency endotracheal intubation and covered stent implantation were performed</td>
</tr>
<tr>
<td>January 19, 2021;</td>
<td>The endotracheal tube was removed; The patient was discharged</td>
</tr>
<tr>
<td>February 15, 2021</td>
<td></td>
</tr>
<tr>
<td>March 1, 2021</td>
<td>At the follow-up, the patient had no complaints, and a CT scan showed the stent in the subclavian artery and an unobstructed common carotid artery</td>
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</table>

CAG: Coronary angiography; PCI: Percutaneous coronary intervention; CT: Computed tomography.

have been applied to seal vascular injury, endovascular treatment with covered stents appears to be less time-consuming and more effective, especially for large, life-threatening perforations, with high success rates of immediate control of bleeding[30,31]. Preventing vascular bleeding complications of PCI is also important. Careful assessment of the individual risk should guide the choice of strategy during different stages of interventional procedures. Avoiding excessive manipulation, controlling intraoperative blood pressure and the activated clotting time, and timely adjustment or termination of the procedure can reduce the occurrence of vascular bleeding complications. Reasons to stop a PCI attempt include a high radiation dose (> 5 Gy air kerma dose), large contrast volume administration (> 3.7 × the estimated creatinine clearance), exhaustion of crossing options, or patient or physician fatigue[32].

CONCLUSION

Subclavian artery bleeding is a lifethreatening complication of PCI. Bleeding at the root of the subclavian artery might manifest as pharyngeal pain and cervical hematoma and requires a prompt decision to proceed with emergency endotracheal intubation. Rapid recognition and prompt treatment with covered stents may significantly improve the prognosis for these patients. Careful assessment of the individual risk and standardized and appropriate interventional procedures can reduce the occurrence of vascular bleeding complications.

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FOOTNOTES

Author contributions: Shi F managed the case and edited the manuscript; Zhang Y assisted with editing and revising the manuscript; Sun LX and Long S read and approved the final manuscript.

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BACKGROUND
Cryptogenic organizing pneumonia (COP), formerly known as bronchiolitis obliterans organizing pneumonia, is an extremely rare disease in pregnancy. In this case, we report on COP diagnosed in recurrent pneumonia that does not respond to antibiotics in pregnant woman.

CASE SUMMARY
A 35-year-old woman with no prior lung disease presented with concerns of chest pain with cough, sputum, dyspnea, and mild fever at 11 wk’ gestation. She was diagnosed with community-acquired pneumonia and treated with antibiotics; her symptoms improved temporarily. Four weeks after discharge, she was re-admitted with aggravated symptoms. Chest computed tomography demonstrated multifocal patchy airspace consolidation and ground-glass opacities at the basal segments of the right lower lobe, at the lateral basal segment of the lower lobe, and at the lingular segment of the left upper lobe. Bronchoalveolar lavage revealed an increased lymphocyte count and a decreased CD4/CD8 ratio. Prednisolone (0.5 mg/kg/d) was administered for 10 d after the second admission. Dyspnea improved after 3 d of steroid treatment and other symptoms improved on the 5th day of steroid administration. Post-delivery transbronchial lung biopsy further revealed the presence of granulation tissue with fibroblasts in small-bronchiole lumens.

CONCLUSION
This case suggests that it is important to differentiate COP from atypical pneumonia in the deteriorated condition despite antibiotic treatment.

Key Words: Antibiotics; Bronchiolitis obliterans organizing pneumonia; Corticosteroid; Cryptogenic organizing pneumonia; Pregnancy; Case report

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Core Tip: Cryptogenic organizing pneumonia (COP) is a diffuse infiltrating lung disease, wherein granulation tissue proliferates in the small bronchiolar epithelium. The COP is an extremely rare in pregnancy. We present the fourth case of COP during pregnancy. This case highlights that it is important to differentiate COP from other types of pneumonia that does not respond and aggravated despite of empirical antibiotics in pregnant woman. The corticosteroid administration is effective in the treatment of COP during pregnancy.

INTRODUCTION

Cryptogenic organizing pneumonia (COP) is a diffuse infiltrating lung disease, wherein granulation tissue proliferates in the small bronchiolar epithelium damaged owing to various causes and consequently obstructs alveolar ducts and alveoli\(^1,2\). The occurrence of COP in pregnancy is extremely rare and pregnancy-related physiological changes may worsen respiratory complications in COP. Previously reported cases had pre-onset underlying diseases such as asthma, fungal infection and Crohn's disease that can cause inflammatory condition (Table 1). Here, we report the fourth case of COP in a pregnant woman without underlying medical history initially diagnosed with community-acquired pneumonia that did not improve with antibiotic treatment.

CASE PRESENTATION

Chief complaints
A 35-year-old woman, gravida 2, para 1, presented with concerns of chest wall pain with cough, sputum, dyspnea, and mild fever of 37.7 °C at 11 wk of gestation.

History of present illness
The mild cough was started ten days ago with gradually aggravated feature.

History of past illness
Her obstetric history included spontaneous vaginal delivery at 40 wk of gestation, with no special medical history. In particular, there was no history of previous pulmonary diseases.

Personal and family history
A 7.5 pack-year history of smoking was noted before the first pregnancy by an antenatal evaluation.

Physical examination
On admission, the patient’s blood pressure was 120/80 mmHg, body temperature was 37.7 °C, pulse rate was 108/min, oxygen saturation was 96%, and respiratory rate was 28/min with a rale in the right lower lung area.

Laboratory examinations
Laboratory tests indicated a white blood cell count of 7.59 × 10^3/µL (74.9% neutrophils, 10.8% lymphocytes, and 3.5% monocytes) with an absolute neutrophil count of 5680 cells/µL, a hemoglobin level of 12.1 g/dL, a platelet count of 284 × 10^3/µL, and an elevated C-reactive protein level of 4.77 mg/dL.

Imaging examinations
Chest radiography showed increased patchy opacities in the right lower lobe (Figure 1), and computed tomography (CT) revealed some patchy lobular consolidation and peripheral ground-glass opacities (GGOs) in the posterior and lateral basal segments of the right lower lobe (Figure 2). The pulmonary function test showed a forced vital capacity (FVC) of 2.87 L (77% of predicted), forced expiratory volume in one second (FEV1) of 2.35 L (74% of predicted), FEV1/FVC ratio of 82%, and peak expiratory flow of 6.19 L/s. The tidal flow-volume curve revealed minimal obstructive lung disease. An ultrasound examination showed that appropriate fetal growth for the gestational age, a normal amount of amniotic
Lee YJ et al. Cryptogenic organizing pneumonia in pregnancy

### Table 1 Characteristics of cryptogenic organizing pneumonia with pregnancy: Previous published case report

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<td></td>
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<td>Futagami et al[10], 2003</td>
<td>Holder et al[5], 2011</td>
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<tr>
<td><strong>Age (yr)</strong></td>
<td>27</td>
<td>33</td>
<td>16</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td><strong>Underlying disease</strong></td>
<td>HIV</td>
<td>ITP, asthma</td>
<td>COP, pulmonary hypertension, asthma, partial right lower-lobe resection</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational age (wk) at diagnosis</strong></td>
<td>26 + 5</td>
<td>38</td>
<td>20</td>
<td>16 + 1</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational age (wk) at delivery</strong></td>
<td>34</td>
<td>38</td>
<td>28</td>
<td>39 + 4</td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Cough, dyspnea, chest pain</td>
<td>Cough, fever</td>
<td>Dyspnea, chest pain, fatigue</td>
<td>Chest pain, cough, dyspnea, sputum</td>
<td></td>
</tr>
<tr>
<td><strong>Radiologic Findings</strong></td>
<td>Diffuse bilateral parenchymal infiltrates (left lower lobe) in chest X-ray</td>
<td>Diffuse bilateral parenchymal infiltrates in chest X-ray</td>
<td>Patchy ground glass infiltrates in chest CT</td>
<td>Multifocal patchy airspace consolidation and GGO</td>
<td></td>
</tr>
<tr>
<td><strong>Initial diagnosis</strong></td>
<td>Asthmatic bronchitis or interstitial; Pneumonia</td>
<td>Asthmatic bronchitis or mycoplasmic pneumonia</td>
<td>Pre-existing COP</td>
<td>CAP</td>
<td></td>
</tr>
<tr>
<td><strong>Definite diagnosis method</strong></td>
<td>Open lung biopsy</td>
<td>BAL, TBLB</td>
<td>NA</td>
<td>BAL, TBLB</td>
<td></td>
</tr>
<tr>
<td><strong>Initial treatment</strong></td>
<td>Trimethoprim (300 mg) + sulfamethoxazole (1500 mg) IV every 6 h + ceftriaxone (2 g) IV daily, methylprednisolone, 60 mg IV every 8 h</td>
<td>Cefmetazole 1 g every 12 h + gabexatemesilate 2 g IV continuously</td>
<td>NA</td>
<td>Ceftriaxone (2 g daily) IV + amoxicillin (250 mg every 8 h), cefpodoxime (100 mg every 12 h) orally</td>
<td></td>
</tr>
<tr>
<td><strong>Final treatment</strong></td>
<td>Dexamethasone, 5 mg IV every 12 h for 72 h, followed by methylprednisolone, 60 mg IV daily for 48 h, then 30 mg IV every 8 h for 4 d; and prednisone 40 mg/d orally</td>
<td>Minocycline 100 mg + methylprednisolone 125 mg every 12 h and every 8 h, for 5 d, followed 40 mg per day orally for 11 d</td>
<td>Nebulizer of a beta-2 agonist and corticosteroids</td>
<td>Prednisolone (0.5 mg/kg/d) for 10 d</td>
<td></td>
</tr>
</tbody>
</table>

**BAL**: Bronchoalveolar lavage; **CAP**: Community acquired pneumonia; **COP**: Cryptogenic organizing pneumonia; **GGO**: Ground glass opacity; **HIV**: Human immunodeficiency virus; **ITP**: Immune thrombocytopenia; **IV**: Intravenous; **NA**: Not available; **TBLB**: Transbronchial lung biopsy; **CT**: Computed tomography.

**Figure 1 Chest radiography findings.** A: Ill-defined increased opacities in the right lower lobe at first onset (black arrow); B: Increased bilateral patchy opacities in both lower lobes with a subpleural portion at second onset (white arrow).

...fluid, and no specific abnormal findings.
**FINAL DIAGNOSIS**

The increased lymphocyte count (40%) and a decrease in the CD4/CD8 ratio (0.6) with the presence of macrophages (25%) and neutrophils (8%) in BAL suggested a diagnosis of COP.

**TREATMENT**

We began steroid treatment with prednisolone (0.5 mg/kg/d), and progressive improvement of radiological findings was noted. Dyspnea improved after 3 d of steroid treatment, and other symptoms were reduced on the 5th day of steroid administration.

**OUTCOME AND FOLLOW-UP**

Post-discharge, the patient did not express any special events during pregnancy and gave birth by vaginal delivery at 39+4 d of gestation (male, 3370 g; Apgar scores of 8 and 9 at 1 and 5 min, respectively). Transbronchial lung biopsy was conducted after delivery without any complications, and the proliferation of granulation tissue into the bronchioles and alveolar duct indicated COP (Figure 3).

**DISCUSSION**

The prevalence of COP is unknown and is mainly observed in individuals aged 50-60 years[3]. COP occurrence during pregnancy is extremely rare, but it could be more severe owing to physiologic changes in pregnant women, such as an elevated diaphragm, increased oxygen demand, decreased functional residual capacity, and decreased chest wall compliance[4]. Thus, previous reports have recommended close antenatal care and regular pulmonary function tests to reduce respiratory complications during pregnancy; further, elective preterm delivery can be an option in more severe cases[5].

The clinical features of COP in the case described above were not notably different from the general clinical features of COP. The respiratory symptoms began with a flu-like illness with cough, mild fever, malaise and progression of shortened breathing to dyspnea[2]. Although a quarter of patients with COP had no special physical findings[3], inhalation rales or crackling were observed in the physical examination in this case.

In general, imaging approaches are employed to diagnose COP. Chest radiography for COP has three characteristic features: multiple alveolar opacities (typical COP), solitary opacity (focal COP), and infiltrative opacities (infiltrative COP). Bilateral multiple opacities are more common than solitary patterns[6, 7]. In our patient, bilateral patchy opacities were observed in both lower lobes. Thin-section CT scans have a correct diagnosis rate of 79% with histologically proved COP[8]. CT findings for COP are patchy GGOs in the subpleural and/or peribronchovascular area (80%), airspace consolidation in bilateral lower lobes (71%), wall thickening and cylindrical dilatation of air bronchogram (71%), ill-defined small nodular opacities (50%), and pleural effusion (in a third of patients)[9]. The specific multifocal patchy...
airspace consolidation, GGOs, and bilateral pleural effusion were observed.

Corticosteroids are administered as the initial treatment for COP and are effective for both typical and focal COP. The recommended treatment regimens include initial dosages of 0.75-1.5 mg/kg prednisolone for 3 mo with gradual reduction according to clinical symptom improvement[10]. In this case, we began with a low initial oral dose of prednisolone of 0.5 mg/kg/d after the patient’s second admission because corticosteroid use in first trimester can be associated with the development of an orofacial cleft. Fortunately, symptoms improved after 5 d of the low-dose administration and maintenance therapy was continued for 5 more days. This rare case is about the COP diagnosed in pregnant women without underlying medical conditions. In addition, it suggests a diagnostic value of COP, which is less effective in conventional initial treatment. In this case, a pregnant woman was initially diagnosed with community-acquired pneumonia and treated with antibiotics; her symptoms seemed to improve temporarily but then recurred with greater severity.

CONCLUSION
COP has similar clinical features with other types of pneumonia and in particular, chest radiographic differentiation of COP could be difficult. The progressive condition indicates a specific clinical aspect of COP; thus, it is important to differentiate COP from other atypical pneumonia that recur despite initial antibiotic treatment.

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FOOTNOTES
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Eosinophilia complicated with venous thromboembolism: A case report

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**Abstract**

**BACKGROUND**

Eosinophilia is an increase of more than $0.5 \times 10^9/L$ in the number of eosinophils; it is a systemic condition with an unknown etiology and is often accompanied by multiple impaired organ functions. The clinical manifestations of the disease are highly variable and diverse, rendering identification of the diagnosis challenging; hence, diagnosis and treatment are often delayed. Very few reports of this disease exist globally, especially with rare manifestations of cerebral venous sinus thrombosis and hemorrhage.

**CASE SUMMARY**

A 32-year-old woman with eosinophilia presented to the hospital with bilateral lower-limb edema as the first clinical manifestation, followed by an extensive maculopapular rash throughout the body. She subsequently developed cerebral venous sinus thrombosis along with bilateral lower-limb deep vein thrombosis. Two weeks earlier, she had received a single course of antibiotics from a local hospital for a low-grade fever and sore throat. After various treatments were administered for anticoagulation, maintaining blood circulation, and relieving blood stasis, the lower extremity edema improved significantly; however, the patient’s eosinophil count gradually increased. She experienced cerebral venous sinus thrombosis, cerebral hemorrhage, and deep vein thrombosis of the lower limbs before being declared brain dead. In this case report, we have elaborated the diagnosis and management of deep vein thrombosis manifested as eosinophilia,
thrombocytopenia, and elevated D-dimer levels.

**CONCLUSION**

Because proper diagnosis is challenging, clinical vigilance is required for patients with eosinophilia, as it can lead to thrombus formation.

**Key Words:** Eosinophilia; Venous thromboembolism; Diagnosis; Management; Venous thrombosis; Case report

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**Core Tip:** A 32-year-old woman with eosinophilia developed venous thromboembolism as the disease progressed, complicated by cerebral venous sinus thrombosis and bleeding, until death. As eosinophilia can cause the blood to be in a hypercoagulable state, this may have been the main cause of the patient’s venous thromboembolism. Therefore, eosinophilia is one of the risk factors of venous thromboembolism, which should arouse clinical attention.


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**INTRODUCTION**

Eosinophilia is defined as an eosinophil count of more than $0.5 \times 10^9$ L in healthy individuals. It is a systemic condition with an unknown etiology and is often accompanied by multiple impaired organ functions that include multi-system involvement, such as gastrointestinal, dermatological, central nervous, cardiovascular, and portal venous systems. The most commonly involved organs are the skin, heart, and brain; however, venous thromboembolism (VTE), membranous nephropathy, ocular manifestations, and torticollis have also been reported[1-3]. The clinical manifestations of the disease are highly variable and diverse, rendering the diagnosis challenging; hence, diagnosis and treatment are often delayed. Very few reports of this disease exist globally, especially with rare manifestations such as cerebral venous sinus thrombosis and hemorrhage.

This is a case report of a patient with eosinophilia who initially presented with bilateral lower-limb edema, followed by an extensive maculopapular rash throughout the body. She subsequently developed cerebral venous sinus thrombosis along with bilateral lower-limb deep vein thrombosis. Further, we describe the diagnosis and management of deep vein thrombosis manifested as eosinophilia, thrombocytopenia, and elevated D-dimer levels.

**CASE PRESENTATION**

**Chief complaints**

A 32-year-old woman presented to the hospital with the chief complaint of bilateral lower limb swelling for two days.

**History of present illness**

The patient had developed bilateral lower limb edema two days earlier, with increased severity on the right thigh; however, the superficial veins of the lower extremities were not tortuous. Color Doppler ultrasound of the lower extremities revealed insufficiency of the right common femoral venous valve, and the patient was admitted to our hospital for further treatment.

**History of past illness**

Two weeks prior, the patient had suffered from a low-grade fever that peaked at 37.3 °C, which was accompanied by a sore throat. She had received a single course of antibiotics from a local hospital, the specifications of which could not be ascertained. Following symptomatic improvement, no further investigations were performed or treatment administered. The patient did not experience discomfort, such as chills or chest tightness.
Personal and family history
There was no history of drug allergy, family history of inherited or systemic diseases, and no history of special exposure.

Physical examination
On admission to the hospital, the patient’s vital signs were within the normal limits, with the presence of bilateral palpable enlarged superficial inguinal lymph nodes. Bilateral lower-limb pitting edema to the mid-thigh was observed, with increased severity on the right side. Furthermore, a mass of approximately 5 cm × 3 cm was palpated on the lateral aspect of the right thigh, which was firm in consistency, non-pulsating, and non-tender. The pulsations of the bilateral dorsal foot arteries were maintained. On cardiopulmonary examination, no abnormalities were detected.

Laboratory examinations
The total leucocyte count in the blood was 10.31 × 10^9/L, comprising 60.3% neutrophils and 15.5% eosinophils; the eosinophil count was 1.60 × 10^9/L; hemoglobin level was 124 g/L; and platelet count was 224 × 10^9/L. The level of high-sensitivity C-reactive protein (hs-CRP) in the blood was 7.31 mg/L; serum electrolyte potassium level was 3.06 mmol/L; and degradation product, D-dimer level was 0.64 mg/L fibrinogen equivalent units (FEU). Liver and kidney function, and routine urine and stool test results were within normal limits; stool test results for liver fluke eggs, fungi, and infectious diseases tests were all negative.

Imaging examinations
Chest radiography revealed no abnormalities in the heart, lungs, and diaphragm; cardiac color ultrasound revealed minimal tricuspid regurgitation and reduced left ventricular diastolic function (35%), while the left ventricular ejection fraction was normal (63%). Superficial inguinal color ultrasound revealed five hypoechoic nodules in the right groin area, the largest measuring approximately 22 mm × 7 mm, and approximately six enlarged left superficial inguinal lymph nodes, the largest measuring approximately 24 mm × 7 mm.

Treatment
After admission, the patient received 4000 U of low-molecular-weight heparin once daily to promote blood circulation and relieve stasis, reduce platelet aggregation, improve valvular function, and prevent infection. After treatment, the lower-limb edema reduced; however, the mass on the lateral right thigh was still palpable. On Day 7 of admission, the patient developed pain in the lateral thigh mass of the right lower limb following intermittent pneumatic compression therapy. Emergency bedside color Doppler ultrasound revealed lower limb muscle edema and no obvious abnormalities in the lower limb vessels. The blood tests were repeated and revealed a leucocyte count of 13.77 × 10^9/L, comprising 59.5% neutrophils and 26.4% eosinophils; hs-CRP, 8.50 mg/L; D-dimer, 1.28 mg/L FEU; and fibrin (proto) degradation product, 5.40 mg/L.

Following the administration of 10 mg morphine hydrochloride injection subcutaneously, the patient’s pain was relieved. Computed tomography (CT) scan of the lower abdomen revealed right thigh subcutaneous edema of approximately 18 cm × 15 cm adjacent to five further enlarged right deep inguinal lymph nodes, the largest measuring approximately 22 mm × 8 mm. Magnetic resonance imaging (MRI) revealed soft tissue swelling and exudative-like changes in the superior portion of the right mid-thigh, with five enlarged deep inguinal lymph nodes adjacent to the iliac vessels, the largest measuring approximately 24 mm × 8 mm.

On Day 10 of admission, the patient developed extensive erythematous macules throughout the body. Anti-allergic treatment was administered, including dexta-methasone 5 mg intravenously (once), 5% glucose injection + calcium gluconate 20 mL intravenous infusion, and loratadine tablets 10 mg once daily orally; anticoagulation treatment was discontinued.

Further diagnostic work-up
The rheumatology and immunology departments were consulted, and color Doppler ultrasound was performed for further examination of the superficial lymph nodes. No obvious enlarged lymph node echo in the bilateral supraclavicular fossae were noticed; however, multiple bilateral axillary lymph nodal echoes were observed, the largest of those measuring approximately 11 mm × 7 mm and 14 mm × 6 mm on the right and left sides, respectively. CT of the chest and upper abdomen revealed bilateral pleural effusion, suspected to be inflammatory exudates (Figure 1); mild enlargement of the bilateral axillary lymph nodes was observed, the largest of those measuring approximately 11 mm × 7 mm and 14 mm × 6 mm on the right and left sides, respectively.

Blood tests were repeated again on Day 10 and revealed a leucocyte count of 15.58 × 10^9/L, comprising 46.5% neutrophils and 36.7% eosinophils; eosinophil count, 5.72 × 10^9/L; platelet concentration, 108 × 10^9/L; hs-CRP, 32.52 mg/L; erythrocyte sedimentation rate, 28 mm/h; D-dimer, 4.18 mg/L FEU; fibrin (proto) degradation product, 5.86 mg/L; and aspartate aminotransferase (for myocardial enzyme spectrum) 88 U/L; the remaining parameters were within normal limits. Liver
A hematology consultation was recommended to further improve the related parameters. The antineutrophil cytoplasmic antibodies, antinuclear antibody spectrum, anticardiolipin antibodies, and direct Coombs test results were all negative, while thyroid function test results were within normal limits. The immune function tests revealed, immunoglobulin E, 348.81 IU/mL; complement C3, 0.83 g/L; and cytomegalovirus IgG antibody, 279.273 AU/L. The leucocyte count was 12.13 × 10^9/L, comprising 23.1% neutrophils and 58.1% eosinophils; eosinophil count, 7.06 × 10^9/L; and platelet count, 120 × 10^9/L.

On Day 14 of admission, the patient was transferred to the rheumatology department for further treatment. Screening tests for gynecological tumors and respiratory viral infections were negative. Bone marrow aspiration and biopsy results were consistent with high eosinophilia and did not support the morphological changes associated with myelodysplastic syndrome, plasma cell myeloma, or lymphoma; the anti-allergic treatment was continued. On Day 15 of admission, rashes over the entire body subsided significantly. Blood tests revealed a leucocyte count of 15.57 × 10^9/L, comprising 33.4% neutrophils and 53.3% eosinophils; eosinophil count, 8.3 × 10^9/L; and platelet count, 80 × 10^9/L.

At 3:00 AM on Day 18 of admission, the patient complained of headache, involuntary movements of the right upper limb, and decreased sensation in both the right limbs; she had no other symptoms, such as diplopia and cough. The results of an urgent cranial MRI + magnetic resonance angiography (MRA) + magnetic resonance venography (MRV) revealed the following (Figure 2): (1) Abnormal signals on the left side at the fronto-parietal junction, indicating the formation of a hematoma; (2) Abnormal signals in the right frontal lobe, indicating the possibility of a small amount of hemorrhage; (3) Hypertrophy of the left inferior turbinate; (4) No obvious abnormalities observed on the MRA scan; and (5) Brain MRV revealing (I) Superior sagittal abnormal changes in the blood vessels above the sinus and in the adjacent areas, indicating the possibility of venous sinus thrombosis and (II) Narrowing in the left transverse sinus compared to the opposite side. The patient was transferred to the neurology department for further diagnosis and treatment.

Physical examination following the transfer revealed the following findings: bilateral pupils reactive and equidistant, central position of the tongue, reduced muscle tone of the right limbs, right upper limb muscle strength level 2, and right lower limb muscle strength level 3. The pain on the right side decreased, no pathological reflex was elicited, and meningeal irritation sign was negative. The patient underwent a lumbar puncture; the pressure was 230 mm H₂O during the procedure; 20% mannitol injection 125 mL was administered every 8 h and citicoline injection 1.0 g was administered once daily.

On Day 18 of admission, an episode of projectile vomiting occurred, along with gradual loss of consciousness and limb stiffness. An urgent head CT revealed increased left frontal and parietal hemorrhage, subarachnoid hemorrhage of 15 mm × 20 mm, midline-shift, and worsening of the brain swelling; the patient underwent neurosurgery on the same day. During the surgery, brain tissue swelling, multiple subarachnoid hemorrhages on the surface, venous congestion and stasis, disappearance of brain tissue pulsation, and a fistula at the superior frontal region with a dark red hematoma at a depth of approximately 1 cm were observed. Anterior and posterior exploration of the hematoma was performed, and it was drained. Venous blood was oozing from multiple points. The bleeding was controlled while removing the dead brain tissue.

After surgery, the left and right pupils measured 3.5 mm and 2.5 mm, respectively, and bilateral loss of response to light was observed. On Day 19 of admission (postoperative day 1), a venous color Doppler ultrasound revealed no thrombosis in the lower limb, and no obvious abnormalities in the heart were observed on the color Doppler ultrasound. Blood tests revealed a leucocyte count of 13.33 × 10^9/L, comprising 65.0% neutrophils and 9.3% eosinophils; eosinophil count, 1.24 × 10^9/L; and platelet...
count, 40 × 10^9/L. Liver function tests revealed albumin, 25.4 g/L and alanine aminotransferase, 50 U/L.

