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Effects of alcohol consumption on viral hepatitis B and C

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Abstract

The liver is the main target organ for hepatitis viruses and the vital organ for alcohol metabolism. These two factors of viral hepatitis and alcohol abuse in combination can exert dual harmful actions, leading to enhanced damage to the liver. Epidemiological studies have revealed a higher prevalence of hepatitis C virus (HCV) infection among alcoholics than the general population. The interaction of alcohol with viral hepatitis [e.g., hepatitis B virus (HBV), HCV] and the underlying mechanisms are not fully understood. The effects of alcohol on viral hepatitis include promoted viral replication, weakened immune response, and increased oxidative stress. Clinically, alcohol abuse is correlated with an increased risk of developing end-stage liver cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis B and C, suggesting that the combination of alcohol and HBV/HCV lead to more severe liver damage. The influence of mild to moderate alcohol drinking on the HBV-induced liver fibrosis, cirrhosis, and hepatocellular carcinoma among patients infected with HBV remains unclear. Unlike HBV infected patients, no safe level of alcohol intake has been established for patients with HCV. Even light to moderate alcohol use can exert a synergistic effect with viral hepatitis, leading to the rapid progression of liver disease. Furthermore, interferon-based therapy is less effective in alcohol drinkers than in control patients, even after abstinence from alcohol for a period of time. Therefore, abstaining from alcohol is highly recommended to protect the liver, especially in individuals with HBV/HCV infection, to improve the clinical efficacy of antiviral treatment and prevent the rapid progression of chronic viral hepatitis.

Key Words: Alcohol; Hepatitis B virus; Hepatitis C virus; Viral hepatitis

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PREVALENCE OF HBV/HCV INFECTION AND ALCOHOL CONSUMPTION

Excessive alcohol use is related to an increased risk of spreading the infection of viruses, including HBV and HCV[9]. In fact, HCV infection is more prevalent in patients with alcohol use disorders (AUDs) than the general population. CHC is associated with excessive current and previous alcohol drinking[10]. The World Health Organization HCV elimination strategy also highlights the requirement for addressing alcohol intake as a co-morbidity among patients with HCV infection[11]. The prevalence of hepatitis C varies from 4.6% to 55.5% in alcoholics up to 30-fold higher in alcoholics compared with the general population[12-18]. A systematic review of 133 publications showed that the prevalence of HCV infection is approximately 10% to 15% of patients with HCV infection are coinfected with HBV[19]. Meanwhile, alcohol abuse is more prevalent in patients with HCV infection who also have a longer duration of alcohol use than the general population. A systematic review of 11 previous studies including 286641 patients with CHC reported that 22.3% of the patients identified with AUDs, a much greater proportion than the general population. A systematic review of 133 publications showed that the prevalence of CHC is approximately 10% to 15% of patients with HCV infection are coinfected with HBV[19].
Scotland, respectively[20]. Rosman et al[21] reported that anti-HCV is significantly more prevalent in alcoholics than non-drinkers, indicating alcohol misuse as an independent risk factor associated with HCV infection. Although direct evidence is lacking, it has been postulated that alcohol use enhances the acquisition of HCV after exposure to the virus[22,23].

Unlike the relatively high incidence of HCV infection in alcohol drinkers, the prevalence of HBV infection in this population is still inconclusive. Some previous studies have revealed a higher frequency of HBV markers in the serum of chronic alcoholics[24-26] as well as of patients with alcoholic hepatitis and liver cirrhosis[27] compared with the general population. A study from Taiwan reported a link of alcohol drinking with a lower prevalence of hepatitis B surface antigen (HBsAg)[28], which is not consistent with the study by Rosman et al[21], indicating that the prevalence of anti-HCV is significantly greater in alcoholics than in non-drinkers, whereas there is no significant difference in the prevalence of HBV between alcohol drinkers and non-drinkers. These previous findings suggest that alcohol abuse is an independent risk factor for HCV but not HBV infection[21], but the reason for the difference remains unclear. Lin et al[29] proposed that HBV infection can play an important role in the evolution of the aldehyde dehydrogenase 2 (ALDH2*2) allele in the Chinese Han population. Geographical areas with a particularly high prevalence of HBV infection are located in Eastern Asia, especially in China. In addition, 30%-40% of Asian populations are deficient in ALDH2, a key enzyme in detoxifying the ethanol metabolite acetaldehyde. Variation in the ALDH gene influences drinking behavior and the risk of alcoholism development through acetaldehyde formation. In the long-term HBV endemic in China, non-alcohol drinking HBV carriers may have evolutionary advantages over alcohol-drinking HBV carriers. Accordingly, HBV carriers who do not drink or drink in moderation may have better chances of surviving than those who drink more alcohol. It has also been hypothesized that the ALDH2*2 allele, through the natural selection of liver diseases, becomes the adaptive gene among Chinese Han population, resulting in a better chance of surviving and facilitating transmission of the virus to the next generation. In summary, HBV selects ALDH gene mutations, which can affect drinking behavior, making HBV-infected people not good at drinking alcohol, and providing more opportunities for long-term survival and transmission of HBV.