On Day 20 of admission (postoperative day 2), the blood test results revealed a leucocyte count of 11.03 × 10^9/L, comprising 78.7% neutrophils and 8.6% eosinophils; eosinophil count, 0.95 × 10^9/L; and platelet count, 47 × 10^9/L.

**FINAL DIAGNOSIS**

(1) Secondary (reactive) eosinophilia; (2) VTE; (3) Cerebral venous sinus thrombosis; and (4) Cerebral hemorrhage.

**TREATMENT**

On Day 12 of admission, low-molecular-weight heparin and amoxicillin/potassium clavulanate were discontinued; potassium chloride sustained-release tablets 1 g twice daily and loratadine oral tablets 10 mg once daily were initiated.

**OUTCOME AND FOLLOW-UP**

On Day 30 of admission (postoperative day 12), lower limb venous Color Doppler ultrasound revealed left lower limb femoral vein, popliteal vein, and posterior tibial vein thrombosis, indicating ineffective anticoagulation treatment due to the occurrence of cerebral hemorrhage; the patient was declared brain dead.

**MANAGEMENT PROCESS**

**First treatment:** Low-molecular-weight heparin 4000 U once daily for 9 d, amoxicillin/potassium clavulanate 1.2 g every 12 h for 12 d.

**Second treatment:** 20% mannitol injection 125 mL every 8 h, citociline injection 1.0 g once daily for 2 d.

**Third treatment:** 20% mannitol injection 125 mL every 8 h, cefoperazone/sulbactam injection 3 g every 8 h, methylprednisolone sodium succinate 3 g every 12 h for 10 d.

**DISCUSSION**

**Causes of VTE**

The patient was a young woman with no history of tropical travel; she had a history of pre-infection and was admitted to the hospital with bilateral lower-limb edema as the chief complaint along with the presence of risk factors for thrombosis. After various treatments were administered for anticoagulation,
maintaining blood circulation, and relieving blood stasis, the lower extremity edema improved significantly; however, the patient’s eosinophil count gradually increased (Figure 3). She experienced cerebral venous sinus thrombosis, cerebral hemorrhage, and deep vein thrombosis of the lower limbs before being declared brain dead.

There are three elements of VTE: (1) Stagnation of blood flow; (2) Hypercoagulable state of blood; and (3) Injury of blood vessel walls. The initiating factor of VTE in this patient was considered to be reactive eosinophilia. While participating in the normal immune defense response, eosinophils can also cause tissue cell damage. Eosinophils can act on the body’s blood coagulation and anti-coagulation system. On the one hand, it promotes blood coagulation and on the other hand inhibits anti-coagulation, which eventually leads to thrombosis. There are three main mechanisms of eosinophilia that can act on the body through multiple pathways to cause VTE[4]: (1) Major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and ethylene glycol dinitrate are released through degranulation. These cytotoxic cations can damage the vascular endothelial cells. At the same time, MBP, ECP, and EPO can also increase the activity of tissue factor, factor VII, factor X, and other coagulation factors; activate the endogenous coagulation pathway; inhibit the production of activated protein C; and cause blood hypercoagulability; (2) Eosinophils can directly activate tissue factors and platelet-activating factors; leukotrienes activate exogenous coagulation pathways, activate and aggregate platelets, and promote thrombosis; and (3) Direct infiltration causes vascular endothelial cell damage. Activated eosinophils can also express CD40 Ligand (CD40L), and the CD40/CD40L system plays a role in inflammation, endothelial cell dysfunction, platelet activation and coagulation activation. Through the effects of all the above aspects, eventually thrombin and fibrin are continuously generated, which eventually leads to thrombus formation.

**Reasons for elevated eosinophils**

Eosinophilia is often accompanied by independent diseases; at present, there is no uniform standard for the classification of eosinophil count; values < 1.0 × 10^9/L, (1.0-5.0) × 10^9/L, and > 5.0 × 10^9/L generally indicate mild, moderate, and severe rise, respectively. Hypereosinophilic syndrome (HES) can be divided into four categories: hereditary (familial) HES, primary (tumor) HES, secondary (reactive) HES, and idiopathic HES[3]. We believe that the cause of HES in our patient was drug cross-reactivity due to previous antibiotic administration; thus, the patient developed secondary HES.

The most common secondary causes of eosinophilia are parasitic infections, drug allergies, allergic conditions, skin diseases, and respiratory and gastrointestinal tract diseases; however, the cause of the findings observed in our patient was not clear. The patient underwent several blood tests in our hospital, including tests for parasitic infection, asthma, skin diseases, and tests for other related causes. Prior to hospital admission, the patient’s blood test results revealed a normal eosinophil count, and a single course of antibiotics was administered (the specific medication is unknown). Therefore, based on the relevant adverse drug reactions identified, clinicians should consider the possibility of cross-allergic reactions to drugs in patients with eosinophilia; thus, adverse reactions to drugs during clinical administration should be predicted and evaluated. This emphasizes the importance of understanding and observing drug allergic reactions to minimize the occurrence of drug-induced diseases. In this case, the causes of death were cerebral venous sinus thrombosis and cerebral hemorrhage. Considering that eosinophilia is caused by the hypercoagulation of blood, it should attract clinical attention; however, the mechanism underlying eosinophilia leading to thrombosis has not been fully elucidated. Nevertheless, patients with eosinophilia are considered to be in a pre-thrombotic state and tend to develop thrombosis[6-8].

**Causes of muscle edema of the right lower extremity**

The patient’s right thigh was swollen and painful. MRI revealed that the soft tissue in the upper and middle part of the right thigh was swollen with exudative-like changes. Considering the patient’s increased eosinophil count, the edema could have been attributed to eosinophilic fasciitis, a connective tissue disease that is usually caused by overwork and a response to immunosuppression[9]. Biopsy is an important means of diagnosis of eosinophilic fasciitis. Fascial skin biopsy showed evidential fascia thickening and infiltration of lymphocytes and plasma cells, giving rise to inflammatory conditions[10]. Fascia fibrosis was also detected. However, the patient did not undergo a muscle biopsy as she had a decreased eosinophil count during follow-up treatment. Moreover, the symptoms of edema of the right thigh muscle disappeared, which also indirectly supports the possibility of eosinophilia.

**Related treatment of eosinophilia with VTE**

This patient had increased eosinophils and a progressive decline in the platelet count (Figure 4). The mechanism underlying this phenomenon could be that eosinophils inhibit bone marrow megakaryocytes, causing the megakaryocytes to mature and become plaque-producing. The reduction of megakaryocytes reduces the number of platelets circulating in the peripheral blood, and further platelets are consumed by the thrombus, thereby exacerbating thrombocytopenia. On one hand, glucocorticoid therapy can effectively control the eosinophil count and avoid target organ damage; on the other hand, it can also restore the number of platelets[2]. However, the patient’s condition progressed rapidly, and she was not treated with glucocorticoids before hemodynamic diseases were
ruled out, which caused platelet activation and aggregation followed by thrombosis. Clinical vigilance is required for eosinophilia because a high eosinophil count can cause vascular endothelial damage and easily lead to thrombus formation[11]; however, the most important cause of VTE events is the release of basic proteins and other substances following degranulation. The eosinophil count indicates the degree of organ damage; therefore, the authors recommend routine peripheral blood smears for patients with eosinophilia to observe whether there are changes in degranulation. If there are changes in degranulation (Figure 5), active treatment to avoid organ damage and VTE events is recommended. For patients with unexplained eosinophilia, active administration of glucocorticoids is recommended in the absence of contraindications for glucocorticoids; similarly, anticoagulation therapy is recommended as soon as possible in the absence of contraindications for anticoagulation therapy. The ultimate goal is to reduce the eosinophil count and to prevent VTE events, especially fatal adverse events such as cerebral venous sinus thrombosis and pulmonary embolism.

This patient had increased eosinophil and D-dimer levels (Figure 6). She was admitted to the hospital with edema of bilateral lower extremities and administered preventive doses of anticoagulant therapy. Anticoagulation therapy was discontinued for allergen screening during follow-up treatment. Cerebral venous sinus thrombosis and deep vein thrombosis of the lower extremities occurred. Due to the
combination of cerebral hemorrhage and thrombocytopenia, anticoagulation therapy was not administered. Anticoagulation therapy may benefit patients in the context of assessing the risk of bleeding; however, further studies are warranted.

In patients with eosinophilia, the skin is one of the most frequently affected organs; pathological features of eosinophilia include eosinophil infiltration and/or eosinophil degranulation [12]. Skin biopsy shows inflammatory changes in blood vessels, and the surrounding blood vessels are mainly infiltrated by mild to moderate eosinophils and monocytes [2]. In 2006, Caputo et al [13] proposed seven classifications for eosinophilic cellulitis: fixed drug eruption, plaque, bullous, granuloma annulare, papule, papule nodular, and urticaria-like. The patient’s skin over the entire body was covered in rashes, which was accompanied by itching, especially at night. Considering that this may be related to diurnal fluctuations in the release of glucocorticoids from the adrenal cortex, the patient was administered symptomatic treatments such as loratadine, levocetirizine, and calcium gluconate; the rash over her body subsided, and the skin and mucous membranes returned to normal.

**CONCLUSION**

In conclusion, eosinophilia can cause hypercoagulation of the blood, which can cause thrombosis in the veins of the lower extremities and heart, or even embolisms in the blood vessels of the lungs and brain. Early diagnosis is difficult; hence, vigilance is recommended to prevent a high mortality rate.
FOOTNOTES

Author contributions: Fu YZ and Su WQ were vascular surgeons who participated in the drafting of the manuscript and reviewed the literature; Xue YB and Suo FF were responsible for the collection of medical history data and literature; Liu SY participated in the revision of the manuscript; Cao MJ and Liu WC reviewed the literature and provided imaging examinations, especially blood smears; all authors issued final approval for the version to be submitted.

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Neck and mediastinal hematoma caused by a foreign body in the esophagus with diagnostic difficulties: A case report

Li-Ping Wang, Zhi-Ying Zhou, Xiao-Ping Huang, Yun-Juan Bai, Hai-Xia Shi, Di Sheng

BACKGROUND
Esophageal foreign body (FB) is a common clinical emergency. Clinically, computed tomography (CT) scans are important in the diagnosis of FBs in the esophagus. Here, we report a case of esophageal perforation and cervical hematoma, caused by a FB, whose uniqueness made rapid diagnosis difficult.

CASE SUMMARY
A 42-year-old man was transferred to our hospital with esophageal perforation, which was accompanied by cervical and mediastinal hematoma. CT scans only revealed a black shadow, approximately 2.5 cm in diameter, in the upper esophagus. After multidisciplinary discussion, he was quickly subjected to mediastinal hematoma resection, peripheral nerve compression release, esophageal FB removal and esophagectomy. Eventually, we removed a small crab with a pointed tip from his esophagus.

CONCLUSION
This was an unusual case of occurrence of sharp polygonal esophageal FBs caused by a small crab. Rapid diagnosis of this FB was difficult, mainly due to its translucent nature. Occurrence of sharp FBs, with cavities that sometimes only appear as black shadows on CT scans, can easily be mistaken for esophageal lumens. More attention should be paid to such sharp polygonal FBs.

Key Words: Esophageal foreign body; Esophageal perforation; Neck hematoma; Case report

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Core Tip: Esophageal foreign body (FB) is a common clinical emergency, a man suffered a sharp polygonal FB caused by the small crab. The FB in this patient was more difficult to detect on computed tomography because of its translucent nature, which increased the difficulty of rapid diagnosis. This case is rare and we should pay more attention at the sharp polygonal foreign body.

INTRODUCTION

Esophageal foreign body (FB), which typically presents with dysphagia, is a common clinical emergency. Patients with FBs sometimes attempt inappropriate clearance approaches, such as vigorous swallowing, which may lead to over-tightening or esophageal perforation, accompanied by life-threatening complications such as mediastinal abscess and esophago-aortic fistula bleeding\[1\]. Here, we report a case of esophageal perforation and cervical hematoma due to a FB in the esophagus. The uniqueness of this FB made rapid diagnosis difficult.

CASE PRESENTATION

Chief complaints
The main complaints were a sudden shortness of breath, neck swelling and dyspnea.

History of present illness
A 42-year-old man, suddenly felt a FB stuck in his throat while eating breakfast (steamed stuffed bun, fried dough stick and seafood soup). Although he tried to clear the obstruction by swallowing steamed stuffed bun and drinking soup, the pharyngeal obstruction was not relieved. Consequently, he developed shortness of breath, neck swelling and dyspnea.

History of past illness
His past medical history was hypertension.

Personal and family history
Home medications included hydrochlorothiazide. He denied any family history of lung diseases and esophageal diseases.

Physical examination
Physical examinations revealed presence of neck hematoma and low oxygen saturation.

Laboratory examinations
Laboratory results showed increased white blood cell counts 18.30 × 10^9/L and elevated levels of C-reactive protein 21.20 mg/L. Nucleic acid-based analysis of the novel coronavirus at the local hospital revealed negative results.

Imaging examinations
He was immediately taken to the local hospital and subjected to computed tomography (CT) scan, 30 min after onset of his illness. Results revealed presence of a large hematoma in his mediastinum and right neck (Figure 1). Due to the complexity of the problem, he was transferred from the local hospital to our hospital, where he was immediately treated with emergency tracheal intubation and respiratory support (3.5 h after onset of the condition). Results from CT angiography, performed on his thoracic aorta approximately 4 h after onset of the condition, revealed a black shadow of approximately 2.5 cm in diameter in the upper esophagus. The object was surrounded by a sharp end and a faint needle-like high-density shadow around it (Figure 2).
Figure 1 Presence of a massive hematoma in the neck and upper mediastinum, constricting the trachea.

Figure 2 The foreign body appeared as black shadow, with a diameter of 2.5 cm, in the upper esophagus, with sharp-pointed ends. A pin high-density shadow can be vaguely seen.

**FINAL DIAGNOSIS**

Through a multidisciplinary discussion, we considered that the patient had a cavernous esophageal FB.

**TREATMENT**

He was immediately subjected to mediastinal hematoma removal, peripheral nerve decompression, maxillofacial FB removal and esophageal reconstruction. This was approximately 10 h after onset of the condition. During surgery, an L-shaped incision was made along the sternocleidomastoid muscle of the right neck, followed by release and protection of the right recurrent laryngeal nerve. The posterior pharyngeal space was accessed through the right tracheoesophageal groove to reveal a large hematoma. The hematoma was aspirated, revealing a small arterial injury. Next, the vessel was closed using a surgical suture (ETHICON, polyglactin 910 suture). The wall of the right esophagus was then incised, and the FB at its entrance removed. This FB turned out to be a small crab, 2 cm × 3 cm (Figure 3) with sharp ends that pierced the esophagus and measured 0.5 cm × 0.3 cm. The patient’s esophagus was repeatedly flushed with dilute iodine, then repaired with surgical sutures (ETHICON, polyglactin 910 suture). Next, two drains were placed in the mediastinum, one in the retropharyngeal space, and a vacuum device was placed to drain the nasogastric tube. After successful surgery, the patient was transferred to the intensive care unit. He regained respiratory and circulatory stability, 1 d after surgery, after which the tracheal tube was removed. He was then transferred to the general ward and maintained on antibiotics. Mediastinal and retropharyngeal space catheters were removed on the fifth day, while the nasogastric tube was postoperatively removed after 11 d.
OUTCOME AND FOLLOW-UP
The patient was discharged when he was free of severe symptoms and is being followed up in the outpatient clinic.

DISCUSSION
Although approximately 20% of all adult patients with esophageal FBs require clinical interventions, most of these FBs will spontaneously pass\cite{2,3}. Esophageal perforation caused by FBs is a relatively rare occurrence, accounting for only 1%-4% of all reported cases. Sharp polygonal or pin-like pointed FBs have been strongly linked with esophageal perforation or rupture, with a risk of up to 35%\cite{4}. Results from a prospective single-center study found that CT was 90%-100% sensitive and 93.7%-100% specific, indicating that it is highly effective in diagnosing accidental ingestions or suspected bone fragments in patients that return negative X-ray results\cite{5-7}.

The FB lodged in the esophagus of the patient in the present study was a small crab, a sharp polygonal FB with only a thin shell and a small amount of crab meat inside. Notably, it looked like an air bubble, based on the CT image, which contrasts with solid FBs such as fish and poultry bones that appear as opaque objects on the CT image. This delayed rapid diagnosis of this patient. CT scans revealed the presence of a black shadow, about 2-3 cm in diameter, in the upper esophagus. In general, the gas-bearing shadow is for esophageal lacuna, but the gas shadow was bigger than normal and clear and sharp on both ends; the surrounding was a dimly visible linear high-density shadow, suggesting that it may not be the lacuna esophagus but a sharp FB. Although it was clinically confusing, a closer look at the shaded border revealed a sharp polygonal FB.

Chung et al\cite{8} reported the first case of a crab-induced esophageal FB, albeit with less damage to the esophagus. Here, we report the second case of crab-associated FB lodged in the esophagus, and the first case of crab-associated esophageal perforation. Upon being stuck in the patient’s esophagus, he tried to push it into the stomach by eating steamed bread. However, this improper approach caused the FB to stick deeper in the esophagus. The FB pierced the esophageal wall and damaged blood vessels, thereby causing a huge hematoma and compressing the airway. Consequently, these phenomena resulted in life-threatening dyspnea and respiratory failure. Improper methods for clearance of esophageal FBs, especially sharp ones, are discouraged. Instead, patients are advised to seek timely treatment to reduce the risk of complications. Delayed treatment leads to esophageal necrosis and predisposes patients to general infection, a situation that has been linked to high mortality rates, ranging from 10%-20\cite{9,10}.

CONCLUSION
Sharp FBs with cavities, which sometimes only appear as black shadows on CT scans, can easily be mistaken for esophageal lumens, thereby making clinical diagnosis difficult. This report elucidates on clinical diagnosis of cavernous FBs. Delayed treatment increases the risk of complications, thus timely performance of clinical management options, such as surgery, are encouraged. We recommend that patients with respiratory distress, caused by lodged FBs, first be subjected to airway stabilization prior to attempting removal or definitive management.
FOOTNOTES

Author contributions: Wang LP and Di S contributed equally to this case, both wrote and revised the text; Zhou ZY, Huang XP, Bai YJ, and Shi HX contributed equally in this case report; all were part of the clinical team that treated the patient, and all contributed to the text.

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REFERENCES

Therapeutic endoscopy of a Dieulafoy lesion in a 10-year-old girl: A case report

Ying Chen, Mei Sun, Xu Teng

Abstract

BACKGROUND
There are multiple causes of sudden gastrointestinal bleeding in children. Reports of Dieulafoy lesions (DLs) in children are scarce. DLs can be fatal without appropriate treatment.

CASE SUMMARY
We present a retrospective analysis of the clinical manifestations, endoscopic features, and treatment of a Chinese girl with a DL, as well as a review of the relevant literature. A 10-year-old girl was admitted to our hospital with sudden massive hematemesis and melena. Abdominal computed tomography revealed suspected submucosal bleeding in the stomach. Finally, the disease was diagnosed with endoscopy due to the typical manifestations. We used electrocoagulation and hemoclips under endoscopy for hemostasis. No recurrence of hematemesis was identified during 4-wk’ follow-up.

CONCLUSION
DLs in children are rare but an important cause of sudden gastrointestinal hemorrhage. Many pediatricians are inexperienced and often miss or delay diagnosis. Endoscopy as early as possible is the first choice for diagnosis and treatment.

Key Words: Pediatric; Dieulafoy lesion; Endoscopy; Treatment; Case report

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Core Tip: Dieulafoy lesions (DLs) are vascular abnormalities consisting of tortuous, dilated aberrant submucosal vessels. We present a 10-year-old girl with acute gastrointestinal hemorrhage due to a DL. We used electrocoagulation and hemoclips under endoscopy for hemostasis. This case highlights that while DLs in children are rare, they can be an important cause of sudden gastrointestinal hemorrhage. Many pediatricians are inexperienced and often miss or delay diagnosis. Endoscopy as early as possible is the first choice for diagnosis and treatment.

Citation: Chen Y, Sun M, Teng X. Therapeutic endoscopy of a Dieulafoy lesion in a 10-year-old girl: A case report. World J Clin Cases 2022; 10(6): 1966-1972
DOI: https://dx.doi.org/10.12998/wjcc.v10.i6.1966

INTRODUCTION
The most common causes of acute gastrointestinal hemorrhage are peptic ulcers and esophageal and gastroduodenal erosions[1]. However, even after careful investigations, such as endoscopy and barium studies, obscure gastrointestinal hemorrhages remain a clinical challenge. Dieulafoy lesions (DLs), also known as Dieulafoy disease, are a rare but fatal cause of gastrointestinal hemorrhage[2]. DLs are defined as vascular abnormalities consisting of tortuous, dilated aberrant submucosal vessels that do not undergo normal distal branching or tapering and subsequently protrudes through a minute defect into the overlying mucosa without ulceration[3]. DLs are scarce and it is hard to determine their true incidence in children. We performed a literature search on PubMed, Medline, and Embase, using the MeSH terms Dieulafoy lesion, Dieulafoy disease, Dieulafoy ulcer, and caliber persistent artery. Only 26 case reports of pediatric DLs were reported worldwide during 1995–2021, and there has been no literature review of DLs in children. Early diagnosis and appropriate treatment are vital. DLs must be considered in the differential diagnosis of gastrointestinal hemorrhage of unknown origin and not just in adults. We report a 10-year-old girl presenting with hematemesis and melena who was diagnosed with DL and successfully treated with electrocoagulation and hemoclips, and our experience in the diagnosis and treatment of DL in this child, and provide some data on DLs to pediatricians.

CASE PRESENTATION

Chief complaints
A 10-year-old Chinese girl with a history of hematemesis was admitted to the Pediatric Intensive Care Unit of Shengjing Hospital of China Medical University with massive hematemesis and melena.

History of present illness
The girl presented with recurrent hematemesis 4-6 times 24 h before admission, with no obvious regularity. She denied overeating or eating excitant food. She did not take in any corrosive or sharp foreign body. She presented with the usual upper abdominal pain. As usual, there was no acid reflux or heartburn. She complained of belching and black stools.

History of past illness
At the age of 8 years, she was hospitalized with massive hematemesis. No erosions or ulcers were detected by endoscopy. After 4 d of treatment with blood transfusions and proton pump inhibitors, the active bleeding stopped, and the patient was discharged with our lack of understanding of DLs.

Personal and family history
She denied any surgical history and was not taking any medication. She denied any history of drug or food allergies. There were no known significant gastrointestinal conditions in the family.

Physical examination
On her admission physical examination, her temperature was 36.5 ℃, heart rate 134 beats/min, blood pressure 96/56 mmHg, respiratory rate 25 breaths/min, and body weight 40 kg. She was pale, but her abdominal examination was unremarkable. No other physical abnormalities were noted.

Laboratory examinations
Her initial laboratory testing revealed microcytic anemia. The coagulation test showed decreased
Chen Y et al. Dieulafoy’s lesion in childhood

fibrinogen. Liver function and myocardial enzymes were normal. In renal function, blood urea nitrogen (BUN) level was elevated, and creatinine was normal. The high level of BUN is an important signal for upper intestinal bleeding. The results of other laboratory tests were unremarkable. Table 1 shows the details of the test results.

**Imaging examinations**
Abdominal enhanced computed tomography showed that the stomach was visibly dilated and filled with fluid, and blood clots were visible (Figure 1).

**FINAL DIAGNOSIS**
On the day of admission, she was managed with a proton pump inhibitor (1 mg/kg/d), fasting, gastrointestinal decompression, and nutritional support. According to the document “Standardize the diagnosis and treatment of acute non-variceal upper gastrointestinal bleeding based on the update guidelines”, gastric lavage was performed with norepinephrine and ice saline[4]. She stopped vomiting but developed another massive melena and her hemoglobin decreased to 6.9 g/dL. Two units of packed red blood cells were transfused.

To find the cause and stop the bleeding, she was transferred to our department. After repeated communication with her parents, gastroscopy with a transparent hood over the head was urgently performed. To fully expose the observation field, we injected gas into the gastric cavity to expand the folds of the gastric mucosa. Then, we used normal saline to clean the blood scab covering the mucosal surface of the gastric body and fundus. Meanwhile, the residual blood in the stomach was continuously sucked out. A careful examination revealed the presence of an actively bleeding protruding vessel in the posterior wall of the body of the stomach (Figure 2A). Based on the patient’s history and typical endoscopic manifestation, DL was finally diagnosed.

**TREATMENT**
We treated the DL with electrocoagulation hemostatic forceps (FD-410LR; Olympus) and hemoclips [ROCC-D-26-195; Micro-Tech (Nanjing) Co. Ltd]. We inserted the hemostatic forceps to the bleeding site through the biopsy hole and accurately clamped the upper end of the bleeding artery. Electrocoagulation lasted 2–3 s and the power used in electrocoagulation (ESG-400) was 40 W. Two endoscopic hemoclips were applied, which achieved full control of the bleeding (Figure 2B). The hemoclips were opened to the maximum, perpendicular to the lesion, and clamped on the mucosa on both sides of the bleeding lesion, placing the bleeding focus in the middle. After sealing the bleeding focus, the two clips were fixed in an upright position and could not move, which indicated that the clips were firmly clamped. After the active bleeding had stopped and the residual blood in the stomach was sucked up, further examination of the gastric and duodenal mucosa showed no other bleeding spots, erosions, or ulcers (Figure 3).

**OUTCOME AND FOLLOW-UP**
The patient had no further complaints at her follow-up at the outpatient clinic 4 wk later.

**DISCUSSION**
DL, first described by the French pathologist Dieulafoy, manifests with spontaneous recurrent gastrointestinal bleeding. It is observed in 0.3%–6.7% of cases of upper gastrointestinal bleeding[5]. There are no accurate statistics on the incidence of this disease in children. From 1995 to 2021, only sporadic cases were reported in children worldwide. DL is a large penetrating artery that is a normal vessel with an unexpectedly large diameter. The vessel caliber is 1-3 mm. This penetrating artery creates a small wall defect with fibrinoid necrosis at the base. The mechanisms of the pathological bleeding of DLs remain unknown. Newborn cases suggest that DLs can be congenital, and a congenital anomaly may develop acute ruptures. Mechanical friction, chemical corrosion, or drugs can induce the rupture of the protruding vessel and massive bleeding[6,7]. In adults, DLs are more common in men than women, and in middle-aged and older people[8]. Unlike adult patients, pediatric cases do not appear to have a gender predominance[9].

The small nature of the lesion and the special sites of the hemorrhage are two features of DLs. Most lesions are in the proximal stomach, particularly within 6–10 cm of the lesser curvature of the stomach,
Table 1 Laboratory data

<table>
<thead>
<tr>
<th>Item</th>
<th>Measured value</th>
<th>Range of normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell</td>
<td>12.7 × 10^9/L</td>
<td>4-10 × 10^9/L</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7.8 g/dL</td>
<td>12-15.5 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>22.25%</td>
<td>37%-47%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>134 × 10^9/L</td>
<td>100-300 × 10^9/L</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>15.3 s</td>
<td>9.4-12.5 s</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>1.4</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.7 g/L</td>
<td>2-4 g/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>35.6 g/L</td>
<td>35-53 g/L</td>
</tr>
<tr>
<td>Alanine transaminase</td>
<td>8 U/L</td>
<td>0-40 U/L</td>
</tr>
<tr>
<td>Glutamic oxalacetic transaminase</td>
<td>14 U/L</td>
<td>5-34 U/L</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>8.95 mmol/L</td>
<td>2.5-7.2 mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>40.1 umol/L</td>
<td>45-84 umol/L</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>63 U/L</td>
<td>&lt; 145 U/L</td>
</tr>
</tbody>
</table>

Figure 1 Abdominal enhanced computed tomography. It showed that the stomach was visibly dilated and filled with fluid, with blood clots visible. The arrow indicates the blood clot.

where blood supply comes directly from the arteriae gastrica sinistra[10]. Nongastric sites, such as the duodenum, jejunum, ileum, rectum, and even the bronchus, are also involved in DLs[11]. In our case, the DL was located in the posterior wall of the body of the stomach.

It is challenging to diagnose DL because of the features of the disease. Endoscopy, angiography, and surgical search are the primary diagnostic modalities. Red blood cell scintigraphy can also detect the site of bleeding. Undoubtedly, endoscopy is the most feasible method. Initial endoscopy can precisely diagnose over 71% of cases[12]. As subtle lesions can exist, multiple endoscopies are needed in some patients. The endoscopic visual criteria of DLs include: (1) Active arterial spurting or micro pulsatile streaming from a mucosal defect < 3 mm; (2) Visualization of a vessel protruding from a slight defect or normal mucosa; or (3) A fresh blood clot adherent to a minute mucosal defect or a normal-appearing mucosa[13,14]. To clearly and safely diagnose a DL, the following principles should be included in an endoscopic examination[15]: (1) During the period of active bleeding, emergency endoscopy should be performed under anti-shock therapy; (2) The DL may be exposed by cleaning the gastric cavity with moderate endoscopic perfusion; (3) During endoscopy, patients may change their body position, if necessary; (4) The search for the cause of the hemorrhage, especially sudden massive hematemesis, should not be stopped after finding a mild peptic ulcer and esophageal varicose veins; and (5) If a DL is suspected, a focal tissue biopsy is strictly prohibited.

Timely endoscopy and treatment can decrease the mortality of DL[16]. Endoscopy is recommended as the first-line method of treatment[17]. Endoscopic treatments include thermal electrocoagulation, heat probe coagulation, laser photocoagulation, regional injection with epinephrine, sclerotherapy, norepinephrine injection, band ligation, and hemoclips[18,19]. Mechanical banding and hemoclips are more effective than thermal electrocoagulation and injection[13]. It has been reported that 23 patients with lesions were found under emergency endoscopy, and all lesions were successfully sealed with
Figure 2 Endoscopic exam. A: Endoscopic changes before hemostasis. The presence of an actively bleeding protruding vessel in the posterior wall of the body of the stomach; B: Endoscopic hemostasis. Electrocoagulation lasted 2-3 s and the power used in electrocoagulation was 40 W. Two endoscopic hemoclips were applied, which achieved full control of the bleeding.

Figure 3 Endoscopic appearance of other parts after hemostasis. A and B: Duodenal mucosa showed no other bleeding spots, erosions, or ulcers; C: Gastric antrum was normal.

hemooclips for hemostasis. During follow-up, there was no recurrence, suggesting that hemoclips are preferred for endoscopic treatment of DLs[20]. The combination of electrocoagulation and hemoclips may be more reliable. This procedure was adopted in our case.

For patients who fail in endoscopic therapy, angiography with gel foam embolization is suggested [21]. Surgical management, previously regarded as the only treatment available, is reserved for patients who are refractory to endoscopy and angiography. Endoscopy combined with laparoscopic surgery is a new procedure that is less invasive than traditional surgery and more readily accepted by patients[22].

Our patient’s endoscopic appearance was a typical manifestation of DL. Electrocoagulation and hemoclip treatment were effective, and no active bleeding occurred during follow-up. This case suggests that although DL is a rare occurrence in children, we cannot ignore it, especially in patients with sudden, acute, severe, or unexplained gastrointestinal bleeding. Moreover, the timing of endoscopy is important. If the patient’s condition permits, gastroscopy should be undertaken as early as possible. Besides diagnostic purpose, endoscopic hemostasis can also be performed.

CONCLUSION

DL, as a cause of life-threatening bleeding, is a rare occurrence in the pediatric population. However, pediatricians should be aware of it as a differential diagnosis of pediatric gastrointestinal bleeding. Endoscopy is still the primary diagnostic tool and the first-line method of treatment. Early diagnosis and treatment are of great significance for a good prognosis in children.

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Chen Y et al. Dieulafoy’s lesion in childhood


Cavernous hemangioma of an intrapancreatic accessory spleen mimicking a pancreatic tumor: A case report

Jia-Yan Huang, Rui Yang, Jia-Wu Li, Qiang Lu, Yan Luo

Abstract

BACKGROUND

Intrapancreatic accessory spleen (IPAS) is an uncommon condition, with the majority of cases presenting as solid lesions. Thus, this condition is frequently misdiagnosed as pancreatic solid neoplasm. Moreover, splenic cavernous hemangioma is a rare disorder, whereas lesions with a cystic appearance arising from IPAS have not been reported.

CASE SUMMARY

Herein, we present a case involving a 32-year-old male who had a complex cystic lesion in the tail of the pancreas revealed by conventional ultrasound. The lesion was misdiagnosed as a pancreatic cystadenoma because of its confusing anatomic location, as well as due to its peripheral nodular and internal septal enhancement patterns on contrast-enhanced ultrasound. After multidisciplinary discussion, the patient finally underwent laparoscopic pancreatic body and tail resections. Postoperative pathology demonstrated the lesion to be a cavernous hemangioma arising from the IPAS.

CONCLUSION

Cavernous hemangioma in the intrapancreatic accessory spleen may mimic pancreatic cystadenoma, which is a condition with the potential to be malignant. Imaging follow-ups or surgical interventions may be helpful for the exclusion of malignant risks in complicated cystic lesions, especially those with parietal and septal enhancements.

Key Words: Intrapancreatic accessory spleen; Pancreas; Diagnosis; Contrast enhanced ultrasound; Case report

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Core Tip: Intrapancreatic accessory spleen (IPAS) is an uncommon condition; however, overlapping imaging manifestations of IPAS and pancreatic tumors may lead to unnecessary surgery. Cystic splenic cavernous hemangioma is a rare disorder, whereas lesions with a cystic appearance arising from IPAS have not been reported. Herein, we report a cavernous hemangioma in the IPAS that was misdiagnosed as being a pancreatic cystadenoma via contrast-enhanced modalities. The diagnosis of cystic lesions in IPAS can be challenging. Imaging follow-ups or surgical interventions may be needed for the possible malignancy risk of a complicated cystic lesion, especially those with parietal and septal enhancements.

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INTRODUCTION

An intrapancreatic accessory spleen (IPAS) is an uncommon condition, with a prevalence ranging from 1.1%-3.4% in individuals[1,2]. An IPAS is typically asymptomatic and has an innocuous nature. However, overlapping imaging manifestations of an IPAS and primary pancreatic tumors may lead to unnecessary surgery[3]. A typical IPAS demonstrates a solid lesion with a round, oval or triangular shape, which is similar to the spleen on both precontrast and contrast-enhanced images. Therefore, this disorder is frequently confused with adenocarcinomas, neuroendocrine tumors or other solid pancreatic entities. When compared with a solid IPAS, cystic lesions arising from an IPAS are rare but necessitate a differential diagnosis with pancreatic cystic neoplasms, especially those possessing the potential to be malignant. Moreover, when considering the high likelihood of false-negative results, biopsy of cystic pancreatic lesions is seldom performed, and surgery is ultimately performed in most patients.

Herein, we report such a case involving a patient who underwent laparoscopic pancreatic body and tail resections because of an indeterminate pancreatic cystic lesion. Postoperative pathology confirmed this lesion as being a cavernous hemangioma arising from an IPAS. Furthermore, the clinical and imaging characteristics of IPAS and pancreatic cystic neoplasms (according to the previous literature) were also reviewed (Table 1).

CASE PRESENTATION

Chief complaints
A 32-year-old male was referred to our hospital because of a suspicious lesion neighboring the hilum of the spleen, which was detected via conventional grayscale ultrasound in a local community hospital. The patient did not complain of obvious discomfort.

History of past illness
The patient had a history of chronic hepatitis B.

Physical examination
The patient did not complain of abdominal pain or any remarkable discomfort during the physical examination.

Laboratory examinations
In addition to a slightly increased albumin-globulin ratio (2.96) and glutamine transpeptidase level (63 IU/L), no abnormal laboratory test results, including those of related tumor markers, were found.

Imaging examinations
The patient underwent contrast-enhanced ultrasound (CEUS) in our department. Before the CEUS, a baseline ultrasound illustrated a complicated cystic nodule measuring 2 cm, with a well-defined border in the tail of the pancreas without salient blood supply on color Doppler ultrasound (Figure 1). For the CEUS, a bolus injection of the US contrast agent SonoVue (Bracco, Milan, Italy) was administered through the antecubital vein, followed by a flush of 5 mL of 0.9% normal saline. The lesion demonstrated peripheral nodular and internal septal isoenhancement in the arterial phase, followed by slight hyperenhancement of the enhanced area in the venous phase. The predominant cystic area of the lesion did not show any enhancement in either phase. According to the aforementioned enhancing pattern in the CEUS, the lesion was suspected to be a pancreatic cystadenoma via CEUS (Figure 1).
Contrast-enhanced computed tomography (CECT) was performed to further examine the lesion. On the unenhanced CT, a nodule with a diameter of 2.2 cm and slightly low density was identified in the tail of the pancreas. Septa were observed, whereas no significant enhancement was presented within the lesion (Figure 2). The nodule was diagnosed as being a pancreatic cystic lesion via the CECT. Moreover, no salient abnormalities were found in the liver, kidney, spleen or biliary system via imaging evaluations.

**FINAL DIAGNOSIS**

The lesion was misdiagnosed as pancreatic cystadenoma by CEUS and CECT.

**TREATMENT**

After multidisciplinary discussion and communication with the patient, as well as with his family, laparoscopic pancreatic body and tail resections were performed.

**OUTCOME AND FOLLOW-UP**

Postoperative pathology demonstrated that the lesion was a splenic cavernous hemangioma in the pancreas (Figure 3). After an uneventful postoperative course, the patient was discharged on postoperative day 5. No obvious abnormality was found in a follow-up abdominal US one month later (Timeline of diagnosis and treatment of the pancreatic lesion is presented in Supplementary Figure 1).

**DISCUSSION**

Intrapancreatic accessory spleen is a rare congenital condition, compared with an accessory spleen
### Table 1 Clinical and radiological characteristics of intrapancreatic accessory spleen and pancreatic cystic neoplasms

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>IPAS</th>
<th>Pseudocyst</th>
<th>SCA</th>
<th>MCA</th>
<th>SPN</th>
<th>IPMN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean: year)</strong></td>
<td>40 to 65</td>
<td>At any age</td>
<td>60</td>
<td>40 to 50</td>
<td>30</td>
<td>65</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Slightly higher in males</td>
<td>Males &gt; females</td>
<td>Older females</td>
<td>Females &gt; males</td>
<td>Young females</td>
<td>Males &gt; females</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>11%-17% of AS</td>
<td>5%-40% after pancreatitis</td>
<td>16% of PCN</td>
<td>29% of PCN</td>
<td>2% and 3% of PCN</td>
<td>20%-50% of PCN</td>
</tr>
<tr>
<td><strong>Benign/malignant</strong></td>
<td>Benign</td>
<td>Benign</td>
<td>Benign</td>
<td>Low malignant potential</td>
<td>Low malignant potential</td>
<td>Malignant potential</td>
</tr>
<tr>
<td><strong>Anatomic location</strong></td>
<td>Tail &gt; head/body</td>
<td>1/3 near the head</td>
<td>Head &gt; body/tail</td>
<td>Body/tail &gt; head</td>
<td>Body/tail &gt; head</td>
<td>Arising from the pancreatic ducts</td>
</tr>
<tr>
<td><strong>Size (mean: cm)</strong></td>
<td>≤ 2</td>
<td>Depending on the duration of disease</td>
<td>5-8</td>
<td>7-10</td>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Potential mimickers</strong></td>
<td>NET and PDAC</td>
<td>MCA</td>
<td>MCA and IPMN</td>
<td>MCA: IPMN and MCAC</td>
<td>MCA: IPMN and MCAC</td>
<td>SCA: MCA and MCAC</td>
</tr>
</tbody>
</table>

#### Radiological diagnosis

**Ultrasound**

- **Baseline US**
  - Hypoechoic lesion with well-defined border
  - Transonic: net separation: irregular internal outline: fluid-containing lesion
  - Small transonic lesions with thin septa inside
  - Unilocular or septated cystic lesions with thickened walls and well-defined margins
  - Encapsulated mixed mass (solid and cystic)

- **Doppler US**
  - Blood supply may from the splenic vessels
  - No obvious blood flow encompass or inside the lesion
  - No obvious blood flow encompass or inside the lesion
  - Blood flow signal around the tumor
  - No obvious blood flow encompass or inside the lesion

- **CEUS**
  - Inhomogeneous hyperenhancement followed by homogeneous hyperenhancement
  - Iso- or hyperenhancement of the cystic wall: without definite washout
  - Isoenhancement of the cystic walls and septa: without definite washout
  - Iso-enhancement of the cystic walls and nodules: without definite washout
  - Rim hyperenhancement in the capsule:centripetal hyperenhancement followed by mild washout in the solid part: no enhancement in the cystic components
  - Iso-enhancement in the cystic wall and nodules

- **CECT**
  - Inhomogeneous hyperenhancement followed by homogeneous hyperenhancement
  - Round or oval fluid collection with a thin: hardly perceptible wall or enhancing thick wall
  - Well-defined: polycystic or honeycomb lesions showing enhancing internal septa and cyst walls
  - Well-circumscribed round/oval macrocystic lesions with enhancement of the walls
  - Hypo-attenuating on pancreatic phase followed by homogeneous gradual enhancement to iso-attenuating on the hepatic venous phase
  - Dilated main/side pancreatic ducts: nodules arising from the ducts manifest hyperattenuating at contrast-enhanced CT

- **CEMRI**
  - Blood products and necrotic components commonly present intrins-
  - High intensity fluid in the cysts
  - Homogeneous low t1 signal intensity
  - Low signal intensity: SPN with hemorrhage presents t1 hyperintensity
  - Loss of t1 signal and delayed uptake of contrast material
T2-W
Homogeneous hyperintensity
The hyperintensity in tissues surrounding the pseudocyst represents the inflammation on T2 fat-suppressed images
Honeycomb pattern (microcysts) or macrocysts manifest signal intensity of simple fluid
Homogeneous high T2 signal intensity
Predominantly solid show mildly increased T2 signal intensity; cystic-dominated present T2 signal intensity closer to that of fluid
Papillary excrecences or nodules in the walls of the dilated ducts present hypointense on T2-weighted images

Management
Usually require no treatment
Serial imaging follow-up
Follow-up or resection depending on the size of the tumor
Surgical resection
Surgical resection
Recommended to be surgically resected

AS: Accessory spleen; IPAS: Intrapancreatic accessory spleen; PCN: Pancreatic cystic neoplasm; SCA: Serous cystadenoma; MCA: Mucinous cystadenoma; SPN: Solid pseudopapillary neoplasm; IPMN: Intraductal papillary mucinous neoplasm; MCAC: Mucinous cystadenocarcinoma; US: Ultrasound; CEUS: Contrast enhanced ultrasound; CECT: Contrast enhanced computerized tomography; CEMRI: Contrast enhanced magnetic resonance imaging; T1-W: T1-weighted; T2-W: T2-weighted.

located at the hilum of the spleen[2,4]. Due to its innocuous nature and infrequent induction of symptoms, IPAS seldom requires therapy unless they cause symptoms as a result of the compression, torsion or spontaneous rupture of a hemorrhage[5,6].

Typical IPAS presents as a solid lesion and demonstrates similar manifestations to the spleen on both precontrast and contrast-enhanced ultrasound[7,8]. However, cystic neoplasm development in IPASs is rare. Sporadic cases of epidermoid cysts in IPASs (known as ECIPASs) have been reported[6,9-11]. The walls of ECIPASs are irregularly thickened and thicker than those of mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs)[9]. Moreover, the evident contrast enhancement of the partially thickened wall of ECIPAS (which is similar to that of the spleen) makes it possible to distinguish ECIPASs from MCNs or IPMNs.

The differential diagnosis was even more considerable in our case. The cystic cavernous hemangioma in the IPAS (known as CHIPAS) presented peripheral nodular and internal septal enhancements, which are frequently observed in pancreatic mucinous cystadenomas (MCAs). Furthermore, the majority of MCAs are located in the tail of the pancreas, where IPASs are also frequently discovered[12]. Therefore, this increases the difficulty of an accurate diagnosis. However, the ancillary features of a fibrous pseudocapsule or calcified contents inside of the MCNs have also been reported[13]. Another pancreatic cystic lesion that warrants vigilant discrimination from the CHIPAS is an IPMN. An IPMN in the main duct possesses a high risk of malignancy, with 38%–68% being confirmed as high-grade dysplasia or pancreatic cancer in postoperative specimens[14]. Fortunately, CEUS is sensitive in being demonstrated in the dilated main pancreatic duct and the polycystic lesion connecting to the pancreatic duct or in developing within the duct in cases of IPMNs[15].

To our knowledge, there is only one case report of solid cavernous hemangioma detected in both the spleen and the IPAS[16]. In this case, the CHIPAS was accurately identified by the investigators because of a similar enhancement pattern of the pancreatic lesion and the splenic lesions on CECT and contrast-enhanced magnetic resonance imaging. An accurate diagnosis was more difficult, as in our patient, because there was no lesion in the spleen for comparison. Moreover, a splenic hemangioma typically shows a hyperechoic and solid appearance. The atypical cystic appearance in our patient increased the
Huang JY et al. Hemangioma of IPAS: A diagnosis challenge

Figure 2 Pre-operative computed tomography scan of the pancreatic lesion. A: A slightly low-density nodule measuring 2.2 cm (arrow) was found in the tail of the pancreas on unenhanced computed tomography (CT); B and C: Septa were faintly visible whereas no salient enhancement was presented within the lesion (arrows) in either the arterial or the venous phases on axial contrast-enhanced CT.

Figure 3 Hematoxylin-eosin staining of the cavernous hemangioma arising from the intrapancreatic accessory spleen. A: Large dilated vascular spaces (asterisk) separated by fibrous septa and endothelial cells (arrows) lining on the surface of the vascular spaces were observed in the intermediate-power view (original magnification, 200×); B: A high-powered photomicrograph (original magnification, 400×) illustrated splenic tissues (triangles) adjacent to the vascular spaces.

difficulty of making an accurate diagnosis.

Herein, we presented an extremely rare case of a cystic cavernous hemangioma arising from an IPAS. Contrast-enhanced ultrasound is sensitive in demonstrating the enhancements of the septa and the parietal nodule. However, an accurate diagnosis of cystic cavernous hemangioma arising from an IPAS via imaging tools is challenging. Imaging follow-ups or surgical interventions may be needed, due to the possible malignancy risk of a complicated cystic lesion with parietal and septal enhancements.

CONCLUSION

Cavernous hemangioma in the intrapancreatic accessory spleen may mimic pancreatic cystadenoma, which is a condition with the potential for malignancy. Imaging follow-ups or surgical interventions may be helpful for the exclusion of malignant risks in complicated cystic lesions, especially those with parietal and septal enhancements.

ACKNOWLEDGEMENTS

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FOOTNOTES

Author contributions: Luo Y performed the contrast-enhanced ultrasound examination for the patient and proposed writing it up as a case report; Huang JY collected the clinical information of the patient, reviewed the literature and contributed to manuscript drafting; Yang R provided the pathological data and helped with creating the figures; Li JW contributed to revising the grammar of the manuscript; Luo Y and Lu Q were responsible for the revision of the
manuscript for important intellectual content; all of the authors issued final approval for this version of the manuscript to be submitted.

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Surgery and antibiotics for the treatment of lupus nephritis with cerebral abscesses: A case report

Qiong-Dan Hu, Li-Shang Liao, Yong Zhang, Qiong Zhang, Jian Liu

BACKGROUND
Systemic lupus erythematosus (SLE) patients are extremely susceptible to opportunistic infections due to glucocorticoid and immunosuppressive treatments, which often occur in the respiratory system, the urinary system and the skin. However, multiple cerebral infections are rarely reported and their treatment is not standardized, especially when induced by a rare pathogen.

CASE SUMMARY
A 46-year-old woman was treated with glucocorticoid and immunosuppressant for SLE involving the hematologic system and kidneys (class IV-G lupus nephritis) for more than one year. She was admitted to hospital due to headache and fever, and was diagnosed with multiple cerebral abscesses. Brain enhanced magnetic resonance imaging showed multiple nodular abnormal signals in both frontal lobes, left parietal and temporal lobes, left masseteric space (left temporalis and masseter region). The initial surgical plan was only to remove the large abscesses in the left parietal lobe and right frontal lobe. After surgery, based on the drug susceptibility test results (a rare pathogen *Nocardia asteroides* was found) and taking into consideration the patient’s renal dysfunction, a multi-antibiotic regimen was selected for the treatment. The immunosuppressant mycophenolate mofetil was discontinued on admission and the dose of prednisone was reduced.
from 20 mg/d to 10 mg/d. Re-examination at 3 mo post-surgery showed that the intracranial lesions were reduced, the edema around the lesions was absorbed and dissipated, and her neurological symptoms had disappeared. The patient had no headaches or other neurological symptoms and lupus nephritis was stable during the 2-year follow-up period.

CONCLUSION
In this report, we provide reasonable indications for immunosuppression, anti-infective therapy and individualized surgery for an SLE patient complicated with multiple cerebral abscesses caused by a rare pathogen, which may help improve the diagnosis and treatment of similar cases.

Key Words: Systemic lupus erythematosus; Multiple cerebral abscesses; Nocardia asteroides; Multi-antibiotic therapy; Case report

INTRODUCTION
Systemic lupus erythematosus (SLE) is an autoimmune disease that is currently managed by long-term glucocorticoid and immunosuppressive treatments. However, such treatments often render patients extremely susceptible to opportunistic infections, which can negatively impact SLE prognosis [1,2]. The respiratory system, urinary system and skin are most commonly affected by opportunistic pathogens, and multiple cerebral infections are rarely reported [3,4]. We here report an SLE patient with renal involvement and multiple cerebral abscesses who was admitted to our hospital in June 2018. In addition to adjusting glucocorticoid and immunosuppressant therapy, we treated the patient with a combination of surgery and multi-antibiotic therapy to eliminate the abscesses and control the infection. After 2 years of follow-up, the patient’s SLE and lupus nephritis (LN) were stable, and the cerebral abscesses resolved. In this case report, we discuss the primary treatment and surgical indications, as well as the postoperative treatment regimen, which may help improve the diagnosis and treatment of similar cases.

CASE PRESENTATION

Chief complaints
A 46-year-old woman was admitted to our hospital due to repeated fever with headache that lasted 10 d and was exacerbated for 1 d.

History of present illness
The patient developed fever without any obvious cause 10 days before admission, with a body temperature of 39 °C, along with headache and vomiting. The patient initially believed that she had upper respiratory infection, and therefore self-administered anti-cold medication, which did not alleviate the symptoms.

History of past illness
SLE involving the hematologic system and kidneys was diagnosed 1 year previously, and renal
### Table 1 History of diagnosis in the past year

<table>
<thead>
<tr>
<th>Diagnosis items</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Eyelid and facial edema with skin tightening sensation, pain in multiple joints, hair loss, reduced urine volume, and facial photosensitivity</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>Urine protein: Positive (+++), WBC: 3.5 x 10⁹/L; Total platelet count: 40 x 10⁹/L; Albumin: 21.7 g/L; Creatinine: 149 μmmol/L; Thyroid function: Serum free T3: 1.9 pmol, serum free T4: 8.1 pmol/L; Anti-nuclear antibody profile: ANA positive (1:320 fine granular type), RNP/sm: Positive (+), SSA: Positive (+++), Ro-52: Positive (+++), SSB: Positive (+++), anti-nucleosome antibody: Positive (++), anti-ribosomal P protein antibody: Positive (++); Complement C3: 0.3 g/L</td>
</tr>
<tr>
<td>Bone marrow cell test</td>
<td>Bone marrow cell test showed: Accelerated granulocyte maturation and active plasma cells</td>
</tr>
<tr>
<td>Pathological biopsy</td>
<td>Class IV-G lupus nephritis</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Class IV-G lupus nephritis; SLE (involving the hematologic system and organs) SLEDAI score 11; Subclinical hypothyroidism; Acute renal insufficiency</td>
</tr>
</tbody>
</table>

SLE: Systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index.

### Personal and family history

Her personal and family history was unremarkable.

### Physical examination

Physical examination upon admission indicated a body temperature 38.7 °C, a conscious but dispirited state, painful expression, Cushing syndrome, anemic appearance, facial edema, butterfly-shaped erythema visible on both maxillofacial regions, and diffused moist rales audible in both lungs. No abnormalities were identified in the heart and abdomen. Nervous system examination indicated neck stiffness (+), Kernig sign (+), Brudzinski’s sign (+), high muscle tension in the lower limbs, and Babinski sign (+).