**INTERACTION OF ALCOHOL WITH HEPATITIS VIRUS AND THE UNDERLYING MOLECULAR MECHANISMS**

Both alcohol and HBV/HCV infection are associated with liver injury, and the interactions of alcohol with hepatitis B and C infections are complex. Although the exact underlying mechanisms are not fully understood, studies have provided evidence that alcohol can increase the replication of HBV/HCV, oxidative stress, and cytotoxicity but decrease antiviral immune responses in the liver[30].

**Alcohol enhances the replication of HBV and possibly HCV**

Existing in vitro and in vivo studies have shown that alcohol intake can increase the replication of HBV, and possibly HCV, as well their host hepatocytes. Larkin et al[31] found that the serum viral DNA load and levels of HBsAg increased by nearly 6-fold in mice treated with alcohol compared with those given the control diet. In the same study, elevated levels of HBV-RNA as well as surface, core, and X antigens were also observed after alcohol treatment, especially in the pericentral regions of the liver in mice. In in vitro studies, Ganesan et al[32] reported that the levels of HBV RNA, covalently closed circular DNA, and HBsAg were increased in response to alcohol treatment in HepG2.2.15 cells. Recently, Lin et al[29] showed that hepatitis B viral load was higher in alcoholic than non-alcoholic HBV patients. Alcohol can promote HBV transcription by regulating some key factors [e.g., peroxisome proliferator-activated receptor alpha, farnesoid-X-receptor alpha, cytochrome P450 2E1 (CYP2E1)] as well as the hypoxia-inducible factor-1α-dependent pathway, which have been proposed as potential molecular mechanisms whereby excessive alcohol consumption increases the replication of HBV in the liver[33-35]. In addition to the direct effect of alcohol on the replication of HBV, alcohol can act on lipid rafts with pivotal roles in viral entry and other processes of the viral life cycle, leading to indirect effects on HBV replication[23].

Unlike HBV, the effect of alcohol on the replication of HCV remains a subject of debate due to conflicting results from different studies. Ran et al[36] showed that alcohol treatment promoted HCV replication in Huh7 cells. Sobhanimonfared et al[37]...
Alcohol suppresses antiviral immune responses
In the cases of HBV and HCV infections, eliciting antiviral immune responses, including innate and adaptive immune responses, are important host defenses in the control of viruses. Excessive alcohol intake adversely affects the antiviral immune system in response to hepatitis viruses, leading to unfavorable outcomes of HBV or HCV infection. In terms of innate immune responses, alcohol exerts inhibitory effects on the antiviral activity of natural killer cells. In addition, long-term alcohol consumption appears to affect innate immune responses to hepatitis virus infection in the production of some important cytokines including interferon (IFN)-α, IFN-γ, tumor necrosis factor-α, transforming growth factor β, and interleukin 10[41-45]. In the adaptive immune responses to hepatitis viruses, alcohol reduces the number of B cells, particularly circulating B cells[46-48]. Alcohol may suppress the adaptive immune response of B cells by reducing the number of B cells, subsequently decreasing the production of antibodies against HBV antigens, thereby leading to persistent HBV infection and development of CHB. Data from animal and human studies have clearly shown that alcohol reduces the number of T cells, alters their patterns, suppresses their activation, and promotes the apoptosis of T cells[49]. Alcohol has also been shown to affect dendritic cells, which are critically important immune cells in adaptive immune responses to virus infection in patients with HCV infection[50,51].

Alcohol intake increases oxidative stress in the liver
Chronic alcohol intake induces the microsomal ethanol-oxidizing system, including that of CYP450. Among the variants of CYP450, CYP2E1 is markedly affected by chronic alcohol consumption, with activity that increases in response to alcohol. Free radicals (e.g., superoxide, hydroxyl radicals, hydrogen peroxide) are generated in ethanol metabolic pathways involving CYP2E1, and excessive oxygen radicals cause oxidative stress. Rigamonti et al[52] showed that moderate alcohol consumption (< 50 g/d) and heavy alcohol drinking (> 50 g/d) increase the risk of developing oxidative stress 3-fold and up to 24-fold, respectively. Oxidative stress can activate nuclear factor kappa B[53], playing a key role in hepatic inflammation, liver injury and regeneration, and the development of HCC[54-56]. Moreover, CYP2E1-associated oxidative stress increases the ethanol-induced transactivation of HBV[57].