### Laboratory examinations

Routine blood tests showed a white blood cell count of 12.34 x 10⁹/L, neutrophil % of 83.6%, hemoglobin of 92 g/L, hematocrit of 28.5%, platelets of 123 x 10⁹/L, high sensitivity C reactive protein of 18.85 mg/L, procalcitonin of 0.296 ng/mL, erythrocyte sedimentation rate of 60 mm/h, creatinine of 233 μmmol/L, albumin of 22.5 g/L, and a CD4/CD8 ratio of 0.31. A urine test for 24 h urine protein was 5769.4 mg to 9443.5 mg/24 h.

### Imaging examinations

Chest computed tomography indicated dispersed inflammation and fibrotic lesions in both lungs. Brain enhanced magnetic resonance imaging (MRI) (Figure 1) showed multiple nodular abnormal signals in both frontal lobes, left parietal and temporal lobes, and the left masseteric space (left temporalis and masseter region).

### Final Diagnosis

Based on the patient’s medical history and laboratory examinations, she was diagnosed with SLE involving the hematologic system and kidneys (class IV-G LN) complicated with multiple infectious cerebral abscesses.

### Treatment

Upon admission, the patient was given dehydration therapy to lower intracranial pressure. Given her history of renal impairment caused by LN, glycerin fructose alternating with furosemide were used as dehydrating agents instead of mannitol and albumin to avoid exacerbation of renal impairment. Mycophenolate mofetil (MMF) was discontinued immediately due to severe infection, but the prednisone dose (20 mg/d) was maintained. The surgical contraindications of anemia and electrolyte
imbalance were corrected by red blood cell transfusion and fluid infusion, respectively. The surgery was performed immediately after correcting the preoperative contraindications 3 days post-admission. Large abscesses in the left parietal lobe and right frontal lobe were resected via the left parietal approach and right frontal approach (Figure 2), respectively. Other small abscesses in the deeper part of the brain were not removed. Local linear incision was made. Through the scalp, bone valve and endocranium, after accurate positioning, brain tissue edema was observed. During brain histostomy, the abscess wall was found intact and tough, and no important cerebrovascular trunk was found around the abscess, and light yellow pus was aspirated from the abscess. The abscess cavity was completely removed, the blood vessels on the abscess wall were cut off, and electrocoagulation hemostasis was performed (Supplementary Figure 1). During the surgery, abscess wall should be removed completely to avoid pus overflow and reduce the damage to the normal vascular and cerebral tissue around the abscess. Finally, the aspirated light yellow pus was sent for bacterial culture and drug susceptibility testing.

The patient reported significant relief from headache after surgery, and neurological symptoms such as hemiplegia, paresthesia and aphasia were not observed. The patient was given routine postoperative treatments including dehydration therapy (as described previously) and fluid infusion. The bacterial culture obtained on postoperative day 4 indicated *Nocardia asteroides*. Based on the drug susceptibility test results and taking into consideration the patient’s renal dysfunction, a multi-antibiotic regimen was
Table 2 History of treatment in the past year

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
<th>Drug-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (April–December</td>
<td>Primary treatment: Methylprednisolone shock therapy (500 mg/d/3D)/hemodialysis 5 times, once every other day</td>
<td>(due to progressive increase in serum creatinine to 455 μmol/L)/intravenous immunoglobulin</td>
</tr>
<tr>
<td>2017)</td>
<td>Phase 1 Adjunt treatment: Symptomatic treatments to control infection/supplement albumin and supplement thyroxine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase 2 Adjunt treatment: Prednisone 60 mg/d QD maintenance/cyclophosphamide shock therapy (European protocol)</td>
<td></td>
</tr>
<tr>
<td>After discharge (December</td>
<td>Primary treatment: Oral prednisone 40 mg/d, outpatient follow-up, monthly gradually reduced to 20 mg/d/oral</td>
<td></td>
</tr>
<tr>
<td>2017 – April 2018)</td>
<td>Phase 1 Adjunt treatment: Infection control/platelet infusion</td>
<td></td>
</tr>
<tr>
<td>Return for treatment due to</td>
<td>Primary treatment: The prednisone and MMF schemes remained unchanged/Immunomodulatory and anti-</td>
<td></td>
</tr>
<tr>
<td>lung infection (April 2018)</td>
<td>Phase 2 Adjunt treatment: Oral prednisone 20 mg/d/oral MMF 1.0 g bid</td>
<td>infective therapy for lung infection</td>
</tr>
<tr>
<td>After discharge (April–May</td>
<td>Primary treatment: Oral prednisone 20 mg/d/oral MMF 1.0 g bid</td>
<td></td>
</tr>
<tr>
<td>2018)</td>
<td>June 2018 Admitted to hospital due to multiple brain abscesses</td>
<td></td>
</tr>
</tbody>
</table>

MMF: Mycophenolate mofetil.

Figure 2 Surgical strategy. A: Orange arrow indicates the left maxillofacial lesion on which puncture aspiration was performed; B and C: Red arrow indicates the smaller non-resected lesions located in the deeper parts of the left frontal and temporal lobes; Green arrows indicate the larger lesions with greater perilesional edema in the right frontal lobe and left parietal lobe which were resected.

selected consisting of sulfamethoxazole-trimethoprim (30 mg/kg, q12h, oral), ceftriaxone (2 g, q12h, i.v.) and amikacin (6 mg/kg, q24h, i.v.) for the first 3 wk post-surgery, and switched to sulfamethoxazole-trimethoprim (30 mg/kg, q12h, oral) and minocycline (0.1 g, bid, oral) based on the patient’s symptoms and vital signs, imaging and laboratory test results, and nephrotoxicity of the antibiotics. The estimated duration of the entire treatment regimen was one year.

OUTCOME AND FOLLOW-UP

Head MRI one month post-surgery indicated complete resolution of abscesses in the left parietal lobe and right frontal lobe, slight perilesional edema, reduced size of small non-resected abscesses in the left frontal lobe and left caudate nucleus, and significant alleviation of edema around these small lesions. The patient was discharged one month after surgery but continued to receive the prescribed antibiotics (see above), along with prednisone (10 mg/d) maintenance treatment and regular follow-up assessments. Re-examination at 3 mo post-surgery showed further reduction in the size of non-resected lesions in the left frontal and temporal lobes compared to that at 1 mo post-surgery, absorption and dissipation of perilesional edema (Figure 3), and complete disappearance of neurological symptoms. Fortunately, renal function was not affected by the administration of multiple antibiotics (Table 3). Conservative treatment was continued after the patient was updated on her condition. No headaches or other neurological symptoms occurred and LN was stable during the 2-year follow-up period (Table 4).
Figure 3 Preoperative and postoperative brain magnetic resonance imaging. A-C: Sequential preoperative enhanced MR-T1WI showing low lesion signals that are slightly higher than cerebrospinal fluid signal, and uniform, intact and round annular enhancement around the lesions. There are also low perilesional edema signals that are slightly higher than the cerebrospinal fluid signal; D-F: Sequential MR-T1WI at 1 mo post-surgery showing absence of the resected lesions in the right frontal lobe and left parietal lobe, and formation of soft lesions. Lesion in the left maxillofacial region on which puncture aspiration was performed was also absent. Non-resected lesions in the left frontal and temporal lobes were reduced in size, and low edema signals can be observed around the lesions in the left temporal lobe; G-I: Sequential MR-T1WI at three months post-surgery showing further reduction in the size of non-resected lesions in the left frontal and temporal lobes compared with those at 1 mo post-surgery. Edema was absorbed and dissipated.

and Figure 4).

DISCUSSION

SLE is an autoimmune disease that affects multiple organs and systems, and is primarily characterized by dysfunctional humoral immunity, reduced CD8+ T cell cytotoxicity, defective CD4+ T cell proliferation, and impaired antigen presentation by mononuclear cells [5,6]. The current primary treatment for SLE includes high doses of corticosteroids and immunosuppressants. Although these treatments can significantly increase the 5-year and 10-year survival of SLE patients, their prolonged use can exacerbate immunodeficiency and increase the risk of infections, especially intracranial infections, which are one of the major causes of SLE-associated mortality [7]. Fever, headache and meningeal irritation are the major symptoms in SLE patients with intracranial infection. However, they can often become atypical after
Figure 4 Systemic lupus erythematosus related indicators were followed up for 2 years after discharge. A: Changes in routine blood levels 1; B: Changes in routine blood levels 2; C: Changes in liver function; D and E: Changes in renal function; F: Changes in C3, C4.

Prolonged use of corticosteroids and immunosuppressants, resulting in misdiagnosis and missed diagnosis. Sometimes, these patients are even diagnosed with lupus encephalopathy. Therefore, in addition to clinical symptoms, imaging and laboratory tests are essential for accurate diagnosis of cerebral involvement in SLE. Cerebrospinal fluid culture and smear are important diagnostic tests, but their positive detection rates are low. Once the abscess is identified by imaging, biochemical, microbiological and pathological testing of pus are useful to determine the subsequent treatment of patients[8].

Nocardia is a genus of obligate aerobic actinomycetes that are widely found in soil, and most species are non-pathogenic parasites that are found in rotting organic matter. The latter are not part of the normal human microflora and generally do not cause endogenous infections. However, they can cause exogenous conditional infections in patients with late stage progressive disease or immune disorders, especially those with Cushing syndrome, diabetes or under long-term usage of corticosteroids, immunosuppressants and broad-spectrum antibiotics[9]. A similar case was reported previously. After treatment with methylprednisone and cyclophosphamide, a 24-year-old woman with LN developed severe pleural pneumonia and occipital abscess, both caused by Nocardioides asteroides. Although she was treated with multiple antibiotics, she ultimately died[10]. Our patient was diagnosed with SLE and LN
one year before presenting at our hospital, and had been receiving corticosteroids and immunosuppressants, and had undergone hemodialysis due to acute kidney injury. Therefore, she was highly likely to be immuno-deficient and was considered Nocardia-susceptible. In addition, the patient had facial pigmentation along both sides of the jaw and previous skin damage, together with an infectious lesion in her left masseteric space. Puncture aspiration indicated Nocardia infection. We believe that the left jaw was the source of infection, from where the bacterium entered the circulation and eventually reached the brain, forming multiple cerebral abscesses.

A previous study demonstrated that sufficient dosage and duration of antibiotic treatment combined with surgery can effectively treat a Nocardia-induced cerebral abscess[11]. However, the treatment has not yet been standardized based on patients’ physical conditions, surgical approach, and selection and timing of postoperative antibiotics. We believe that the satisfactory outcome of our patient was the result of two factors: the development of a personalized surgical procedure, and immediate identification of the pathogen and its antibiotic susceptibility following surgery. Resection of the two largest cerebral abscesses rapidly resolved the primary symptom (severe headache) of the patient at diagnosis, and prevented further complications that might have been caused by an increase in intracranial pressure. Our patient developed multiple non-uniform cerebral abscesses, most of which were located in important functional regions of the brain. However, preoperative head MRI revealed that the patient’s intracranial pressure was mainly caused by the two large abscesses and perilesional edema in the left parietal lobe and right frontal lobe. Given that the patient was in poor physical condition before surgery (multi-organ damage due to SLE), we selectively resected the two lesions in the left parietal lobe and right frontal lobe, and applied conservative treatment for the smaller lesions in the deeper parts of the brain. A phase II resection strategy was also planned, to be performed when necessary. In addition, we developed a rational anti-microbial regimen taking into account the patient’s renal function. Testing of pus samples aspirated from the cerebral abscesses and maxillofacial region confirmed Nocardia asteroides infection. As a review of the literature indicated that sulfonamides are currently the first-line treatment for Nocardia[12,13], we selected a combination of sulfamethoxazole-trimethoprim, ceftriaxone and amikacin to ensure treatment efficacy. After 3 wk of intravenous administration, the patient no longer experienced fever, and routine blood testing during follow-up indicated resolution of the infection. To reduce nephrotoxicity of the drugs and prevent further renal impairment, we switched to continuous oral sulfamethoxazole-trimethoprim plus minocycline for one year[14,15]. The antibiotic regimen described above showed good results and avoided secondary surgery. In addition, stopping immunosuppressants was also the right decision.

**CONCLUSION**

In summary, we can draw three conclusions from this case. First, SLE patients often have secondary infections due to corticosteroid and immunosuppressive treatments, and due to more emphasis on the lungs, the brain and other organs are often not screened. Second, timely discontinuation of MMF during infection was conducive to improving the patient's own immunity to fight the infection. This also indirectly relieved SLE due to reduction of the systemic inflammatory response, rather than suddenly aggravated by withdrawal of MMF. This also reflects the need for a holistic immune balance in the body. Third, timely identification of the pathogen and source of infection, treatment adjustment, by means of surgery, and development of a personalized antibiotic regimen can result in a satisfactory treatment outcome for rare diseases.
### Table 4 Indices of lupus nephritis and infection after 2 years follow-up

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<th>Date</th>
<th>WBC (10^9/L)</th>
<th>Neu (%)</th>
<th>RBC (10^12/L)</th>
<th>HGB (g/L)</th>
<th>PLT (10^9/L)</th>
<th>ALB (g/L)</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>BUN (mmol/L)</th>
<th>CREA (μmol/L)</th>
<th>eGFR (mL/min)</th>
<th>24 h PRO in urine (mg/24h)</th>
<th>C3 (g/L)</th>
<th>C4 (g/L)</th>
<th>ESR (mm/h)</th>
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HGB: Hemoglobin; PLT: Platelets; ALB: Albumin; AST: Aspartate transaminase; ALT: Alanine transaminase; BUN: Blood urea nitrogen; CREA: Creatinine; eGFR: Estimated glomerular filtration rate; PRO: Protein; C3: Complement 3; C4: Complement 4.

### FOOTNOTES

**Author contributions:** Hu QD and Liao LS contributed equally to this study. Hu QD was the patient’s nephrologist, searched the literature, collected data, wrote, and edited the manuscript; Liao LS was the patient’s neurosurgeon; Liao LS and Zhang Y reviewed the literature and contributed to manuscript drafting; Zhang Q and Liu J were responsible for revision of the manuscript for important intellectual content; all authors issued final approval of the version to be submitted.

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REFERENCES


Median arcuate ligamentum syndrome: Four case reports

Ji Eun Kim, Poong Lyul Rhee

**Abstract**

**BACKGROUND**
Median arcuate ligamentum syndrome (MALS) is a disease entity with unclear pathogenesis. If it is not considered in advance, the clinical diagnosis of the disease is very difficult because patients complain of digestive discomfort including pain. However, this characteristic is not specific to MALS. There have been no studies to assist in making a quick diagnosis. The aim of this case series was to recognize that MALS must be considered as a differential factor in the cause of abdominal pain.

**CASE SUMMARY**
We described cases in which four patients complained of abdominal pain over a long period but in whom a diagnosis of MALS could not be made. If the gastroenterologist does not take into account abdominal pain in advance, the patient is considered an asymptomatic gallstone patient and has their gallbladder removed despite imaging evaluation. The patient may also be considered a psychiatric patient and may be administered psychiatric drugs over a long period. In all four cases in this report, the patients experienced abdominal pain. In three cases, the diagnosis was possible by the clinician’s judgment considering both clinical symptoms and imaging techniques shortly after the onset of symptoms. However, in one case that lasted over 20 years, a clear diagnosis was not possible. Even after complaining of colicky pain and performing a cholecystectomy, the diagnosis was made only after the symptoms persisted. In all four cases, the symptoms were relieved by neuromodulators.

**CONCLUSION**
MALS is a rare disease and it is easy to miss because it is not malignant, but patients can suffer from pain over a long period. For the accurate diagnosis of a patient complaining of abdominal pain, the diagnosis must be differentiated. In addition, as there are asymptomatic patients, patients who need treatment should be carefully selected, and improvement with medical treatment can be expected. Large-scale studies are also needed.
**Key Words:** Median arcuate ligamentum syndrome; Abdominal pain; Missed diagnosis; Neuromodulator; Celiac artery compression; Case report

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**Core Tip:** A considerable number of median arcuate ligamentum syndrome patients are overlooked in the diagnosis of patients complaining of abdominal pain. They are unable to lead a normal life due to severe excruciating pain. However, without an accurate diagnosis, they are misunderstood as symptomatic gallstone patients and have their gallbladder removed or experience pain for a long time. In addition, as the currently known treatment involves surgery based on a mechanistic hypothesis, there are concerns about its complications. Therefore, medical drug treatment should be prioritized to determine whether improvement occurs.

**INTRODUCTION**

Median arcuate ligamentum syndrome (MALS) is a disease entity with unclear pathogenesis\[1,2\]. If it is not considered in advance, the clinical diagnosis of the disease is very difficult because patients complain of digestive discomfort including pain, but this characteristic is not specific to MALS\[3-6\]. Most of the studies conducted through a retrospective analysis of incidental celiac artery compression in asymptomatic patients have been imaging studies\[7-10\], but the data are difficult to apply in actual clinical practice. This is because accidental image discovery does not require treatment. In addition, the surgical cases experienced by many surgeons only concern surgical methods for diseases that have already been diagnosed through complex processes\[11,12\], and no studies have been conducted to help make a quick diagnosis in these patients.

Therefore, it is necessary to introduce MALS as a causal disease, which should be considered in patients complaining of digestive symptoms at the gastroenterology department. Here, we present four patients diagnosed with MALS.

**CASE PRESENTATION**

**Chief complaints**

**Case 1:** A 63-year-old male patient with no specific medical history visited our clinic complaining of epigastric pain with heartburn symptoms that started 2 years earlier.

**Case 2:** A 64-year-old female patient, complaining of indigestion for 20 years had been treated for stress-induced gastritis, irritable bowel syndrome with constipation, and reflux esophagitis.

**Case 3:** A 62-year-old female patient with an underlying alcohol-related disorder complained of indigestion 3 d earlier and took digestive medicines, but there was no improvement.

**Case 4:** A 47-year-old female patient was admitted with severe abdominal pain that started several years ago.

**History of present illness**

**Case 1:** The location of the pain was in the upper abdomen, and the pain lasted for 2 to 3 min. The patient mentioned that the pain intensity sometimes even woke him up and that it subsided when he walked and slightly improved when he bent over. Although he had been administered a proton pump inhibitor (PPI), motility-increasing agent, and mucosal protective agent at local clinics for several years, there was no improvement. Endoscopy and a computed tomography (CT) were already done at other hospitals. The CT readings at the other hospitals showed normal findings and malignancy was excluded.

**Case 2:** She underwent cholecystectomy at another hospital because of colicky pain, but she was still complaining of unbearable abdominal pain and came to our hospital. Endoscopy and a CT scan were
performed again and normal findings were reported.

**Case 3:** She visited the emergency room for severe abdominal pain but returned home without any specific findings on the CT scan. An outpatient clinic history was done again. Her squeezing pain persisted for more than 10 min at one time and was sometimes accompanied by chills.

**Case 4:** She felt excruciating pain in the upper abdomen that lasted several minutes to hours and the pain was not related to eating or defecation. Extreme pain even woke her up at night. It occurred once or twice a year, and PPI and prokinetics administration had no effect. The pain intensity decreased when leaning forward or breathing in.

**History of past illness**
The patients had a free previous medical history.

**Physical examination**
The patients’ abdomen was soft and had no tenderness.

**Laboratory examinations**
Blood analyses were normal.

**Imaging examinations**

**Case 1:** We reviewed the medical history based on the characteristics of pain and the CT again, and a focal point of CT stenosis in the celiac axis was suspected (Figure 1A). Therefore, CT angiography (CTA) was performed. On the CTA, it was observed that the celiac trunk originating from the upper abdominal aorta was compressed by the diaphragmatic crus (Figure 1B). As a result, the origin of the celiac trunk showed focal tight narrowing, and along with clinical symptoms, the diagnosis could be made.

**Case 2:** Considering the patient's clinical features, we thought of diseases that could be missed by imaging techniques. Celiac artery compression was confirmed by reviewing the imaging studies (Figure 2A-C). This time, the collateral vessels around the pancreas were reviewed for narrowing of the celiac artery.

**Case 3:** CTA was performed based on clinical suspicion and celiac luminal narrowing was found due to focal calcification in the imaging tests (Figure 3A and B).

**Case 4:** There were no specific findings on endoscopy and abdominal ultrasonography, so based on clinical symptoms, an abdominal CT was performed, and MALS was diagnosed (Figure 4A-C).

**FINAL DIAGNOSIS**
The final diagnosis of the presented four cases is median arcuate ligamentum syndrome.

**TREATMENT**

**Case 1**
The patient’s condition improved after the administration of amitriptyline 10 mg to treat visceral neurologic symptoms and Tegoprazan 50 mg. The patient showed an immediate symptom improvement response to amitriptyline before active analgesic administration. Thus, even before active treatment, through diagnosis alone, improvement was already demonstrated. During follow-up, if any pain remains after observation for more than 3 mo, a pain relief agent and an active agent for reducing neurotransmitters will be used.

**Case 2**
Neuropathic pain was relieved after the administration of gabapentin 100 mg, meloxicam 20 mg, and famotidine 20 mg b.i.d.

**Case 3**
Gabapentin 100 mg, meloxicam 7.5 mg b.i.d, and esomeprazole were prescribed. She was due for an outpatient visit in 3 mo. The patient was asked to visit our hospital again if the symptoms worsened. She has been living without recurrence for a month after being prescribed medications.
**Figure 1** Imaging examinations of case 1. A: Computed tomography (CT) shows the celiac trunk originating from the upper abdominal aorta rather than in the normal case; B: CT angiography shows narrowing of the orifice of the celiac trunk due to compression by the diaphragmatic crus.

**Figure 2** Computed tomography shows the proximal celiac axis narrowing with collateral vessel formation. A: Axial view; B: Sagittal view; C: Computed tomography angiography confirmed the diagnosis.

**Figure 3** Computed tomography angiography shows mild luminal narrowing at the orifice of the celiac trunk with adjacent abdominal aortic calcification. A: Axial view; B: Sagittal view.

**Case 4**
She was prescribed gabapentin 100 mg, meloxicam 7.5 mg, and famotidine 20 mg b.i.d, and her symptoms improved significantly.

**OUTCOME AND FOLLOW-UP**
The symptoms of all 4 patients were much relieved with medical treatment, and they are being followed up on an outpatient clinics.
DISCUSSION

In all four cases, the patients experienced abdominal pain. In three cases, the diagnosis was possible by the judgment of the clinician shortly after the onset of symptoms. However, in one case that lasted over 20 years, a clear diagnosis was not possible. Even after complaining of colicky pain and performing a cholecystectomy, the diagnosis was made only after symptoms persisted. In all four cases, the symptoms were relieved by neuromodulators.

There are two current common hypotheses of MALS, which have been defined through several studies. The first one is neurologic pain caused by the compression of the celiac plexus and the other one is defined by compression of the celiac artery\cite{2,10}. However, most hypotheses are based on images that were retrospectively analyzed and a defined protocol for making a diagnosis has not been developed. If this is due to ischemic arteriality, collateral vessels may develop, but the pain caused regardless of the produced collateral vessels. Importantly, ischemia cannot be reversible when the pain is maintained for a long time.

Therefore, the imaging diagnosis is only an auxiliary diagnosis. If the clinician does not suspect this diagnosis, the latter will happen very late. Most of the patients who came to the outpatient clinic of the department of gastroenterology at the tertiary hospital for indigestion and abdominal pain underwent an endoscopy and CT. However, it is not easy to identify rare diseases without providing clinical information from tens of thousands of still images. In addition, since the focus is on the exclusion of malignant tumors related to mortality pain is often considered a psychological disease despite its chronic nature, and is ignored.

A report in 2017 reported only one case\cite{13}. Other case reports that dealt with diagnosed cases relied on images and explained the pathological mechanisms for bowel ischemia, but they could not explain the absence of symptoms of intestinal damage due to ischemia\cite{14}. Surgical treatments, such as gangliectomy along with arterial reconstruction, have been proven to be effective\cite{11}, but considering that there are no symptoms even when pressed, physical removal may not be the only solution. This case is very novel because no cases have reported the outcomes of medical treatment and it raises awareness about a diagnosis that should not be missed. This case was written to suggest that a gastroenterologist must make a differential diagnosis. And since the gastroenterologist judges all the clinical results together, the evaluation is performed after confirming these. The following algorithm illustrates this process (Figure 5).

A limitation of this study was that the number of cases studied was too small. However, given that numerous MALS diagnoses have been missed, it is necessary to review many patients in the future and establish the diagnostic flow, considering the possibility that the etiology itself may be wrong. Since considering only four cases is insignificant, it will be necessary to review patients experiencing abdominal pain who have numerous missed diagnoses in the future. A common diagnostic flow is also required.

CONCLUSION

MALS is a rare disease and it is easy to miss because it is not malignant, but patients experience pain over a long period. For the accurate diagnosis of a patient complaining of abdominal pain, the diagnosis must be differentiated. In addition, as there are asymptomatic patients, patients who need treatment should be carefully selected, and improvement with medical treatment can be expected. Large-scale studies are also needed.
Figure 5 Algorithm for median arcuate ligament syndrome diagnosis through imaging modalities and clinical history. MALS: Median arcuate ligament syndrome; NRS: Numeric pain rating scale; GB: Gallbladder; CT: Computed tomography; CTA: Computed tomography angiography.

FOOTNOTES

Author contributions: Rhee PL did study concept and design; Kim JE did data acquisition, drafting of the manuscript and critical revision of the manuscript for important intellectual content; all authors did approval of final manuscript.

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REFERENCES


Novel \(\text{ABCB4}\) mutations in an infertile female with progressive familial intrahepatic cholestasis type 3: A case report

Tian-Fu Liu, Jing-Jing He, Liang Wang, Ling-Yi Zhang

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Peer-review model: Single blind

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Abstract

BACKGROUND
Mutations that occur in the \(\text{ABCB4}\) gene, which encodes multidrug-resistant protein 3, underlie the occurrence of progressive familial intrahepatic cholestasis type 3 (PFIC3). Clinical signs of intrahepatic cholestasis due to gene mutations typically first appear during infancy or childhood. Reports of PFIC3 occurring in adults are rare.

CASE SUMMARY
This is a case study of a 32-year-old infertile female Chinese patient with a 15-year history of recurrent abnormal liver function. Her primary clinical signs were elevated levels of alkaline phosphatase and \(\gamma\)-glutamyl transpeptidase. Other possible reasons for liver dysfunction were eliminated in this patient, resulting in a diagnosis of PFIC3. The diagnosis was confirmed using gene detection and histological analyses. Assessments using genetic sequencing analysis indicated the presence of two novel heterozygous mutations in the \(\text{ABCB4}\) gene, namely, a 2950C>T; p.A984V mutation (exon 24) and a 667A>G; p.I223V mutation (exon 7).

After receiving ursodeoxycholic acid (UDCA) treatment, the patient’s liver function indices improved, and she successfully became pregnant by in vitro fertilization. However, the patient developed intrahepatic cholestasis of pregnancy in the first trimester. Fortunately, treatment with UDCA was safe and effective.

CONCLUSION
These novel \(\text{ABCB4}\) heterozygous mutations have a variety of clinical phenotypes. Continued follow-up is essential for a comprehensive understanding of PFIC3.

Key Words: Progressive familial intrahepatic cholestasis type 3; \(\text{ABCB4}\) gene; Infertility; Intrahepatic cholestasis of pregnancy; Case report

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Core Tip: This is the first case report of an adult patient with progressive familial intrahepatic cholestasis type 3 (PFIC3) and infertility. Gene detection was central to making a definitive diagnosis. The novel ABCB4 heterozygous mutations observed exhibited a variety of clinical phenotypes. A genetic predisposition to infertility may also be present in this patient and requires further research. The discovery of these new mutations has enriched the information on the clinical features of PFIC3 and contributed to a more comprehensive understanding of ABCB4 disease.

DOI: https://dx.doi.org/10.12998/wjcc.v10.i6.1998

INTRODUCTION
Progressive familial intrahepatic cholestasis (PFIC) comprises several rare, hereditary autosomal-recessive hepatic diseases that occur predominantly in neonates and infants. Intrahepatic cholestasis is the primary clinical sign observed in patients with PFIC[1]. As the disease progresses, patients develop liver fibrosis, which progresses to cirrhosis and eventually hepatic failure[2]. Based on the specific mutations in the gene, six types of PFIC have been defined, among which classical types 1, 2 and 3 are more common[3]. In terms of biochemical and histological characteristics, there are significant differences between PFIC3 and other types (Table 1). In particular, PFIC3 presents with elevated serum γ-glutamyl transeptidase (GGT)[4]. We found few reports of cases of PFIC3 in our search of the published literature, which included the last ten years. In particular, fertility in adult PFIC3 patients has not been reported.

CASE PRESENTATION

Chief complaints
A 32-year-old female patient had experienced abnormal serum liver enzyme levels for 15 years.

History of present illness
Fifteen years previously, the patient was diagnosed with abnormal serum liver enzyme levels during the course of a high school physical examination. As she did not exhibit any symptoms of overall liver dysfunction, no action was taken at that time. Four years later, liver function index abnormalities were observed during an occupational health examination. The patient was admitted to a local hospital with no apparent cause of her abnormal serum enzyme levels. The patient was treated with some liver-protective drugs, but her liver function indices did not improve. The patient was not experiencing any adverse effects at that time and did not actively have her liver function indices monitored in subsequent years. One month prior to her admission to our hospital, the patient visited a maternal and child health hospital due to infertility, but routine examination on admission revealed significantly abnormal liver function indices. For further diagnosis and treatment, she was admitted to the Department of Hepatology at our hospital.

History of past illness
Thirteen years previously, the patient had undergone splenectomy due to a ruptured spleen caused by a car accident and recovered well.

Personal and family history
During her ten years of marriage, the patient experienced continued infertility and did not take any infertility medications or oral contraceptives. One year previously, salpingography at a maternal and child health hospital showed partial obstruction of the fallopian tube, and the natural conception rate was low. The fertility tests of the patient’s spouse were normal. Therefore, in vitro fertilization (IVF)-assisted reproduction was recommended. However, due to financial reasons, the patient did not receive IVF.

The patient indicated that she did not have a history of alcohol intake or the use of any hepatotoxic drugs. Her father had undergone surgery years previously to treat intrahepatic bile duct stones and recovered well from the surgery. Her mother, who died from a brain hemorrhage three years earlier, did not have liver disease in her medical history. Her brother’s liver function was normal.
Table 1 Gene, clinical and histological features of different types of progressive familial intrahepatic cholestasis type 3

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PFIC: Progressive familial intrahepatic cholestasis; FIC1: Familial intrahepatic cholestasis 1; BSEP: Bile salt export pump; MDR3: Multidrug resistance class 3; ALT: Alanine aminotransferase; GGT: γ-glutamyl transpeptidase; TBA: Total bile acid.

Physical examination
The patient’s vital signs were all stable, and physical examination revealed no noteworthy positive signs.

Laboratory examinations
Analysis of her laboratory data (November 3, 2020) revealed the following results: total bilirubin, 28.1 μmol/L; direct bilirubin, 16.1 μmol/L; alanine aminotransferase (ALT), 151 U/L; aspartate aminotransferase (AST), 119 U/L; alkaline phosphatase (ALP), 226 U/L; GGT, 1025 U/L; total bile acid (TBA), 17.2 μmol/L; and albumin, 41.8 g/L (Table 2). Several markers for hepatitis viruses (hepatitis A, B, C, and E) were determined to be negative. The analyses for antibodies to cytomegalovirus antibodies and Epstein-Barr virus DNA were also negative. All autoimmune antibodies, including antimitochondrial and antinuclear lupus-related antibodies and Sjogren’s syndrome-related antibodies were negative. We also assessed serum copper levels as well as ferritin and ceruloplasmin, and the levels were within normal ranges. Routine blood analysis, coagulation function, thyroid function, and several additional laboratory test results were found to be unremarkable.

Imaging examinations
Abdominal magnetic resonance imaging (MRI) revealed an increased hepatic interstitium and multiple patchy abnormal signal shadows in hepatic segments VII and VIII. The presence of nodule regeneration was considered after enhanced examination using gadolinium-ethoxybenzyl-diethyleneetriamine pentaacetic acid, which is a hepatocellular-specific contrast agent. No obstructions associated with the extrahepatic and intrahepatic bile ducts were observed following detailed examination using magnetic resonance cholangiopancreatography (Figure 1). Cardiac ultrasound and chest radiography showed no abnormalities.

Specialized examinations
We examined the sclera of the patient’s eyes for Kayser-Fleischer rings, but no rings were present. The transient elastography assessment for liver fibrosis was 14.6 kPa.

Pathological findings and immunohistochemical staining
With the consent of the patient, we performed an ultrasound-guided liver biopsy. Pathological examination revealed cholestatic liver fibrosis (modified Scheuer score S2). An analysis of histological samples revealed a significant decrease in multidrug-resistant protein 3 (MDR3) protein staining compared to the levels of staining observed in samples from healthy subjects (Figure 2).

Gene mutational analysis
Genomic DNA was purified from peripheral blood samples. Based on Illumina NovaSeq® 6000 instruments and the xGen® sequencing Exome Research Panel, high-throughput sequencing was used to detect genomic mutations. The genetic testing results revealed two novel heterozygous mutations in the ABCB4 gene: a 2950C>T; p.A984V mutation (exon 24) and a 667A>G; p.I223V mutation (exon 7) (Figure 3).
<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Discharge</th>
<th>Before pregnancy</th>
<th>13th week of pregnancy</th>
<th>21st week of pregnancy</th>
<th>30th week of pregnancy</th>
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<tr>
<td>ALT (7-41 U/L)</td>
<td>151</td>
<td>18</td>
<td>12</td>
<td>85</td>
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<tr>
<td>AST (13-35U/L)</td>
<td>119</td>
<td>48</td>
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<tr>
<td>TBil (3.0-21.0 μmol/L)</td>
<td>28.1</td>
<td>14.1</td>
<td>21.1</td>
<td>27.4</td>
<td>21.5</td>
<td>33.2</td>
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<tr>
<td>DBil (0.1-6.8 μmol/L)</td>
<td>16.1</td>
<td>9.3</td>
<td>12.0</td>
<td>15.3</td>
<td>11.3</td>
<td>20.8</td>
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<tr>
<td>GGT (7.45U/L)</td>
<td>1025</td>
<td>459</td>
<td>301</td>
<td>470</td>
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<td>148</td>
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<td>ALP (35-100 U/L)</td>
<td>226</td>
<td>126</td>
<td>147</td>
<td>223</td>
<td>133</td>
<td>251</td>
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<tr>
<td>TBA (0.0-10.0 μmol/L)</td>
<td>17.2</td>
<td>19.9</td>
<td>15.3</td>
<td>40.5</td>
<td>52.1</td>
<td>81.8</td>
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</table>

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: γ-glutamyl transpeptidase; TBil: total bilirubin; DBil: Direct bilirubin; TBA: Total bile acid.

**Figure 1** Liver magnetic resonance images. A: T1-weighted image. The size and shape of the liver are normal, and patchy low signal intensity can be seen in the SVII segment, with a diameter of approximately 15 mm. Loss of spleen; B: T2W spectral attenuated inversion recovery image. The interstitium increased in the liver, and the lesions in the SVII segment showed high signal intensity; C: Gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid 15MIN_Delay image. The signal intensity of SVII segment lesions was basically consistent with that of normal liver; D: Magnetic resonance cholangiopancreatography image. No stricture or dilatation of the intrahepatic or extrahepatic bile duct was observed.

**FINAL DIAGNOSIS**

According to the above case data, the patient’s liver function, particularly the increase in serum GGT, was abnormal for many years. Immunohistochemical analysis of liver tissue showed that MDR3 staining was significantly decreased, and gene detection showed that there were two heterozygous mutations in the ABCB4 gene. The final diagnosis of the presented case was PFIC3.

**TREATMENT**

The patient received treatment with ursodeoxycholic acid (UDCA) 750 mg/d.
Figure 2 Pathological examination of liver biopsy specimens. A: The interstitial fibrous tissue in the portal area proliferates, and the fibrous septum is formed (Masson; original magnification × 100); B: The portal area was enlarged with moderate mixed inflammatory cell infiltration and mild interfascial inflammation (hematoxylin and eosin; original magnification × 100); C: Irregular arrangement of the epithelium of the small bile duct in the portal area (hematoxylin and eosin; original magnification × 200); D: Absence of small bile duct in part of the portal area (CK7; original magnification × 200); E: Multidrug resistance protein 3 (MDR3) protein staining decreased significantly (immunohistochemical staining; original magnification × 200); F: Liver biopsy specimens from a healthy person showing normal expression of the MDR3 protein (immunohistochemical staining; original magnification × 200).

OUTCOME AND FOLLOW-UP
When the patient was discharged, the GGT decreased significantly, and the other liver function indices were close to the normal values (Table 2). After consulting with family members and saving money, the patient went to the maternal and child health care hospital again, successfully became pregnant via IVF, and stopped UDCA treatment on her own. Skin pruritus occurred at the 13th week of pregnancy, and serological examination showed that her liver function was significantly abnormal, in particular, TBA was higher than the initial value. The diagnosis was PFIC3 combined with intrahepatic cholestasis of pregnancy (ICP), and UDCA therapy was recommended. Her symptoms of itching were subsequently alleviated, and all liver function indices except TBA were improved. Fortunately, fetal indicators were normal. The liver function test results during the course of the disease are shown in Table 2.

DISCUSSION
PFIC3 occurs rarely and is primarily a sporadic disease[5], and the incidence of PFIC3 in the general population has not been reported definitively. A previous assessment of disease occurrence demonstrated that PFIC3 incidence might be 1 in 500000 people[6]. Patients exhibiting PFIC3 commonly develop cholestasis later in childhood and up to adolescence. Individuals with PFIC3 often exhibit recurring episodes of pruritus, jaundice, pale clay-like stools, hepatosplenomegaly, and gastrointestinal bleeding, which can progress to cirrhosis and liver failure before the onset of adulthood[7,8]. Gastrointestinal bleeding that is associated with cirrhosis or the occurrence of portal hypertension is often the first presenting sign of the disorder in older children or young adults[9].
In this case study, we analyzed a 32-year-old female Chinese patient who was asymptomatic. We used laboratory, MRI, and histological examinations to exclude other possible etiologies, including primary biliary cholangitis, Alagille syndrome, primary sclerosing cholangitis, Wilson's disease, and drug-induced liver injury. Subsequently, we highly suspected that this patient might have PFIC3 based on her high level of GGT. Therefore, we carried out a gene mutation analysis that revealed two novel heterozygous mutations in ABCB4, namely, a 2950C>T; p.A984V mutation and a 667A>G; p.I223V mutation. Based on immunostaining for MDR3 in liver samples and genetic testing, the patient was...
diagnosed with PFIC3. PFIC3 is caused by a mutation in the ABCB4 gene, which encodes MDR3. MDR3 is classified as a p-glycoprotein (pGp) and has been shown to be expressed in hepatocyte canalicular membranes. The MDR3 protein transfers phospholipids from hepatocytes into the bile ducts. Normally, phospholipids combine with bile salts that subsequently form microparticles. This process results in increased hydrophilicity and reduces the descaling effects produced by bile salts. These actions protect bile duct cells from toxic damage that can be induced by bile salts. A major function of phospholipids in the liver is to neutralize the detergent-like effects produced by hydrophobic bile salts. Thus, defects in the MDR3 protein can result in damage to the biliary epithelium and bile canaliculi, which ultimately can produce cholestasis. It should be noted that the primary defect that occurs with MDR3 deficiency does not lead to the retention of bile acids in hepatocytes, so cholestasis is not a direct result of the disorder. Symptoms, including cholestasis, develop as a result of the damage caused by the eventual cholangiopathy. Even patients who exhibit complete MDR3 deficiency may not present clinical symptoms for several years. When MDR3 function is only partially lost, patients commonly exhibit slow disease progression. Therefore, MDR3 deficiencies can result in a range of disease manifestations and ages at presentation.

Nearly 300 ABCB4 variants that cause disease have been reported, of which approximately 50 are associated with PFIC3. The age at which the patient first exhibits signs of cholestatic disease, severity of the liver disorder and response to treatment have been shown to be correlated with the different mutations that occur in the ABCB4 gene. Patients with homozygous mutations tend to exhibit progressive intrahepatic cholestasis, which usually leads to liver failure in early childhood and requires liver transplantation. On the other hand, the age of disease onset in patients with heterozygous mutations is relatively high, and clinical symptoms are mild. New evidence demonstrates a spectrum of diseases resulting from heterozygous mutations in ABCB4, ranging from the severe form seen in PFIC3 to milder, intermittent forms such as low-phospholipid-associated cholelithiasis syndrome (LPAC), ICP and adult-onset biliary fibrosis or cirrhosis. Previous studies have shown that reduced or absent transport of phosphatidylcholine is indeed associated with intrahepatic sludge or stone formation. The father of the patient had a genetic mutation in ABCB4, including a 2950C>T; p.A984V mutation, and his preexisting intrahepatic bile duct stone may have been a phenotypic form of LPAC. Although the majority of cases of ICP present in the third trimester and are usually thought to be multifactorial in etiology, the patient’s early pregnancy presentation may have been attributed to an underlying genetic susceptibility. ABCB4 gene defects are one of the major causes of biliary fibrosis, and Bernardo et al. reported that PFIC3-associated biliary fibrosis can be partially reversed after UDCA treatment. However, the coexistence of ABCB4 variants and infertility has not been reported in previously published literature. While not proof of causality, the mutations identified in our patient certainly suggest a possible susceptibility for her rare and unique presentation.

Genetic sequencing of the ABCB4 gene in our patient revealed two novel heterozygous mutations, namely, a 2950C>T; p.A984V mutation and a 667A>G; p.I223V mutation. These two mutations were not included in the Human Gene Mutation Database or the ClinVar database. The effects on function resulting from the two mutations were evaluated using Polymorphism Phenotyping v2, Sorting Intolerant from Tolerant, and MutationTaster. The two novel mutations were predicted to have uncertain significance. Based on the familial identification, the locations of these two mutations were determined to be on different chromosomes, which resulted in a compound heterozygous mutation that might have resulted in a partial loss of function for MDR3. It is due to this compound heterozygous mutation that this patient has a rare and unique clinical phenotype.

UDCA is typically used as the initial treatment for PFIC3. Some studies have shown that a dose of 10-30 mg/kg/day can successfully treat PFIC3 and resolve the presence of cholestasis in patients. UDCA has been shown to be effective in two-thirds of PFIC3 patients. Korkut et al. reported that UDCA treatment was effective in improving conception in women who had intrahepatic cholestasis and were infertile. Here, the patient successfully became pregnant after UDCA treatment following a single IVF treatment, and UDCA treatment may have had some potential beneficial effects. The patient responded well to UDCA therapy. After UDCA treatment, the serum GGT in this patient decreased significantly, and the other liver function indices basically returned to normal. However, after the combination of ICP, UDCA improved the symptoms of pruritus and liver function, but TBA showed an upward trend. The increase in TBA may harm the fetus, so it is necessary to closely monitor the fetal index and deliver early if necessary. The remaining one-third of patients may require additional intervention due to the degree of disease progression and inadequate symptom relief. When other treatments are unsuccessful, liver transplantation has been shown to be effective in PFIC3 patients. However, long-term follow-up to monitor the patient’s liver function is necessary.

**CONCLUSION**

We were able to definitively diagnose PFIC3 in a 32-year-old female Chinese patient based on her
clinical symptoms, pathological examination, and gene detection. Successful gene detection was essential to the diagnosis. This case illustrates the heterogeneity of genetic mutations. These novel \textit{ABCB4} heterozygous mutations have a variety of clinical phenotypes that respond well to UDCA therapy. A genetic predisposition to infertility may also be present in this patient, and this requires further research. The discovery of these new mutations has enriched the information on the clinical features of PFIC3 and contributed to a more comprehensive understanding of \textit{ABCB4} disease.

\textbf{ACKNOWLEDGEMENTS}

The authors thank the patient for agreeing to report her case and for providing a detailed medical history.

\textbf{FOOTNOTES}

\textbf{Author contributions:} Liu TF reviewed the literature and was responsible for manuscript drafting and organization of illustrations; He JJ and Wang L analyzed and interpreted the pathological findings, immunohistochemical findings, and genetic mutations; Zhang LY was responsible for revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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Primary duodenal dedifferentiated liposarcoma: A case report and literature review

Nah Ihm Kim, Ji Shin Lee, Chan Choi, Jong Hee Nam, Yoo Duk Choi, Hee Joon Kim, Sung Sun Kim

BACKGROUND
Dedifferentiated liposarcoma (DDLPS) is an extremely rare neoplasm that exhibits various morphologies. The tumor is characterized by immunoreactivity to MDM2 and CDK4 and can be confirmed by detecting MDM2 amplification via fluorescence in situ hybridization (FISH). Herein, we report an unusual case of DDLPS arising from the duodenum.

CASE SUMMARY
A 64-year-old man presented with repeated abdominal pain and weight loss. Radiologic studies revealed a mass of the duodenum involving the pancreas. The patient was treated with pylorus-preserving pancreaticoduodenectomy. Histologically, the tumor showed a high-grade sarcoma. Immunohistochemistry demonstrated that the tumor cells were positive for MDM2 and CDK4 expression. MDM2 amplification was detected via FISH, leading to the final diagnosis of DDLPS. Following surgery, the patient was treated in the intensive care unit due to peritonitis, and died 60 d after surgery.

CONCLUSION
To the best of the authors’ knowledge, this is the first case of primary duodenal DDLPS in Korea and the third case in the English-language literature. Care must be taken not to misdiagnose DDLPS as another high-grade tumor. Liposarcoma should be in the differential diagnosis list.

Key Words: Liposarcoma; Primary; Small bowel; Duodenum; Immunohistochemistry;
Core Tip: Primary dedifferentiated liposarcoma (DDLPS) originating from the duodenum are rare and can be diagnosed based on histology, immunohistochemistry and MDM2 amplification via fluorescence in situ hybridization. Differential diagnoses are required along with consideration of DDLPS.

INTRODUCTION
Liposarcoma is the most common form of malignant soft tissue tumor and tends to occur in the retroperitoneum, deep soft tissues of the trunk, and extremities[1]. Primary liposarcoma of the gastrointestinal tract is extremely rare, with only a few cases reported in the literature[2-10]. In this report, we describe a unique case of dedifferentiated liposarcoma (DDLPS) originating from the duodenum and review previously reported cases. Pathologists should keep liposarcoma in the differential diagnosis list.

CASE PRESENTATION
Chief complaints
A 64-year-old male presented with a 7-d duration of repeated abdominal pain.

History of present illness
The patient also complained of 8 kg weight loss in 3 mo.

History of past illness
The patient had been on antihypertensive medication for 20 years.

Personal and family history
He had no other significant personal or family medical history.

Physical examination
Physical examination revealed diffuse abdominal tenderness, but a palpable mass was not detected.

Laboratory examinations
Laboratory findings showed slight elevation of aspartate aminotransferase (55 U/L). Tumor markers including carcinoembryonic antigen (2.13 mg/mL), were within the normal range.

Imaging examinations
Abdominal computed tomography (CT) revealed a 3 cm-sized heterogeneously enhancing mass in the pancreaticoduodenal groove, causing the obstruction of the second portion of the duodenum.

FINAL DIAGNOSIS
The preoperative differential diagnosis was duodenal adenocarcinoma, gastro-intestinal stromal tumor (GIST), or leiomyosarcoma (LMS). An accurate diagnosis via preoperative upper endoscopy was not possible because only the mucosal surface was collected due to duodenal stenosis. The duodenal tumor was diagnosed as DDLPS by combining all clinical, radiologic, and intraoperative findings and histologic data (Figure 1 and Figure 2).
Figure 1 Radiologic findings. A, B: Abdominal computed tomography scan demonstrated a heterogeneously enhanced mass in the pancreaticoduodenal groove with duodenal obstruction.

Figure 2 Features of tumor cells. A: The tumor was located in the submucosal layer of the duodenum (Hematoxylin-and-eosin stain, ×20); B: At a higher magnification, undifferentiated tumor cells were shown to have marked nuclear atypia with brisk mitotic activity (Hematoxylin-and-eosin stain, ×200); C: Immunohistochemistry revealed positivity for MDM2 in the tumor cells (Immunohistochemistry, ×200); D: MDM2 amplification was detected by MDM2/CEN12 fluorescence in situ hybridization assay (MDM2-green signals, CEN12-red signals, ×1000).

TREATMENT

The patient underwent pylorus-preserving pancreaticoduodenectomy with en bloc right hemicolecction, superior mesenteric vein segmental resection, and inferior vena cava wedge resection. Intraoperatively, the duodenal mass invaded the pancreas and hepatic flexure of the colon, resulting in gastric and duodenal distension. The tumor also appeared to invade adjacent large blood vessels. Although the duodenal mass was surgically removed, the entire tumor could not be completely removed as the tumor had already spread throughout the body.

Upon macroscopic examination, the surgical resection specimen appeared to have originated from the submucosal layer of the duodenum, measuring 3x3 cm at its greatest dimension. The nodular mass showed a white-to-tan colored cut surface with a focal area of hemorrhage. Pathologic evaluation revealed a tumor arising from the duodenum and extending to the pancreas, colon, and omentum. Histology showed the epicenter of the tumor was the submucosal layer with normal-looking mucosa. The tumor was relatively well circumscribed and composed of high-grade pleomorphic cells. The tumor
was arranged in a haphazard, fascicular growth pattern with telangiectatic-like feature. The majority of the tumor cells exhibited marked nuclear atypia with brisk mitotic activity. Undifferentiated tumor cells displayed large vesicular or hyperchromatic nuclei and prominent macronucleoli. Discohesive polygonal giant cells with abundant eosinophilic cytoplasm were also observed. Immunohistochemistry was positive for MDM2 and CDK4 but was negative for CK, Actin, Desmin, CD117, CD34, ERG, SI00, TFE3, Melan A, and HMB45. The tumor was also found to harbor MDM2 amplification via fluorescence in situ hybridization (FISH).

OUTCOME AND FOLLOW-UP

Subsequently, chest CT and whole-body positron emission tomography/CT scans were performed to check for preexisting and unidentified intraabdominal liposarcoma outside the gastrointestinal tract and secondary duodenal involvement. No specific abnormalities or metastases were found.

However, due to the vessel invasion of the tumor, cancer seeding contributed to anastomotic dehiscence. Seven days after initial surgery, a 5 mm-sized leakage of the hepaticojejunal anastomosis occurred, leading to generalized peritonitis. The patient underwent a second operation. Large amounts of necrotic fluid had filled the abdominal cavity, and severe adhesions were observed. Hepaticojejunal anastomosis repair with superior mesenteric vein thrombectomy was performed. Fourteen days later, the patient developed sepsis due to the perforation of the gastrojejunal-anastomosis. A life saving emergency operation was performed. Intraoperatively, massive hematoma and bowel adhesion were observed in the upper abdomen. Overall, the tissue was very friable and edematous due to severe inflammation. An external stent was inserted and repaired using a T-tube in the gastrojejunal perforation site. Since the possibility of perforation was very high in the case of primary repair of the jejunal limb, an external stent was inserted using a hemovac drain. After massive irrigation, the operation was terminated.

Unfortunately, the patient did not recover from disseminated intravascular coagulation and peritonitis, and he died 60 d after surgery.

DISCUSSION

Liposarcomas are subclassified as atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS), DDLPS, myxoid liposarcoma, pleomorphic liposarcoma, or myxoid pleomorphic liposarcoma according to the World Health Organization classification[11]. WDLPS is a typically indolent histologic subtype that presents as slowly growing masses but can be locally aggressive with minimal to no distant metastatic potential, while DDLPS is a higher grade histology with the potential for rapid growth and distant metastatic potential[12,13].

The term DDLPS was first introduced by Evans in 1979[14] and is defined as a combination of ALT/WDLPS and a high-grade non-lipogenic sarcoma-like component of variable histologic grade. DDLPS can occur de novo (90%), with about 10% occurring from a pre-existing WDLPS[15]. The histologic hallmark of DDLPS is the transition from ALT/WDLPS to non-lipogenic sarcoma, although a well-differentiated component may not be identifiable.

The tumor usually presents as a large painless mass in late adult life with an equal distribution between males and females. The retroperitoneum is the most common location and occurrence in the extremities and subcutaneous tissue is very rare[16]. Since DDLPS primarily involving the intestine is extremely unusual, less than 10 cases have been reported to date[1-3,5-10,17]. Of those tumors arising in the small bowel, four originated in the jejunum, five in the ileum, and two in the duodenum (Table 1). Clinical information on the precise locations of the other three small bowel tumors is not available. The literature reveals that occurrences of DDLPS in the small intestine can cause various symptoms, such as intussusception, bleeding, obstruction, and abdominal discomfort. Since Okabayashi et al[6] reported the first case in 2013, there has only been one additional report of DDLPS in the duodenum[10].

Microscopically, the tumor exhibits variable histologic features but mostly undifferentiated pleomorphic cells with striking nuclear atypia. Such tumors with unusual locations and histopathological features may pose a diagnostic challenge. Thus, sarcomatoid carcinoma, GIST, LMS, malignant melanoma and other high-grade sarcomas should be among the list of differential diagnoses.

Sarcomatoid carcinomas should be considered as the primary differential diagnosis. These tumors are predominantly composed of poorly differentiated spindle cells and/or undifferentiated bizarre anaplastic cells resembling fibrosarcoma or LMS. Sarcomatoid carcinomas can be diagnosed by immunohistochemistry using cytokeratin to demonstrate epithelial derivation.

GIST may occur anywhere in the gastrointestinal tract with 30% arising in the small bowel, including the duodenum. The tumor also exhibits a broad morphologic spectrum. While most instances of GIST are spindle or epithelioid cell tumors, progression to high-grade sarcomatous morphology can be seen rarely. The majority of GISTs show expression of CD117, DOG1 and CD34, which may be helpful for diagnosis.
Table 1 Clinicopathologic features of liposarcoma from small bowel described previous and in present reports

<table>
<thead>
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<th>No.</th>
<th>Ref.</th>
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<th>Sex</th>
<th>Clinical presentation</th>
<th>Location</th>
<th>Histology</th>
<th>Treatment</th>
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<td>Atik et al[2]</td>
<td>58</td>
<td>F</td>
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<td>2</td>
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<td>52</td>
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<td>WDLPS</td>
<td>Small bowel resection</td>
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<td>WDLPS</td>
<td>Segmental resection</td>
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<td>59</td>
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<td>Resection</td>
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<td>Jejunum</td>
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<td>55</td>
<td>M</td>
<td>Melena</td>
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<td>Ileocecal resection</td>
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<td>51</td>
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<td>M</td>
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<td>Ileum</td>
<td>DDLPS with WD component</td>
<td>Segmental ileectomy</td>
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<td>53</td>
<td>M</td>
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<td>Jejunum</td>
<td>DDLPS</td>
<td>Segmental jejunectomy</td>
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<td>M</td>
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<td>Small intestine</td>
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</tr>
<tr>
<td>14</td>
<td>Whitham et al[10]</td>
<td>59</td>
<td>F</td>
<td>Fatigue, palpitation, shortness of breath</td>
<td>Duodenum</td>
<td>DDLPS</td>
<td>Segmental duodenal resection and distal gastrectomy</td>
</tr>
<tr>
<td>15</td>
<td>Present case</td>
<td>64</td>
<td>M</td>
<td>Abdominal pain, weight loss</td>
<td>Duodenum</td>
<td>DDLPS</td>
<td>Pylorus-preserving pancreaticoduodenectomy</td>
</tr>
</tbody>
</table>

F: Female; M: Male; LPS: Liposarcoma; DDLPS: Dedifferentiated liposarcoma; WDLPS: Well differentiated liposarcoma.

Gastrointestinal LMS is also very rare, with fewer than 100 cases reported in the English-language literature since 2000[18-21]. Typical LMS shows spindle cells with blunt-ended nuclei and eosinophilic fibrillary cytoplasm. The tumor cells are arranged in intersecting fascicles with varying degree of nuclear atypia, necrosis, and brisk mitotic activity. LMS can exhibit a poorly differentiated, pleomorphic appearance in addition to typical areas; this is known as pleomorphic LMS or dedifferentiated LMS[22, 23]. For this diagnosis to be established, morphological features characteristic of classic LMS must be present, and are usually positive for at least one myogenic marker, although staining is often weaker and more focal than in typical leiomyosarcomatous areas[22,23]. The diagnosis of LMS should be made on the basis of immunohistochemical stains along with the appropriate morphological features.

Most melanomas of the gastrointestinal tract are metastases from the skin, and primary small bowel melanoma of duodenal origin is extremely rare[24,25]. Because malignant melanomas display various histologic appearance, strong clinical suspicion and precise evaluation are needed to diagnose primary duodenal melanoma.

Based on the morphology of tumor cells in DDLPS, other types of high-grade tumors such as undifferentiated pleomorphic sarcoma, malignant peripheral nerve sheath tumor, and angiosarcoma should be included among the differential diagnoses. The tumor in the present case showed positive immunoreactivity for MDM2 and CDK4. DDLPS was diagnosed based on the histological and immunohistochemical findings combined with MDM2 amplification via FISH.

Dual staining with MDM2 and CDK4 has been shown to be both sensitive and specific to DDLPS[26]. This is a result of the overexpression of the protein product from chromosomal amplification in the 12q13–15 region of the MDM2 and CDK4 oncogenes. Amplification of these genes can then be confirmed with FISH if diagnostic uncertainty remains[27,28].

However, MDM2 positivity by immunohistochemistry is not a specific indicator of MDM2 amplification because MDM2 positivity is observed in many other sarcomas, including WDLPS, DDLPS, intimal sarcoma, LMS, angiosarcoma, and myxofibro-sarcoma[29]. Validation of MDM2 amplification by FISH, which is currently a gold standard, is mandatory to confirm the diagnosis of DDLPS.
While the biologic behavior of DDLPS appears to be unfavorable, the most effective treatment modality is surgical resection. There have been no published studies of adjuvant therapy due to the paucity of intestinal DDLPS. Because there are only a limited number of cases, we cannot predict the outcomes for DDLPS arising in the small bowel, but we expect similar prognoses compared with soft tissue DDLPS.

**CONCLUSION**

We presented a unique case of DDLPS originating from the duodenum, one of the rarest locations for gastrointestinal sarcomas. DDLPS should be thoroughly distinguished from its morphological mimickers, as the tumor may be more highly aggressive and extensive than clinically and radiologically expected. While histopathologic features and immunohistochemistry offer evidence of DDLPS, MDM2 FISH is essential to confirm the diagnosis. Pathologists should keep DDLPS among the initial histologic differential diagnoses for high-grade tumors of the gastrointestinal tract.

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**FOOTNOTES**

**Author contributions:** Kim NI, Choi YD, and Kim SS conceptualized the manuscript; reviewed the literature; and interpreted the H&E slides, immunohistochemistry slides, and fluorescence in situ hybridization; Lee JS, Choi C, and Nam JH contributed to the manuscript draft; Kim HJ contributed to the operative performance; all authors read and approved the final manuscript.

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Kim NI et al. Primary duodenal dedifferentiated liposarcoma

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Implant site development using titanium plate and platelet-rich fibrin for congenitally missed maxillary lateral incisors: A case report

Tian-Shou Zhang, Mahmoud Mudalal, Si-Cong Ren, Yan-Min Zhou

Abstract

BACKGROUND
Bone deficiency and soft tissue atrophy in the absence of maxillary lateral incisors are among the most challenging problems for implant clinicians. Autologous bone grafting is the gold standard for bone augmentation, but not without limitations. Platelet-rich fibrin (PRF), a biodegradable autologous biomaterial, has been widely used for bone and soft tissue management. Moreover, titanium plate is an advantageous barrier due to its good space-maintaining ability. However, there is a lack of literature on implant site development using titanium plate and PRF for congenitally missing maxillary lateral incisors.

CASE SUMMARY
The patient was a 19-year-old girl with a congenitally missing tooth (#12). She underwent implant placement and simultaneous autologous bone grafting with titanium plate and PRF. At the follow-up visit 15 d post-procedure, the vascularization of soft tissue was visible. There was no swelling or pain after the surgery. Six months postoperatively, bone regeneration was evident. Subsequently, the definitive restoration was placed, and the patient was satisfied with the esthetic outcomes.

CONCLUSION
Implant site development using titanium plate and PRF for congenitally missing maxillary lateral incisors is a feasible procedure. In this case, the labial bone plate was displaced but remained connected to the base bone, ensuring blood supply. The titanium plate fixed the labial bone plate and maintained the osteogenic space, while the PRF provided growth factors and leukocytes for bone and soft...
tissue regeneration. Furthermore, the procedure reduced the surgical complexity and adverse reactions, displaying outstanding esthetic outcomes.

**Key Words:** Implant placement; Platelet-rich fibrin; Missing incisor; Bone augmentation; Soft tissue regeneration; Case report

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**Core Tip:** The procedure reported in this paper reduced the surgical complexity and adverse reactions, besides displaying outstanding esthetic outcomes by: (1) Displacement of the labial bone plate that remained connected to the base bone, ensuring blood supply; (2) Fixing the labial bone plate and maintaining the osteogenic space with a titanium plate; and (3) Providing growth factors and leukocytes for bone and soft tissue regeneration by leukocyte-platelet rich fibrin.

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**INTRODUCTION**

Missing maxillary lateral incisors is a common congenital and developmental anomaly that affects the esthetics due to their position on the denture. Patients are offered several treatment options in such cases, including dental implant treatment, orthodontic space closure, or prosthetic rehabilitation. Dental implant treatment is a popular choice because it offers maximum restoration of tooth function and esthetics. Sufficient quality and quantity of alveolar bone and soft tissue are essential at the implant recipient sites, especially in the esthetic zone for this treatment. Most studies indicated that labial bone and soft tissue thickness should exceed 2 mm to ensure the best outcome and esthetics for implants[1]. Conversely, an extensive bone and soft tissue deficiency with congenitally absent maxillary lateral incisors poses a challenge for dental implant treatment.

Autologous bone grafting is the gold standard for bone augmentation but not without its limitations, such as low blood supply, unpredictable resorption, and donor site morbidity, contributing to research intensification for suitable alternatives[2]. Some studies have reported reconstruction in severe bone deficiency using autologous bone with bone substitute materials in the first procedure to expand the available bone volume and reduce the resorption of autologous bone[3,4]. An adequate blood supply is essential in this procedure, and space creation/maintenance is necessary for bone ingrowth. In addition, primary closure is crucial to ensure uneventful healing[5]. Nevertheless, perfect primary closure may not always occur, especially with the incidence of soft tissue atrophies due to the congenitally missing maxillary lateral incisors. Platelet-rich fibrin (PRF), a biodegradable autologous biomaterial, promotes angiogenesis and bone and soft tissue regeneration and prevents infection since it contains platelets, growth factors, and leukocytes[6,7]. Meanwhile, titanium plate is an advantageous barrier due to its good space-maintaining ability.

In this case report, a procedure was designed to restore a congenitally missing maxilla lateral incisor. First, the labial bone plate was displaced but remained connected to the base bone for bone augmentation using a titanium plate to create/maintain the space. Then, PRF was applied for angiogenesis, bone and soft tissue regeneration, and infection prevention.

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**CASE PRESENTATION**

**Chief complaints**

A 19-year-old girl visited the Department of Oral Implantology with congenitally absent tooth #12.

**History of present illness**

The clinical examination found that the spacing was in the maxillary anterior region, and tooth #12 was missing. In addition, keratinized gingiva atrophy and alveolar crest absorption were observed in the edentulous space. After consultation with orthodontists, an interdisciplinary treatment plan was drawn up (Figure 1).
History of past illness
The patient denied any systemic diseases, and her family history was unremarkable.

Personal and family history
Family history was unremarkable.

Physical examination
Physical examination revealed no remarkable findings.

Laboratory examinations
Complete blood count and common urine analysis were performed, which showed no abnormalities.

Imaging examinations
Cone-beam computed tomography (CBCT) showed no residual root and other abnormal conditions, although substantial alveolar bone was lost at the edentulous space (buccal bone thickness = 3.0 mm; alveolar crest height = 12.8 mm) (Figure 2).

FINAL DIAGNOSIS
Tooth #12 congenital absence.

TREATMENT
Pre-operatively, the patient rinsed her mouth with 0.12% chlorhexidine solution every 3 min, thrice. Then, two PRF clots were established using the standard protocol (two whole blood samples were collected in two glass-coated 10 mL plastic tubes without anticoagulant and immediately centrifuged at 3000 rpm for 10 min). Subsequently, one PRF clot was mixed with the xenograft bone substitutes, while the other was pressed into the membranes with a sterile dry gauze to cover the bone granulates. Following local anaesthesia, the #12 alveolar ridge crest mucoperiosteum was excised angularly, followed by flap surgery. First, the bone was expanded to form a receptor site for implant using the ridge splitting set (Helmut, Zepf, Germany) without any bone removal. Then, the labial bone plate was displaced carefully, ensuring that its base remained attached. Next, an implant (Nobel replace 3.5 mm × 13 mm) was inserted at the prepared site (Figure 3A), and the bone block was then fixed with a titanium plate to maintain the bone block (Figure 3B), which was grafted with the PRF and xenograft bone substitute mixture (Bio-oss, 2.5 g, Geistlich) (Figure 3C). Finally, resorbable and PRF membranes were used to double cover the defect site (Figure 3D and E), and the recipient site was loosely sutured (Figure 3F).
Zhang TS et al. Implant with platelet concentrates

Figure 2 Cone-beam computed tomography revealed considerable alveolar bone loss.

Figure 3 The surgical procedure. A: The implant was placed at the recipient site #12 after the labial bone plate displacement; B: A T-type titanium plate was used to fix the bone block; C: The mixture of bone grafts and platelet-rich fibrin (PRF) clot covered the T-type titanium plate and the socket walls; D: Resorbable membrane covered the bone grafts; E: PRF membrane covered the resorbable membrane and alveolar crest; F: The wound was non-tightly sutured.

For antibiotic therapy, 500 mg azithromycin was prescribed twice daily for 5 d. Additionally, the patient was instructed to avoid chewing in the surgical area and continue using mouthwash with chlorhexidine 0.12% for 10 d. The sutures were removed after 15 d.

OUTCOME AND FOLLOW-UP

The patient denied any swelling and pain after the surgery. Furthermore, the vascularization of soft tissue at the surgery site was visible at the follow-up visit on day 15 (Figure 4). Later, implant osseointegration was evident after a healing period of 6 mo. During the second surgery, the area was explored using the same flap design. Upon reopening the surgical site for titanium plate and healing abutment replacement, it was found that the shoulder of the implant was surrounded by bone, and the titanium
Figure 4 Intraoral condition at the 15d follow-up visit: The vascularization of soft tissue was visible.

Figure 5 Second stage surgery. A: The implant was surrounded by bone and the titanium plate was covered by the new bone; B: The incision was non-tightly sutured.

plate was covered by the new bone (Figure 5A), indicating that the bone defect had completely regenerated. Then, the recipient site was sutured (Figure 5B). After 14 d of gingiva stabilization, the sutures were removed, and a final impression was taken to construct a conventional permanent superstructure for restoration. Subsequently, the definitive restoration was placed (Figure 6). Later, a 1-year follow-up revealed the integration of soft tissue and tooth with the adjacent tooth (Figure 7A-C). Apart from that, CBCT showed that the bone around the implant was stable (Figure 7D). Thus, the patient was satisfied with the esthetic and functional outcomes.

DISCUSSION
Dental implant treatment is often selected based on their functional and esthetic outcomes in congenitally missing maxillary lateral incisors with available space. However, insufficient bone and soft tissue become obstacles to successful implant treatment. An adequate supporting bone around the implant is essential for the long-term stability and esthetic results of the implant. Some studies proposed combining autologous bone with bone substitute materials for the reconstruction of severe alveolar ridge defects to reduce autologous bone resorption. Titanium plate effectively prevents connective tissue colonization and has good mechanical strength to maintain the osteogenic space during the alveolar ridge reconstruction[8,9]. Meanwhile, Strauss et al[10] reported that PRF with Bio-Oss had an outstanding ability in promoting osteogenesis due to its abundant growth factors.

In this report, the labial bone plate was first displaced, ensuring that the base of the labial bone plate was attached to the basal bone for blood supply. Afterwards, a titanium plate was placed to fix the labial bone plate and maintain the bone formation space. Then, the bone substitute materials and PRF were mixed to cover the bone defect. Upon reopening of the surgical site for titanium plate removal and replacement of healing abutment, it was found that the implant shoulder was surrounded by bone, and the titanium plate was covered by the new bone, indicating that the bone defect had completely regenerated. In addition, CBCT displayed adequate supporting bone around the implant during the 1-
In the esthetic zone, sufficient soft tissue is mandatory for successful implant outcomes. Primary closure is vital to ensure uneventful healing and the soft tissue abundance ensures the esthetic results and long-term health of the implant. Some studies suggested that obtaining primary closure through the relaxation of incision or connective tissue free flap may disrupt the blood supply, accompanied by higher surgical complexity[11]. Recently, concentrated platelets have been recommended as an efficient strategy for wound healing[12,13]. PRF, a second-generation platelet concentrate, contains various growth factors, platelets, and leukocytes[14]. The three-dimensional fibrin scaffold of PRF continuously releases growth factors[15] that promote local tissue vascularization and regeneration during wound healing[16]. Moreover, PRF plays a crucial role in wound healing as an excellent anti-inflammatory and antibacterial agent[17,18].

In addition, Miron et al[19] reviewed the effects of PRF on wound healing and highlighted its positive effects on the management of soft tissue. Meanwhile, Cui et al[20] reported that the PRF membrane without a tight flap closure could achieve excellent soft tissue regeneration. In the present case, bioguide membrane and PRF membrane were utilized to double cover the bone substitute materials
without a tight flap closure for mechanical barrier and soft tissue regeneration. The patient denied any swelling and pain after the surgery, which might be attributed to the anti-inflammatory and antibacterial activity of PRF. Furthermore, at the follow-up on day 15, the vascularization of soft tissue was visible, and excellent gingival contour was obtained when the definitive restoration was placed. On top of that, the 1-year follow-up revealed harmony and stability of the gingival contour.

### CONCLUSION

Bone regeneration and soft tissue management pose challenges for dental implant treatment in congenitally missing maxillary lateral incisors. In the present case, the labial bone plate was displaced but remained connected to the base bone, ensuring blood supply. A titanium plate was used to fix the labial bone plate and maintain the osteogenic space. Meanwhile, the PRF supplied growth factors and leukocytes for bone and soft tissue regeneration. This procedure reduced the surgical complexity besides demonstrating fewer adverse reactions and outstanding esthetic outcomes.

### FOOTNOTES

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Successful embolization of an intrahepatic portosystemic shunt using balloon-occluded retrograde transvenous obliteration: A case report

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Abstract

BACKGROUND
A congenital intrahepatic portosystemic shunt (IPSVS) is a rare vascular abnormality that is characterized by an anomalous intrahepatic venous tract that connects the intrahepatic portal vein with the hepatic venous system. Hepatic encephalopathy is an indication for IPSVS embolization, which is technically challenging because rapid blood flow through shunts can induce the migration of embolization material to systemic veins. This case report discusses the efficacy of percutaneous balloon-occluded retrograde transvenous obliteration for treating patients with IPSVSs.

CASE SUMMARY
A 75-year-old woman presented with a six-month history of repeated hepatic encephalopathy due to an IPSVS without liver cirrhosis. We successfully embolized the IPSVS using percutaneous balloon-occluded retrograde transvenous obliteration with interlocking detachable coils. After the procedure, the patient exhibited no symptoms of hepatic encephalopathy for 14 mo.

CONCLUSION
Balloon-occluded retrograde transvenous obliteration with detachable coils can be effective for the endovascular treatment of an IPSVS.

Key Words: Hepatic veins; Portal vein; Hepatic encephalopathy; Endovascular procedures; Embolization; Therapeutic; Case report
Core Tip: Portosystemic venous shunts are generally formed in patients with hepatic fibrosis and cirrhosis due to portal hypertension. Adult cases of congenital intrahepatic portosystemic shunt (IPSVS) are extremely rare. Hepatic encephalopathy is an indication for IPSVS embolization. Minimally invasive treatments that use interventional techniques, such as transcatheter embolization, are being utilized increasingly recently; however, shunt embolization is technically challenging because rapid blood flow through shunts can induce the migration of embolization material to systemic veins. Balloon-occluded retrograde transvenous obliteration with detachable coils can be effective for the endovascular treatment of an IPSVS.

INTRODUCTION

An intrahepatic portosystemic shunt (IPVS) is a rare vascular abnormality that is characterized by an anomalous intrahepatic venous tract that connects the intrahepatic portal vein with the hepatic venous system. An IPSVS was first reported by Raski et al.[1] in 1964. Since then, reports of these abnormalities have increased with the development of imaging modalities[2-4]. An IPSVS connects the portal and systemic venous circulation; it has a diameter of > 1 mm, and at least some part of it is located inside the liver. This condition may be congenital or acquired secondary to portal hypertension[1,5,6]. Treatment is required when an IPSVS causes hepatic encephalopathy[3]. Recently, transcatheter embolization using balloon-occluded retrograde transvenous obliteration (B-RTO) has been used to treat symptomatic IPSVSs. B-RTO is a well-known method for treating gastric varices or hepatic encephalopathy in patients with hepatic fibrosis and cirrhosis. A mixture of 5% ethanolamine oleate (Oldamin; Takeda Pharmaceutical, Osaka, Japan) and iopamidol (Iopamidol; Schering, Osaka, Japan) (5% EOI), is usually injected as a liquid embolic agent to treat gastric varices. However, in cases of IPSVSs, it is difficult to prevent migration of the 5% EOI because the shunt length is short, and blood flow through the shunt is rapid, even when the flow is controlled with a balloon catheter. Herein, we present a case of a symptomatic IPSVS that was embolized using B-RTO with detachable coils.

CASE PRESENTATION

Chief complaints
The patient was a 75-year-old unemployed Asian woman who was 170 cm tall and weighed 50 kg. She presented with a six-month history of repeated episodes of unconsciousness.

History of present illness
The patient consulted a doctor because of a loss of consciousness. Hepatic encephalopathy due to IPSVS was diagnosed because laboratory tests and ultrasound showed elevated ammonia levels and IPSVS, respectively. Since hepatic encephalopathy did not improve with drug treatment, embolization was performed.

History of past illness
The patient had no history of liver disease or trauma and was receiving treatment for pulmonary stenosis. She had a past medical history of hypertension, breast cancer surgery, and thyroid cancer surgery, and she was taking Bisoprolol (2.5 mg), Olmesartan Medoxomil (20 mg), Azenlidipine (16 mg), and Eszopiclon (2 mg). She did not have any known allergies.

Personal and family history
The patient’s personal and family history was not significant.
Physical examination
The patient demonstrated flapping tremors. However, there was no hepatomegaly, splenomegaly, abdominal tenderness, edema, or ascites present.

Laboratory examinations
Laboratory tests revealed an abnormally high ammonia level (214 μg/dL; normal range, 27–73 μg/dL). Other laboratory test results were as follows: White blood cell count, 41 × 10^9/μL; red blood cell count, 442 × 10^12/μL; hemoglobin level, 14.0 g/dL; hematocrit level, 41.9%; platelet count, 18.5 × 10^11/μL; C-reactive protein, 0.09 mg/dL; aspartate aminotransferase level, 45 U/L; alanine aminotransferase level, 43 U/L; total bilirubin level, 0.8 mg/dL; direct bilirubin level, 0.3 mg/dL; total protein level, 6.5 g/dL; albumin level, 3.5 g/dL; glutamyl transferase level, 36 U/L; prothrombin time, 13.1 s (86.3% of normal); international normalized ratio, 1.14; creatinine level, 0.65 mg/dL; and blood urea nitrogen level, 16.7 mg/dL. The patient tested negative for serum HBs Ag, anti-HBc, and anti-HCV antibodies in a viral screening.

Imaging examinations
Contrast-enhanced computed tomography (CECT) revealed multiple anomalous vessels that were communicating with the dilated right portal and hepatic veins (Figure 1). The shunt measured 14 mm in diameter, and the left portal vein was narrow due to blood flow steal. The morphology and CT attenuation value of the liver were normal, and no cystic formation was observed in the liver.

FINAL DIAGNOSIS
The patient was diagnosed with hepatic encephalopathy secondary to an IPSVS in the right lobe of the liver; therefore, we performed an IPSVS embolization.

TREATMENT
The patient provided consent for the publication of this case report and any additional related information. Subsequently, the following procedures were performed under local anesthesia: We inserted a 4-Fr shepherd-hook catheter (Terumo Clinical Supply, Tokyo, Japan) into the right femoral artery. Next, we performed superior mesenteric arterial portography, and the presence of an IPSVS between the right portal and hepatic veins was confirmed (Figure 2A). We inserted an 8-Fr sheath introducer (Medikit, Tokyo, Japan) into the right femoral vein to facilitate the insertion of a 6-Fr shepherd-hook catheter with a 20-mm-diameter balloon (Terumo Clinical Supply, Tokyo, Japan). Further, an 8-Fr sheath introducer (Medikit, Tokyo, Japan) was inserted into the right femoral vein to facilitate the insertion of a 6-Fr shepherd-hook catheter with a 20-mm-diameter balloon (Terumo Clinical Supply, Tokyo, Japan) into the right hepatic vein. Subsequently, coaxial passage of a 0.20-inch microcatheter (Masters Parkway; ASAHI INTECC J-sales, Inc., Tokyo, Japan) through the IPSVS into the portal vein was performed. Three IPSVSs were observed following the injection of contrast media via the microcatheter in the portal vein (Figure 2B). The pre-embolization pressures of both the portal and right hepatic veins were 230 mm H₂O. The balloon catheter was inflated to decrease the hepatofugal blood flow in the IPSVS and avoid coil migration into the systemic venous circulation (Figure 2C). Re-injection of contrast media via the microcatheter in the portal vein showed hepatofugal blood flow stasis in the IPSVS. The microcatheter in the IPSVS was replaced, and all three IPSVSs were embolized with ten interlocking detachable coils (Boston Scientific, Watertown, MA, United States; interlock diameters: 10–12 mm, 6–8 mm, and 4–6 mm; length: 30 cm, 20 cm, and 15 cm).

OUTCOME AND FOLLOW-UP
Superior mesenteric arterial portography was performed after balloon deflation, and it revealed sufficient IPSVS embolization (Figure 2D). The patient’s liver function was normal, and the right hepatic venous pressure decreased to 155 mm H₂O after the embolization. There were no procedural complications. The serum ammonia level normalized to 55 μg/dL on the first post-intervention day, and a CECT scan that was performed one week after the procedure revealed sufficient embolization of the IPSVS and expansion of the left portal vein (Figure 3). Currently (14 months post-intervention), the patient has no hepatic encephalopathy symptoms, and her clinical condition is good.
Figure 1 Contrast-enhanced computed tomography. A: Axial contrast-enhanced computed tomography (CECT) image shows an intrahepatic portosystemic shunt (IPSVS, arrow) extending from the right posterior portal vein to the right hepatic vein; B: An axial CECT image shows the IPSVS (arrow) and narrow left portal vein (arrowhead); C: An axial CECT image shows the IPSVS (arrowhead) communicating with the right hepatic vein (arrow); D: An oblique reformatted computed tomography image shows the IPSVS with a shunt tract (arrowheads) that extends to the right posterior portal vein.

**DISCUSSION**

Portal-systemic venous shunts are formed in patients with hepatic fibrosis and cirrhosis due to portal hypertension\([7]\). While it is unclear how these shunts are formed in patients without cirrhosis, portal hypertension, trauma, and portal vein aneurysm ruptures are considered possible causes\([6]\). For patients with no history of these conditions, however, IPSVS a congenital cause is considered. Between the third and fourth months of fetal life, development of the intra- and extrahepatic portal venous systems occurs through selective persistence of the vitelline and umbilical systems\([6]\). The cause of congenital IPSVSs is supposedly persistence of communication between the cranial and caudal hepatic sinusoids formed by the vitelline and umbilical veins\([6]\). This communication generally closes during the fetal stage or after birth\([6,8]\); therefore, adult cases of congenital IPSVSs are extremely rare.

IPSVSs are categorized into four morphologic types as follows\([3]\): Type I is characterized by a single, large tube with a consistent diameter connecting the right portal vein to the inferior vena cava; type II by a localized peripheral shunt wherein there are communications (single or multiple) between the peripheral branches of the portal and hepatic veins in a hepatic segment; type III by a connection between the peripheral portal and hepatic veins through an aneurysm; and type IV by multiple diffuse communications between the peripheral portal and hepatic veins in both lobes. Our patient had features characteristic of type II IPSVS.

Patients with an IPSVS with hepatic encephalopathy have increased blood flow through the shunt that requires treatment\([3]\). Traditionally, shunts are surgically occluded\([1]\); in recent years, however, less invasive treatments that incorporate interventional techniques, including transcatheter embolization, are increasingly being used\([6,9]\).

It is technically challenging to embolize large shunts under rapid blood flow conditions. Therefore, selecting appropriate embolic materials and blood flow control are important for the success of the procedure. When selecting embolic materials, detachable coils, such as the ones used in the present case,
and the Amplatzer Vascular Plug™ (AVP) are preferred over pushable coils because detachable coils and AVPs can be advanced or withdrawn freely before being released, resulting in accurate and safe placement. Conversely, pushable coils cannot be withdrawn after the coils have been pushed from the cartridge into the introducer catheter. Consequently, these coils cannot be replaced, which results in an increased risk of migration to systemic veins. In addition, it is more difficult to use liquid embolus material, such as the 5% EOI, which is usually employed for portosystemic shunts in the treatment of cirrhosis, to prevent migration to systemic veins than metallic embolus materials, even when the flow is controlled using a balloon catheter. In this case, we opted to use detachable coils because embolization of large shunts with an AVP requires a large delivery system, and it is sometimes technically challenging. Furthermore, the risk of migration remains despite the use of detachable coils or AVPs. Occlusion of the hepatic vein, which communicates with the IPSVS through inflation of a balloon catheter, can decrease blood flow to the IPSVS and prevent coil migration. Moreover, detachable coils of various lengths and diameters are available, and this may enable their use in the treatment of lesions with large or high-flow shunts[10].

CONCLUSION

Balloon-occluded retrograde transvenous obliteration with detachable coils can be effective for the endovascular treatment of IPSVSs.
Figure 3 An axial contrast-enhanced computed tomography image that was obtained one week after the procedure reveals sufficient embolization of the intrahepatic portosystemic shunt and expansion of the left intrahepatic portal vein (arrow).

**FOOTNOTES**

**Author contributions:** Saito H and Murata S treated the patient, reviewed the literature, and contributed to manuscript drafting; Sugihara F, Ueda T, Yasui D, and Miki I participated in the patient treatment and analyzed and interpreted the imaging findings; Hayashi H and Kumita SI critically reviewed the manuscript; all authors issued final approval for the version to be submitted.

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**L-Editor:** A
**P-Editor:** Fan JR

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Bilateral pneumothorax and pneumomediastinum during colonoscopy in a patient with intestinal Behcet’s disease: A case report

Tong Mu, Hua Feng

**Abstract**

**BACKGROUND**
Colonscopy is essential for the diagnosis of intestinal Behcet’s disease (BD), which is characterized by a typical oval-shaped ulcer in the ileocecal region. However, potential risks of colonoscopy have rarely been reported.

**CASE SUMMARY**
Herein, we describe a patient with intestinal BD who presented with decreased oxygen saturation and shortness of breath during a diagnostic colonoscopy. Bilateral pneumothorax, pneumomediastinum, pneumoperitoneum, pneumoretroperitoneum and subcutaneous emphysema of the neck, chest, abdomen, back and scrotum were confirmed by computed tomography scan. The sudden change in condition was considered to be associated with iatrogenic bowel perforation. After receiving closed thoracic drainage and conservative therapy, the patient was discharged in stable condition.

**CONCLUSION**
Endoscopists should be aware of the risks of colonoscopy in patients with intestinal BD and the possibility of pneumothorax associated with intestinal perforation and make adequate preparations before colonoscopy.

**Key Words:** Intestinal Behcet’s disease; colonoscopy; Intestinal perforation; Pneumothorax; Case report

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Core Tip: Colonoscopy is necessary for diagnosing intestinal Behcet’s disease and determining the severity of gastrointestinal involvement. Endoscopists should be aware of the potential risks of colonoscopy in patients with intestinal Behcet’s disease and the possibility of pneumothorax associated with intestinal perforation.

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INTRODUCTION

Intestinal Behcet’s disease (BD) is a rare, chronic, relapsing inflammatory disorder. As a special type of BD, it is characterized by a typical oval-shaped ulcer in the ileocecal region in addition to recurrent oral and genital ulcers, ocular and skin lesions, and a positive pathergy test[1]. Abdominal pain, diarrhea and hematochezia are common complaints[1]. Spontaneous bowel perforation is also a complication that could lead to intra-abdominal infection and even death[2].

Colonoscopy is necessary for diagnosing intestinal BD and determining the severity of gastrointestinal involvement. However, potential risks have rarely been mentioned in previous studies. In this article, we report a case of colonic perforation during diagnostic colonoscopy in a patient diagnosed with intestinal BD in which bilateral pneumothorax and respiratory distress occurred.

CASE PRESENTATION

Chief complaints
The patient presented with intermittent abdominal pain and bloating for six months and sudden shortness of breath and confusion during diagnostic colonoscopy.

History of present illness
A 58-year-old man presented with intermittent abdominal pain, bloating and reduced defecation in the past six months. To determine the severity of intestinal lesions and rule out intestinal tumors, the patient underwent a routine diagnostic colonoscopy using air insufflation under nontracheal intubation intravenous general anesthesia (propofol). Upon withdrawal of the colonoscope, the patient suddenly experienced shortness of breath and confusion and gradually developed cyanosis.

History of past illness
The patient underwent a colonoscopy 12 years prior, and colonic ulcers were observed. Because the patient had oral and perianal ulcers and the colonic ulcers were considered to be a manifestation of intestinal BD, the patient was diagnosed with intestinal BD by a rheumatologist. He had suffered severe pain in the right lower abdomen 11 years prior. Acute appendicitis was initially suspected, but spontaneous ileocecal perforation was confirmed during an emergency exploratory laparotomy, and surgical repair of the ileocecal perforation was performed. He still suffered from the recurrence of oral and perianal ulcers but did not experience unbearable abdominal symptoms after taking prednisone and leflunomide irregularly.

Personal and family history
The patient had a 30-year history of smoking (1 pack per day).

Physical examination
The physical examination upon admission showed tenderness in the right lower abdomen. When cyanosis occurred, the oxygen saturation dropped to 68%, and the heart rate was 130 beats/min. Assisted mask ventilation was initiated with 100% oxygen, but the patient’s saturation did not improve. An abdominal examination revealed a distended abdomen on palpation and drum sounds on percussion. On auscultation, breath sounds were absent on the right side and diminished on the left side of the chest.

Laboratory examinations
The patient had an antinuclear antibody titer of 1:320 (granular type, cytoplasmic type) and a positive
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fecal occult blood test upon admission. The laboratory results were not available during rescue.

**Imaging examinations**

The computed tomography (CT) scan of the abdomen and pelvis before colonoscopy revealed bowel wall thickening in the terminal ileum, ileocecal area and appendix, ileocecal stenosis and incomplete bowel obstruction.

Colonoscopy revealed deformation, mucosal hyperplasia and multiple deep ulcers in the ileocecal region (Figure 1). The possibility of perforation could not be ruled out. The colonoscope could not enter the small intestine due to stenosis and deformation of the ileocecal valve. Pseudopolyps in the ascending colon and ring ulcers in the transverse colon and descending colon were also shown on colonoscopy. Biopsies were taken from the ileocecal region, ascending colon and transverse colon. Pathology revealed chronic active mucosal inflammation in the ileocecal region and chronic mucosal inflammation in the ascending and transverse colon.

The CT scan of the chest, abdomen and pelvis after chest drain tube insertion showed bilateral pneumothorax, pneumomediastinum, pneumoperitoneum, pneumoretroperitoneum and subcutaneous emphysema of the neck, chest, abdomen, back and scrotum (Figure 2A-C).

**FINAL DIAGNOSIS**

The final diagnosis of the presented case was bowel perforation during the colonoscopy, resulting in bilateral pneumothorax, which is a life-threatening complication. The biopsies were taken from the mucosa at the edge of the ulcers without damage to the muscle layer, and no perforation after the biopsies was seen on endoscopy. Due to the past history of spontaneous ileocecal perforation and the presence of ileocecal stenosis and deep ulcers, it was speculated that this perforation occurred in the ileocecal area and was caused by a pressure-related injury to the muscle layer of the deep ulcers induced by air insufflation during the endoscopy.

**TREATMENT**

Orotracheal intubation was immediately attempted by the anesthesiologists after the patient suffered shortness of breath and confusion but failed due to recurrent oral ulcers. Meanwhile, diagnostic abdominal paracentesis and thoracentesis were performed, and pneumothorax and pneumoperitoneum were confirmed. With the release of gas in the pleural cavity, the patient’s oxygen saturation gradually increased, and he gradually recovered consciousness. Therefore, orotracheal or nasotracheal intubation was not required in the subsequent treatment. We urgently contacted the thoracic surgeon, and the right thoracic drainage tube was subsequently inserted. Then, the patient’s vital signs were stable. To confirm the diagnosis, the patient was transferred to the imaging department for an emergency CT scan, the results of which are described above (Figure 2A-C). The thoracic surgeon reassessed the patient and considered that the left pneumothorax could be absorbed without inserting the left thoracic drainage tube. Then, the patient received conservative therapy (antibiotics and parenteral nutrition).

**OUTCOME AND FOLLOW-UP**

After rescue, the patient did not experience fever or severe abdominal pain. The white blood cell count was 11.87 \( \times 10^9 \) /L, C-reactive protein level was 22.00 mg/L, and procalcitonin level was 0.24 ng/mL on the day of the perforation. The chest drainage tube was removed 3 d after perforation. The white blood cell count was 6.92 \( \times 10^9 \) /L, C-reactive protein level was 20.75 mg/L, and procalcitonin level was 0.18 ng/mL 7 d after perforation. The CT scan of the chest, abdomen and pelvis 7 d after the perforation showed significant improvement of bilateral pneumothorax, pneumomediastinum, pneumoperitoneum, pneumoretroperitoneum and subcutaneous emphysema (Figure 2D). The patient stopped receiving total parenteral nutrition and consumed a liquid diet 8 d after perforation. He was satisfied with our rescue and discharged 9 d after perforation. Then, he took azathioprine to treat BD under the guidance of a rheumatologist.

**DISCUSSION**

Intestinal oval-shaped deep ulcers are characteristic lesions in patients with intestinal BD that can involve the intestinal muscle layer. Therefore, bowel perforation, especially ileocecal perforation, may occur as a complication of intestinal BD. In this case, spontaneous ileocecal perforation had occurred 11
Adult patients with spontaneous bowel perforation usually have specific causes, such as Crohn’s disease, scleroderma, intestinal non-Hodgkin’s lymphoma and intestinal BD. The incidence of spontaneous bowel perforation in patients with Crohn’s disease was reported to be 1.5%[3], but the incidence is unclear in patients with BD. Spontaneous bowel perforation in patients with intestinal BD could be single or multiple and is not limited to the ileocecal region[4,5]. Patients can experience severe abdominal pain, abdominal distention, nausea, vomiting, obstipation and fever[2,4-6] and often require surgical intervention[2,4,5,7], such as colonic repair and enterectomy. BD with spontaneous intestinal perforation could be confused with other common acute abdominal diseases, for example, acute suppurative appendicitis, due to the similarities of the abdominal symptoms and signs. An abdominal X-ray or a CT scan before colonoscopy or surgery can facilitate the detection of the occurrence of spontaneous bowel perforation.
It is estimated that the incidence of iatrogenic intestinal perforation is 0.016%-0.8% for diagnostic colonoscopies and 0.02%-8% for therapeutic colonoscopies[8]. Iatrogenic colonoscopic perforation could be detected while performing colonoscopy or after colonoscopy based on early symptoms, such as persistent abdominal pain and distention, or later symptoms and signs, such as fever, leukocytosis and abdominal rebound tenderness as a result of peritonitis[9]. In general, the sigmoid colon is the most common site of perforation (53%-65%)[8]. Due to the existence of ileocecal deep ulcers, patients with intestinal BD are at higher risk of perforation, and the ileocecal area may be the most common site of perforation. Insufflation and biopsy may lead to pressure-related and mechanical injuries of the colonic wall. Therefore, for patients with suspected intestinal BD, careful operation is required for endoscopy. It is necessary to reduce the amount of air insufflation or use carbon dioxide (CO₂) insufflation. Biopsies should be taken from the mucosa at the edges of the ulcers. Endoscopists should pay attention to the patient’s abdominal signs, especially when performing colonoscopy under general anesthesia.

In this case, bilateral pneumothorax occurred on the basis of intestinal perforation, resulting in shortness of breath and confusion. Both pneumoperitoneum and pneumoretroperitoneum were revealed by a CT scan. Massive air in the retroperitoneal space might leak out of the intestine directly through extraperitoneal intestinal perforation or indirectly through intraperitoneal intestinal perforation [10]. The free air could then extend upward along the esophageal hiatus or aortic hiatus to the mediastinum and pleural space[11], resulting in pneumomediastinum and bilateral pneumothorax. The air could then spread along the muscles and fascia to the subcutaneous tissue [12], resulting in subcutaneous emphysema of the neck, chest, abdomen, back and scrotum. Severe intra-abdominal infection did not occur because of bowel preparation. Surgery was not required; therefore, we could not determine the location or number of perforations.

Pneumothorax during or after a routine colonoscopy could appear in patients without underlying bowel diseases, as well as in those with diverticulosis, inflammatory bowel disease, previous colectomy, stricture and fecal impaction[13]. To our knowledge, this is the first report of pneumothorax and subcutaneous emphysema related to bowel perforation in a patient with intestinal BD. In this case, tracheal intubation was impossible due to the patient’s limited mouth opening caused by recurrent oral ulcers, which undoubtedly increased the difficulty of rescue.

CONCLUSION

Patients with intestinal BD should be fully assessed and adequately prepared before colonoscopy. Endoscopists and anaesthesiologists should be aware of the possibility of pneumothorax related to intestinal perforation when a patient’s oxygen saturation drops during a colonoscopy, especially under general anesthesia.

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We are grateful to the nurses, anaesthesiologists and thoracic surgeon for their assistance to the rescue.

FOOTNOTES

Author contributions: Mu T drafted the article. Feng H collected the data of the patient, revised the article and made the decision to submit for publication; all authors read and approved the final manuscript.

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Acute kidney injury due to intravenous detergent poisoning: A case report

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Abstract

BACKGROUND
Detergent poisoning mostly occurs through oral ingestion (> 85%), ocular exposure (< 15%), or dermal exposure (< 8%). Reports of detergent poisoning through an intravenous injection are extremely rare. In addition, there are very few cases of renal toxicity directly caused by detergents. Here, we report a unique case of acute kidney injury caused by detergent poisoning through an accidental intravenous injection.

CASE SUMMARY
A 61-year-old man was intravenously injected with 20 mL of detergent by another patient in the same room of a local hospital. The surfactant and calcium carbonate accounted for the largest proportion of the detergent. The patient complained of vascular pain, chest discomfort, and nausea, and was transferred to our institution. After hospitalization, the patient’s serum creatinine level increased to 5.42 mg/dL, and his daily urine output decreased to approximately 300 mL. Renal biopsy findings noted that the glomeruli were relatively intact; however, diffuse acute tubular injury was observed. Generalized edema was also noted, and the patient underwent a total of four hemodiafiltration sessions. Afterward, the patient’s urine output gradually increased whereas the serum creatinine level decreased. The patient was discharged in a stable status without any sequelae.
CONCLUSION
Detergents appear to directly cause renal tubular injury by systemic absorption. In treating a patient with detergent poisoning, physicians should be aware that the renal function may also deteriorate. In addition, timely renal replacement therapy may help improve the patient’s prognosis.

Key Words: Detergents; Poisoning; Intravenous injection; Acute kidney injury; Acute tubular injury; Case report

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Core Tip: Reports of detergent poisoning through an intravenous injection are extremely rare. Here, we report a case of acute kidney injury caused by detergent poisoning through an accidental intravenous injection. The patient progressed to acute kidney injury after administration of detergent. Kidney biopsy showed diffuse acute tubular injury. This case demonstrates that detergent directly cause tubular injury by systemic absorption. In addition, this case shows that renal replacement therapy at an appropriate time is helpful for the patient’s prognosis.

INTRODUCTION
Detergent poisoning mostly occurs through oral ingestion (> 85%), ocular exposure (< 15%), or dermal exposure (< 8%)[1]. According to a previous study, 36% of the cases of chemical poisoning were caused by detergents; in most cases, children accidentally ingested the detergents[2]. Ingesting detergents primarily causes gastrointestinal symptoms such as oral cavity hyperemia, pharyngeal irritation/pain, drooling, and vomiting[3,4]. Although rare, respiratory depression[3,5], central nervous system depression [6], and metabolic acidosis with hyperlactatemia[7] have been reported.

Reports of renal toxicity due to detergent ingestion are rare. A previous report noted that acute kidney injury (AKI) occurred due to rhabdomyolysis[8], while another noted that AKI occurred without any signs of rhabdomyolysis. The authors suggested that the systemic absorption of the detergent resulted in the direct toxicity of the renal tubules, causing AKI[9]. Another report of renal cortical necrosis after detergent ingestion showed that acute tubular necrosis and thrombotic microangiopathy were noted in renal biopsy[10].

Reports of detergent poisoning through an intravenous injection are extremely rare[11]. In addition, there are very few cases of renal toxicity directly caused by detergents[9,10]. Therefore, our report discusses a case of AKI caused by an intravenous injection of detergent.

CASE PRESENTATION
Chief complaints
A 61-year-old man was injected with detergent through the venous line and presented to the emergency department of our institution complaining vascular pain, dizziness, nausea, and chest discomforts.

History of present illness
The patient was admitted to a local hospital two months ago because of second degree burn. While undergoing burn treatment, another patient in the same room injected an unknown bubbling liquid through the patient’s venous line in the left greater saphenous vein, under the pretext of clearing the blocked fluid line. Within minutes of being injected with detergent, the patient complained of vascular pain, dizziness, nausea, and chest discomforts. He was then prompted admission to the emergency department of our institution.

The National Forensic Service compared the components of the liquid in the patient’s intravenous infusion line and the bathroom detergent in the hospital room of the local hospital. The detergent contained the following ingredients: Surfactant (dodecyltrimethylamine oxide, sodium alkylbenzene...
sulfonate), stabilizer (water, ethanol, octane-1,2-diol, sodium sulfate, silicon dioxide), cleaning aid (sodium hydrogen carbonate), antifoam (dimethylsiloxane), abrasive (calcium carbonate), and perfume (2,6-dimethyl-7-octen-2-ol, linalool, (E)-dodec-2-en-1-al, (R)-p-mentha-1,8-dien) (Table 1). The surfactant and calcium carbonate, which accounted for the largest proportion, were also detected in the intravenous infusion line. It was revealed that approximately 20 mL of detergent was injected.

**History of past illness**

The patient was maintained on atorvastatin 10 mg for dyslipidemia.

**Personal and family history**

The patient has no relevant family history.

**Physical examination**

At the emergency department, the patient’s vital signs showed the following: Blood pressure, 120/60 mmHg; heart rate, 88 beats per minute; respiratory rate, 14 per minute; body temperature, 36.1 °C. On physical examination, the breath sounds were clear, and the heart rhythm was regular without murmurs. Erythema was observed around the left greater saphenous vein.

**Laboratory examinations**

The initial laboratory findings revealed mild leukocytosis (14.8 × 10^3/μL) and elevated levels of aspartate transaminase (AST) (111 IU/L), total and direct bilirubin (3.48 mg/dL and 1.02 mg/dL, respectively), and lactate dehydrogenase (LDH) (1726 IU/L) (Table 2). Arterial blood gas analysis did not show metabolic acidosis or hyperlactatemia. The dipstick urinalysis results revealed protein 3+ and blood 3+, and urine microscopy revealed the presence of numerous red blood cells (RBCs) (Table 3).

**Imaging examinations**

The chest radiography and electrocardiogram readings showed no abnormal findings. A computed tomography (CT) scan of the abdomen and pelvis was performed to determine the cause of bilirubin elevation. The CT images revealed mild common bile duct dilatation, which was seen as a senile change, and the absence of any lesions that could elevate the bilirubin level. The kidney sizes and shapes were relatively normal, but both renal parenchymal enhancements were decreased, which was suggestive of AKI (Figure 1).

**Further diagnostic work-up**

On the 2nd day of hospitalization, the patient complained of general weakness and nausea. A decrease in hemoglobin from 12.6 mg/dL to 10.1 mg/dL was observed in laboratory findings on the 2nd day of hospitalization. LDH, AST, and bilirubin elevation were observed in the initial laboratory findings, and since hemolysis may be caused by detergent[12,13], further diagnostic work up was performed. Peripheral blood smear showed normal RBCs and reticulocyte counts without schistocytes. Serum haptoglobin level was also within normal range (Table 4).

White blood cell count, AST, bilirubin, and LDH, which were increased in the initial laboratory findings, all decreased at the 2nd day of hospitalization; however, blood urea nitrogen (BUN) and serum creatinine (Cr) levels were increased to 44.0 mg/dL and 3.59 mg/dL, respectively. Oliguria was noted as the patient’s daily urine output was only 350 mL. On the 3rd day of hospitalization, the BUN and serum Cr levels further increased to 55.7 mg/dL and 5.42 mg/dL, respectively. Oliguria (daily urine output 320 mL) persisted and generalized edema, which did not respond to diuretics, was noted.

Renal biopsy was performed on the 4th day of hospitalization. Light microscopy examination of renal biopsy specimen revealed up to 15 glomeruli that appeared normal in size and cellularity. The tubules showed diffuse swollen cytoplasms with vacuolar degeneration, focal loss of brush border with focal regenerative nuclear change and mitotic figures. Some tubular lumina contain a few RBCs and granular casts, sloughed cells and calcium concretions. There were focal interstitial fibrosis and infiltration of lymphocytes and some neutrophils. Segmental trace immunofluorescence staining for IgG, IgM and fibrinogen in mesangium was suggestive of a nonspecific trapping. Electron microscopic examination revealed tubular degeneration and granular casts in distal tubular lumina. Thus, the diagnosis was diffuse acute tubular injury (Figures 2 and 3).

**FINAL DIAGNOSIS**

The final diagnosis of the presented case is acute kidney injury due to direct renal tubular injury by detergent injection.
Table 1 Detergent composition and molecular weight

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Molecular weight (g/mol)</th>
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<tr>
<td>Dodecyldimethylamine oxide</td>
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<tr>
<td>Sodium alkylbenzene sulfonate</td>
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<td>2,6-dimethyl-7-octen-2-ol</td>
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<td>Linalool</td>
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<tr>
<td>(E)-dodec-2-en-1-al</td>
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<tr>
<td>(R)-p-mentha-1,8-dien</td>
<td>136.23</td>
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</table>

Table 2 Complete blood cell count and serum chemistry findings until 3rd day of hospitalization

<table>
<thead>
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<th>2nd day of hospitalization</th>
<th>3rd day of hospitalization</th>
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<td>9.9</td>
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<td>Hb (g/dL)</td>
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<td>10.1</td>
<td>10.7</td>
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<td>PLT (× 10^3)/μL</td>
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<td>109</td>
<td>110</td>
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<tr>
<td>BUN (mg/dL)</td>
<td>23.7</td>
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<td>55.7</td>
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<tr>
<td>Cr (mg/dL)</td>
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<td>5.42</td>
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<tr>
<td>AST (IU/L)</td>
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<tr>
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<td>4</td>
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<tr>
<td>Total bilirubin (mg/dL)</td>
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<tr>
<td>Direct bilirubin (mg/dL)</td>
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<td>LDH (IU/L)</td>
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<td>9.06</td>
<td>9.10</td>
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<td>3.77</td>
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<td>4.59</td>
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<td>139</td>
<td>136</td>
<td>137</td>
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<tr>
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<tr>
<td>Total CO₂ (mmol/L)</td>
<td>25.1</td>
<td>22.9</td>
<td>22.5</td>
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</table>

ALT: Alanine transaminase; AST: Aspartate transaminase; BUN: Blood urea nitrogen; Ca: Calcium; Cl: Chloride; CO₂: Carbon dioxide; CPK: Creatine phosphokinase; Cr: Creatinine; Hb: Hemoglobin; K: potassium; LDH: Lactate dehydrogenase; Na: Sodium; P: Phosphorus; PLT: Platelet; WBC: White blood cell.

**TREATMENT**

On the day after admission, the patient presented with oliguria and generalized edema that did not respond to diuretics. Thus, on the 3rd day of hospitalization, we performed hemodiafiltration (HDF) to
<table>
<thead>
<tr>
<th>The dipstick urinalysis findings</th>
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<tbody>
<tr>
<td>Color</td>
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<td>Cloudy</td>
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<td>Specific gravity</td>
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</tr>
<tr>
<td>pH</td>
<td>6.5</td>
</tr>
<tr>
<td>Protein</td>
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</tr>
<tr>
<td>Glucose</td>
<td>-</td>
</tr>
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<td>Ketone</td>
<td>-</td>
</tr>
<tr>
<td>Blood</td>
<td>3+</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>-</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>-</td>
</tr>
<tr>
<td>Nitrite</td>
<td>-</td>
</tr>
<tr>
<td>WBC</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urine microscopy findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro RBC (/HPF)</td>
<td>Many (&gt; 20)</td>
</tr>
<tr>
<td>Micro WBC (/HPF)</td>
<td>0-2</td>
</tr>
<tr>
<td>Micro sediment</td>
<td>No cast and crystal</td>
</tr>
</tbody>
</table>

HPF: High power field; RBC: Red blood cell; WBC: White blood cell.

<table>
<thead>
<tr>
<th>Tests</th>
<th>2nd day of hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral blood smear</td>
<td>RBC: Normocytic and normochromic RBCs with mild anisopoikilocytosis</td>
</tr>
<tr>
<td></td>
<td>WBC: Normal WBC counts with no toxic granulation and vacuolations</td>
</tr>
<tr>
<td></td>
<td>PLT: Decreased PLT counts</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>1.6</td>
</tr>
<tr>
<td>Hemosiderin stain</td>
<td>Negative</td>
</tr>
<tr>
<td>Haptoglobin (mg/dL)</td>
<td>45</td>
</tr>
<tr>
<td>Homocysteine (μmol/L)</td>
<td>8.66</td>
</tr>
</tbody>
</table>

RBC: Red blood cell; WBC: White blood cell; PLT: Platelet.

<table>
<thead>
<tr>
<th>OUTCOME AND FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>The patient’s symptoms and serum Cr level showed improvement from the 12th day of hospitalization, and the patient discharged on the 17th day without any sequelae. One week after discharge, the serum Cr level (0.83 mg/dL) returned to normal, and the urinalysis results did not reveal proteinuria or hematuria.</td>
</tr>
</tbody>
</table>
DISCUSSION

This is a case of AKI caused by an intravenous detergent injection in which the renal biopsy findings revealed acute tubular injury. Detergent poisoning commonly occurs through the oral route, and this is the first case of detergent poisoning through an intravenous injection in the Republic of Korea.
To the best of our knowledge, there has only been one case report of detergent poisoning through an intravenous injection in the literature. Okumura et al.[11] reported a case of a patient injecting 40 mL of detergent into his vein during a suicide attempt. Unlike our patient, this patient showed more serious clinical features including ventricular tachycardia, AKI, rhabdomyolysis, hemolysis, and coagulation dysfunction. The renal biopsy findings of this patient were acute tubular necrosis without any other abnormality, similar to our patient. The differences between the previous case and our case are the components and amounts of detergent (40 mL vs 20 mL, respectively). The detergent in the previous case was composed of 8% surfactant (alkylbetain, sodium fatty acid, alkanol amide, sodium alkylether sulfate, benzalkonium salt, and alkylglycoside). Although there was no information on the other ingredients, the surfactant itself was different from our case. The differences in the components and administered amounts of detergent may have resulted in the different clinical features of each case.

Rhabdomyolysis after the oral ingestion of a detergent has been reported to cause AKI[8]; however, this was not observed in our patient (Table 2). The creatine phosphokinase levels were consistently within normal range from hospitalization to discharge. The patient’s body temperatures were within the
normal range during hospitalization, no signs of infection were observed, and the results of the blood cultures were negative. Therefore, the possibility of AKI due to infection was also thought to be scarce. In the previous case report, it was reported that AKI occurred without any factors that could cause secondary AKI such as rhabdomyolysis. The authors suggested that the tubular injury was directly caused by the systemic absorption of the detergent[9]. Similarly, our case had no other secondary cause of AKI other than acute tubular injury, which was the main clinical feature. Therefore, it is likely that direct tubular toxicity occurred in our patient.

There are some studies on the interactions between surfactants and the cell membrane[14]. Surfactants have a hydrophobic and hydrophilic part. It is believed that the hydrophobic component can partition into the lipophilic part of the membrane and increase its fluidity, leading to cell disruption and leakage, and cell death[15]. This mechanism may explain why surfactants cause hemolysis[16] and death of Escherichia coli[17]. However, there was no evidence of hemolysis in our case, and the AST and bilirubin elevation were occurred due to direct hepatotoxicity of detergent, presumably. The results of renal biopsy suggest that the detergent caused the destruction of the kidney tubules. Therefore, it can be considered that the surfactant of the detergent acted on the cell membranes of the kidney tubules and caused acute tubular injury. However, it is difficult to determine why other cells such as RBCs or myocytes were not affected. Calcium carbonate also accounted for a large proportion of the detergent injected into our patient. Excessive use of calcium carbonate can lead to milk-alkali syndrome and cause AKI[18]. However, our patient’s serum calcium level was within the normal range (Table 2). Thus, it seems unlikely that calcium carbonate caused AKI in our case.

We performed HDF for control of intractable generalized edema and removal of remained potential toxic substances from the patient’s blood. However, considering the molecular weight of the detergent component investigated retrospectively (Table 1), conventional hemodialysis (HD) and HDF could have had no difference in potential toxin removal capacity.

CONCLUSION

Although detergent poisoning through an intravenous injection is very rare, its components could cause direct renal toxicity. Therefore, regardless of the route, detergent poisoning can cause renal toxicity. When detergent poisoning occurs, the renal function should be closely monitored, and the timing of renal replacement therapy may improve the patient’s survival.

FOOTNOTES

Author contributions: Park S and Park Y were the patient’s attending physician, reviewed the literature and contributed to manuscript drafting; Ryu HS, Lee JK, Park SS, Kwon SJ involved in the data curation; Park MH interpreted the pathologic findings, reviewed the literature and drafted the manuscript; Hwang WM and Yun SR supervised the findings of this work; Park Y were responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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S-Editor: Xing YX
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## REFERENCES


Vaginal enterocele after cystectomy: A case report

Shuai-Hong Liu, Yu-Hao Zhang, Hai-Tao Niu, Dong-Xu Tian, Fei Qin, Wei Jiao

BACKGROUND
After undergoing radical cystectomy combined with hysterectomy, female patients may suffer from pelvic organ prolapse due to the destruction of pelvic structures, which mainly manifests as the prolapse of tissues of the vulva to varying degrees and can be accompanied by symptoms, such as bleeding and inflammation. Once this complication is present, surgical intervention is needed to resolve it. Therefore, preventing and managing this complication is especially important.

CASE SUMMARY
The postoperative occurrence of acute enterocele is rare, and a case of acute small bowel vaginosis 2 mo after radical cystectomy with hysterectomy is reported. When the patient was admitted, physical examination revealed that the small bowel was displaced approximately 20 cm because of vaginocoele. A team of gynecological, general surgery, and urological surgeons was employed to return the small bowel and repair the lacerated vaginal wall during the emergency operation. Eventually, the patient recovered, and no recurrence was seen in the half year of follow-up.

CONCLUSION
We review the surgical approach for such patients, analyze high-risk factors for the disease and suggest corresponding preventive measures.

Key Words: Acute enterocele; Complication; Pelvic organ prolapse; Prevention; Repair; Case report
Core Tip: After undergoing radical cystectomy combined with hysterectomy, female patients may suffer from pelvic organ prolapse due to the destruction of pelvic structures, which mainly manifests as the prolapse of tissues of varying degrees in the vulva and can be accompanied by symptoms, such as bleeding and inflammation. Once this complication is present, we need surgical intervention to resolve it. So how to prevent and manage this complication is especially important. We review the surgical approach for such patients, analyzes high-risk factors for the disease and focuses on suggesting corresponding preventive measures.

INTRODUCTION

Bladder cancer is the most common malignant tumor of the urinary system. The incidence rate in males is 3-4 times that in women. Although the probability of male cancer is far greater than that of female cancer, the possibility of myometrial invasion is greater in women[1]. The preferred choice of treatment for women with muscle-invasive bladder cancer is radical cystectomy and urinary diversion. However, for patients with locally advanced disease, it may be necessary to enucleate the uterus and bilateral adnexa and even a segment of the anterior vaginal wall for bladder removal, thereby reducing the likelihood of recurrence and metastasis after surgery. Given that destruction of the original structure of the pelvic cavity combined with the loss of some tissues, such as ligaments and fascia, leads to the absence of support for the vagina and vulvar region of the patient, the probability of developing pelvic organ prolapse (POP) after surgery increases.

In patients with an orthotopic neobladder, the presence of POP can lead to compression of the neobladder, triggering urinary retention and dysuria. POP causes patients to experience a reduction in quality of life, and surgical treatment is often indicated for patients with sexual needs. However, patients with acute enterocele are at risk of bowel rupture as well as mesenteric torsion, which subsequently triggers intestinal avascular necrosis, requiring timely multidisciplinary joint surgical intervention[2]. The patient's previous surgical history can indicate whether it is likely that various levels of intra-abdominal adhesions are present. In addition, the absence of pelvic tissues (muscles, ligaments, and vaginal supporting tissues) undoubtedly increases the difficulty of surgical repair. Two surgical approaches are available: transabdominal or transvaginal approaches using vaginal atresia[3] or posterior vaginal wall repair to reduce the probability of secondary POP after surgery. It has also been reported that pelvic mesh placement results in good outcomes. To reduce patient suffering and expense, we believe that preventive measures are needed to reduce the incidence of POP after radical cystectomy in women. Importantly, doctors need to understand the anatomy of the female reproductive system, reduce the damage to important ligaments and fascia during surgery, and preserve vaginal support as much as possible[4,5]. However, more important is adequate preoperative preparation and individualized postoperative care.

CASE PRESENTATION

Chief complaints
The patient was a 72-year-old woman who experienced sudden spontaneous small bowel bulging into the vagina during defecation at home and was transferred to our hospital 10 h after onset for treatment.

History of present illness
The patient suffered from excruciating abdominal pain and had assumed and maintained a hunched posture for over 10 h.

History of past illness
The patient was pregnant three times, gave birth two times, and miscarried once. Her height, weight and body mass index were 158 cm, 56 kg and 22.4 kg/m², respectively. The patient had no history of chronic disease. She underwent radical cystectomy, uterine and double adnexectomy and bilateral ureterolithotomy due to bladder malignancy two months prior. Postoperative pathology confirmed high-grade invasive urothelial carcinoma invading the deep muscularis without involvement of urethral resection margins and bilateral ureteral stumps.
Personal and family history
The personal and family history of the patient was unremarkable.

Physical examinations
The patient’s temperature was 37.6°C, heart rate was 98 bpm, respiratory rate was 19 breaths per minute, blood pressure was 170/85 mmHg and oxygen saturation in room air was 99%. Physical examination after admission revealed that the small intestine had prolapsed approximately 20 cm, and its color was dark red (Figure 1). The initial diagnosis was vaginal enterocele (Aa6, Ba7, C9, AP-4, BP6 stage IV prolapse) according to the POP-Q system[6,7].

Laboratory examinations
Blood analysis revealed mild leukocytosis of 11.5 × 10⁹/L, with predominant neutrophils (85%) and a normal hematocrit and platelet count. Prothrombin and partial thromboplastin times were normal, and the d-dimer value was 0.71 μg/mL. Serum C-reactive protein was normal, and the erythrocyte sedimentation rate was 32 mm/h. The blood biochemistry and urine analyses were normal. The electrocardiogram, chest X-ray and arterial blood gas results were also normal.

Imaging examinations
In the initial imaging evaluation with a pelvic computed tomography (CT) scan, the patient’s uterus and bladder were not visualized. A partial small bowel herniation from the pelvic region was discovered (Figure 1B), and the abdominal CT showed no other abnormalities.

MULTIDISCIPLINARY EXPERT CONSULTATION
Wei Jiao, MD, PhD, Chief Doctor, Professor, Department of Urology, The Affiliated Hospital of Qingdao University, provided the following assessment: The patient underwent laparoscopic radical cystectomy and hysterectomy 2 mo earlier. Based on the patient's medical history and physical examinations, acute vaginal enterocele was considered.

Yu-Fang Xia, MD, PhD, Chief Doctor, Assistant Professor, Department of Gynecology, The Affiliated Hospital of Qingdao University, provided the following assessment: After undergoing radical cystectomy combined with hysterectomy, female patients may suffer from POP due to the destruction of pelvic structures. If the patient presents vaginal bacteria proliferation, damage to pelvic internal tissues due to inflammation resulting in edema can result in acute vaginal enterocele.

Guo-De Sui, MD, PhD, Chief Doctor, Assistant Professor, Department of Emergency Surgery, The Affiliated Hospital of Qingdao University, provided the following assessment: The patient's physical examination after admission revealed that the small intestine had prolapsed approximately 20 cm, and its color was dark red (Figure 1). We were concerned that the patient might have bowel rupture, and open surgical exploration was urgently needed.

FINAL DIAGNOSIS
The final diagnosis of the presented case was acute vaginal enterocele after cystectomy.

TREATMENT
The patient’s exposed small bowel outside the vagina was dark red, and due to the risk of small bowel ischemic necrosis and rupture, we quickly performed open surgical exploration to ensure that the small bowel was free of mesangial torsion and necrosis. Intraoperatively, an abdominal median incision approximately 10 cm in length was made in the abdominal cavity for exploration. The patient had no obvious adhesion in the abdominal cavity. A small amount of ascites was observed in the pelvic cavity, and the sigmoid colon was palpable with a larger mass of hard feces. Intraoperatively, approximately 20 cm of the small intestine was dislodged from the vaginal stump. After being placed back and moistened with warm saline for 15 min, the dislodged small intestine exhibited good revascularization and peristalsis (Figure 2A). A small portion of the intestinal wall serosal layer was broken. We used 4-0 VICRYL (Ethicon) for suture repair. The patient’s vaginal stump exhibited edema and inflammatory changes, and the suture was reinforced using 0-0 VICRYL (Ethicon) (Figure 2B). After washing of the pelvic cavity with warm saline and dilute iodophor, the pelvic floor wound was assessed to ensure that it was not bleeding. The incision was closed layer by layer.
Figure 1 The small intestine had prolapsed. A: Vaginal enterocele appears dark red in color; B: Pelvic CT suggested partial small bowel prolapse into pelvic cavity.

Figure 2 Open surgical exploration to ensure that the small bowel was free of mesangial torsion and necrosis. A: During the operation, the prolapsed small intestine was still active after hot compress with warm saline solution; B: The repaired vaginal stump was reinforced to the posterior vaginal wall using a figure of eight suture.

OUTCOME AND FOLLOW-UP

Postoperatively, we used cefoperazone sulbactam to prevent infection and observed that the patient's routine inflammatory indicators gradually recovered to normal levels 3 d after surgery. Routine blood tests returned to normal values before discharge, but mild anemia was noted. The patient began to flatulate on postoperative day 2 and defecate on postoperative day 3. The patient did not show symptoms such as intestinal root obstruction and intestinal necrosis during hospitalization. The patient recovered well and was discharged on the 5th postoperative day. During the follow-up assessment approximately 6 mo after the patient was discharged from the hospital, no new prolapse and no cancer recurrence were noted.

DISCUSSION

Currently, no definite incidence rate of POP after radical cystectomy has been reported. However, after radical cystectomy and hysterectomy, the rate of pelvic cavity structure prolapse is not minimal[8]. The patients mainly have chronic symptoms. Acute enterocele patients are rare, and clinicians lack relevant treatment experience. Both urgent and elective revision surgeries are difficult and require the skill of an experienced physician.

In our literature review, representative cases of acute and chronic POP after radical cystectomy (including cases treated with laparoscopic and robotic-assisted surgery) due to bladder cancer published in recent years were retrieved. Table 1 summarizes the patient's basic conditions, surgical approach, and follow-up in these cases. Most of the surgeries were performed using the vaginal approach. In addition, nonurgent repair surgery was supplemented with mesh reinforcement, and
Table 1 Vaginal enterocele case literatures review

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Case</th>
<th>Age</th>
<th>Surgery</th>
<th>Time to pop after surgery</th>
<th>Type and stage</th>
<th>Approach</th>
<th>Method</th>
<th>Relapse</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okada et al [13]</td>
<td>1</td>
<td>78</td>
<td>Cystectomy and Hysterectomy</td>
<td>3 mo</td>
<td>Stage III Anterior enterocoele</td>
<td>Transvaginal</td>
<td>Suture with Polytetrafluoroethylene mesh</td>
<td>No</td>
<td>6 mo</td>
</tr>
<tr>
<td>Shaker [8]</td>
<td>1</td>
<td>75</td>
<td>Cystectomy and Hysterectomy</td>
<td>10 mo</td>
<td>Stage III Anterior enterocoele</td>
<td>Transvaginal</td>
<td>Suture</td>
<td>No</td>
<td>4 mo</td>
</tr>
<tr>
<td>Stav et al [14]</td>
<td>1</td>
<td>70</td>
<td>Cystectomy</td>
<td>16 mo</td>
<td>Stage III Anterior enterocoele</td>
<td>Transvaginal</td>
<td>Suture with polypropylene mesh</td>
<td>Yes</td>
<td>2 mo</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>Cystectomy</td>
<td>18 mo</td>
<td>Stage IV Anterior enterocoele</td>
<td>Transvaginal</td>
<td>Suture</td>
<td>No</td>
<td>10 mo</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>Cystectomy, hysterectomy and Anterior vaginal repair</td>
<td>10 mo</td>
<td>Stage IV Anterior enterocoele</td>
<td>Transvaginal</td>
<td>Suture</td>
<td>No</td>
<td>5 mo (Died)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>Cystectomy, ileal conduit and chemotherapy</td>
<td>2 mo</td>
<td>Stage III Anterior enterocoele</td>
<td>Transvaginal</td>
<td>Suture with bilateral iliococcygeal suspension</td>
<td>Three weeks later developed a colo-vaginal fistula</td>
<td>10 mo (Died)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>Cystectomy, ileal conduit</td>
<td>7 mo</td>
<td>Stage IV Anterior enterocoele</td>
<td>Transvaginal</td>
<td>Colpocleisis</td>
<td>Yes</td>
<td>6 mo</td>
<td></td>
</tr>
<tr>
<td>Graefe et al [15]</td>
<td>1</td>
<td>67</td>
<td>Cystectomy, ileal conduit</td>
<td>8 mo</td>
<td>Stage IV Anterior enterocoele</td>
<td>Transvaginal</td>
<td>Suture with Polypropylene mesh</td>
<td>No</td>
<td>16 mo</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>Cystectomy, ileal conduit</td>
<td>12 mo</td>
<td>Stage IV Anterior enterocoele and vaginal vault prolapse</td>
<td>Transvaginal</td>
<td>Suture with Polypropylene mesh</td>
<td>No</td>
<td>4 mo</td>
<td></td>
</tr>
<tr>
<td>Lin et al [2]</td>
<td>1</td>
<td>55</td>
<td>Robotic-assisted cystectomy with ileal conduit (previous hysterectomy)</td>
<td>4 mo</td>
<td>Stage IV with denuded anterior vaginal wall enterocoele</td>
<td>Transvaginal</td>
<td>6 wk later native tissue repair, 52 wk later Suture with biological graft, 78 wk completion perineorrhaphy</td>
<td>Yes, 6 wk later vaginal wall dehiscence 52 wk later recurrent dehiscence 78 wk recurrent dehiscence</td>
<td>5 yr</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>Robotic-assisted cystectomy with ileal conduit (previous hysterectomy)</td>
<td>1 yr</td>
<td>Stage II prolapse of the anterior wall and vault anterior vaginal wall prolapse</td>
<td>Transvaginal</td>
<td>56 wk later suture and reconstruction for an enterocoele prolapsing, 80 wk later partial vaginectomy, 86 wk suture with biological graft</td>
<td>Yes, 56 wk later anterior vaginal wall prolapse, 80 wk later recurrent vaginal bulge, 86 wk later recurrent bulge</td>
<td>21 mo</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>Robotic-assisted radical cystectomy, hysterectomy and ileal conduit</td>
<td>14 wk</td>
<td>Anterior vaginal wall prolapse</td>
<td>Transvaginal</td>
<td>Suture</td>
<td>No</td>
<td>11 mo</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>Robotic-assisted radical cystectomy hysterectomy</td>
<td>28 mo</td>
<td>Vaginal eversion and vaginal dehiscence</td>
<td>Transvaginal</td>
<td>Suture and colpocleisis, levatorplasty, perineorrhaphy</td>
<td>Yes, 4 mo later vaginal dehiscence</td>
<td>3 wk</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>Robotic-assisted radical cystectomy hysterectomy</td>
<td>11 wk</td>
<td>Vaginal dehiscence and window of thickened peritoneal tissue</td>
<td>Transvaginal</td>
<td>Suture and enterocoele repair, colpocleisis and aperineorrhaphy</td>
<td>No</td>
<td>8 mo</td>
<td></td>
</tr>
</tbody>
</table>

Polytetrafluoroethylene polymer composites were the mesh material most often used. Some scholars, such as Lin et al [2], have also chosen to use biological grafts. Zimmer and Wang [9] believed that the placement of mesh reduces the chance of POP recurrence to some extent and benefits patients in the long term. The placement of a matched mesh by surgical repair is currently the most popular surgical approach for treating POP. However, there is a possibility of recurrence postoperatively. In the case reported by Lin, some patients experienced a second or even third recurrence after repair and ultimately...
opted for a more extreme complete vaginal suture procedure. Multiple recurrences of POP cause considerable harm to patients, both psychologically and physiologically, while also increasing their financial burden. We reviewed previous case reports and found that the main factors reported to be responsible are type of surgery and lack of judgment and corresponding preventive measures against the etiology of the disease. We propose some humble opinions in this regard.

We have summarized the etiology of acute enterocele based on reported cases as follows: (1) Patients were discharged from the hospital with mixed hygiene strategies and occasionally lacked the necessary perineal care, had vaginal bacteria proliferation, had damage to pelvic internal tissues due to inflammation resulting in edema, and had difficulties in securing vaginal posterior wall sutures due to edema and the weakened state of inflammatory tissues (which result in slippage of sutures); (2) As was found in the patients in these cases, a history of constipation was present in some patients with increased pressure in the pelvic cavity during bowel movements leading to enterocele; and (3) Clinicians mainly focus on tumor recurrence and prognosis, and reexamination is mainly based on imaging and biochemical examination. Reexamination often lacks a meticulous physical examination, and early enterocele is easily overlooked. In response to the above pathogenetic factors, we have focused on proposing corresponding preventive measures. Expedite the patient’s postoperative recovery and reduce the risk of postoperative infection. In addition to the proper use of antimicrobials, prophylactic measures are routine in surgical procedures, such as avoiding intraoperative hypothermia in patients, controlling perioperative blood glucose, and adhering to strict aseptic procedures[10]. Patients should be referred to gynecologic perioperative practice for anti-infection options when undergoing radical cystectomy and hysterectomy. The most notable of these strategies is the disinfection of the vagina preoperatively and intraoperatively, and we recommend the preoperative use of a 1:3000 potassium permanganate dilution by sitting in a bath and flushing the vagina once each morning and night. Intraoperatively, the scope of skin disinfection of the perineal area should be appropriately expanded, and the vagina should be rinsed again using dilute iodophor. Cleaning agents may also include chlorhexidine. The above approach has been used to reduce the number of bacteria on the skin of the perineal region and in the vagina with the aim of alleviating the inflammatory reaction in the vaginal wall tissue during and after surgery, thereby alleviating tissue edema and reducing the risk of suture slippage in the posterior vaginal wall after surgery. In addition, in the instructions before discharge, patients need to be reminded to pay attention to perineal hygiene postoperatively and to change their underpants on a regular basis. Postoperatively, increased abdominal pressure is one of the predisposing factors for POP and can be induced by coughing, laughing, improper movement, and constipation. Compared with extrinsic factors, such as coughing, laughing, and participating in sports, constipation is often overlooked by clinicians and patients[11].

In the present case, the patient had a long history of constipation with vaginal enterocele occurring during defecation and a large, hard fecal mass was palpable in the sigmoid colon on intraoperative exploratory laparotomy. We believe that constipation is a high-risk factor for acute vaginal enterocele. Therefore, it is important to correct constipation problems, and we recommend routine bowel preparation before surgery and propose individualized postoperative bowel movement management protocols for patients with a history of constipation[12]. Patients are encouraged to use glycerin enemas postoperatively. Softened stools facilitate expulsion, and osmotic laxatives, such as polyethylene glycol, may also be used if necessary. When patients are reexamined postoperatively, clinicians should emphasize physical examination unconstrained by imaging and laboratory test results, though they are important measures to detect early POP.

CONCLUSION

We report a case of a female patient who presented with a sudden, spontaneous small bowel bulging into the vagina. Exploratory laparotomy, small bowel recovery and vaginal repair were performed. Acute enterocele is a relatively intractable problem for surgeons once it occurs. If the patient has a history of surgery, adhesions in the abdominal viscera may be present, increasing the difficulty of surgery. According to the patient's actual situation, a transabdominal or transvaginal surgical approach can be taken. We have referred to the treatment methods of other scholars including Okada, Stav, and Graefe[13-15], which had good guiding significance for us. In our case, we chose the potentially cumbersome intraperitoneal approach because of additional concerns about revascularization of the patient's bowel. In addition, inflammation, adhesions and pain all contribute to increased local tissue oxidative stress in patients. Oxidative stress is one of the principal factors associated with mesh foreign-body reactions[16]. Therefore, we did not place meshes to prevent aggravation of inflammation. However, we found that mesh placement in cases without inflammation may benefit patients[17]. Acute vaginal enterocele causes great distress to patients both psychologically and physiologically while increasing the financial burden on patients. We believe that adequate preoperative preparation along with detailed postoperative education is one of the important means to prevent this complication. Other means of prevention await further study.
FOOTNOTES

Author contributions: Liu SH, Niu HT, Jiao W were the patient's urologists, reviewed the literature analyzed the data and contributed to manuscript drafting; Zhang YH reviewed the literature; Qin F and Tian DX contributed to manuscript drafting; Jiao W analyzed and interpreted the imaging findings; all authors issued final approval for the version to be submitted.

Informed consent statement: This case is for the promotion of medical research only, publication of partial information on the patient in the text has been obtained with the patient's own consent and signed informed consent.

Conflict-of-interest statement: There is no conflict of interest among the authors.

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