Oxidative stress is a negative effect exerted by reactive oxygen species, highly reactive oxygen intermediates that can chemically modify the structure of various molecules and thus pose a threat to the living cell. High levels of reactive oxygen species induce oxidative DNA damage, such as 8-hydroxy-2-deoxyguanosine (8-OHdG), an important biomarker for oxidative stress. Wong et al[58] showed that HBV- and HCV-induced hepatic inflammation and alcohol consumption can induce oxidative stress, with alcohol consumption correlated with 8-OHdG. The accumulation of 8-OHdG associated with alcohol in hepatocytes may establish a possible link between HBV infection and hepatic carcinogenesis[59]. These findings provide an explanation for the enhanced progression of disease in hepatitis patients with alcohol abuse.

In addition, the interaction of alcohol with hepatitis virus may involve activation of the unfolded protein response[60], promotion of hepatic steatosis[61], increase in iron storage[62,63], and induction of hepatocytes apoptosis[64-66]. Moreover, in the progression of liver disease, these mechanisms can interact with each other. For example, higher levels of oxidative stress affect innate immunity, resulting in the more rapid spread of the virus and progression to end-stage liver disease.

EFFECTS OF ALCOHOL DRINKING ON THE PROGRESSION OF HBV OR HCV ASSOCIATED LIVER DISEASE
Alcohol intake has a synergistic effect with viral hepatitis on the liver disease progression. For example, a case control study found synergism between positive
HBsAg or HCV RNA and heavy alcohol drinking. Among patients coinfected with HBV and/or HCV, alcoholic patients tended to be younger and had a higher male-to-female ratio, worse performance status, more severe liver cirrhosis, more advanced cancer stage, and higher tumor burden compared to non-alcoholic patients. In terms of HCC, the values of multivariate odd ratios (ORs) [95% confidence intervals (CIs)] were 15.3 (4.3-54.4), 12.6 (2.5-63.1), 4.5 (1.4-14.8), and 4.3 (1.9-9.9) for anti-HCV, HBsAg, heavy alcohol intake (> 80 mL ethanol per day), and diabetes mellitus, respectively. There were synergistic interactions between heavy alcohol intake and chronic viral hepatitis (OR: 53.9, 95% CI: 7.0-415.7).

Effects of alcohol on the progression of HBV-associated liver disease

A study of 1113 Japanese patients with CHB revealed that the prevalence of hepatitis B e antigen (HBeAg) tended to be higher and decrease more slowly with age in heavy drinkers (> 60 g alcohol per day) than in nondrinkers, indicating that alcohol misuse may delay the loss of HBeAg. Other studies in the Japanese population found that alcohol intake, particularly excessive alcohol intake (> 60 g alcohol per day), can increase viral inflammatory changes in the liver in patients with persistent HBs-antigenemia or HBsAg carriers. Li et al. documented that interactions of alcohol and HB synergistically promote high-fat diet-induced hepatic steatosis in mice. The same study showed that alcohol consumption is associated with an increased risk of developing hepatic steatosis in HBV-infected patients.

Alcohol abuse in patients with CHB is correlated with an elevated risk of developing liver cirrhosis and HCC. In agreement with the above findings, Lin et al. indicated that heavy alcohol consumption significantly increased the risk of HCC in patients with HBV-related liver cirrhosis. It was also shown that HCC occurred in 28.8%, 15.8%, and 10.4%, respectively, in cirrhotic patients with HBV infection and alcoholism, cirrhotic patients with HBV infection, and cirrhotic patients with alcoholism. In addition, the 10-year cumulative incidences of HCC were 52.8%, 39.8%, and 25.6%, respectively, and the annual incidences of HCC were 9.9%, 4.1%, and 2.1%, respectively, in cirrhotic patients with HBV infection and alcoholism, cirrhotic patients with HBV infection, and cirrhotic patients with alcoholism. Notably, these incidences were significantly greater in cirrhotic patients with HBV infection and alcoholism than in those in patients with HBV infection alone.

Heavy alcohol consumption accelerates the progression of liver disease into liver cirrhosis and eventually into HCC with a 1.3- to 8.4-fold increased risk. A longitudinal study of healthy blood donors with positive HBsAg in Japanese population spanning the period between 1972 and 1975 demonstrated that alcohol intake > 27 g/d was associated with more than a 5-fold increase in the relative risk (RR) of developing HCC. A prospective cohort study of 610 patients with consecutive positive HBsAg noted that cumulative alcohol intake of 500 kg and more was significantly associated with the rate of carcinogenesis, with a RR (95% CI) of 8.37 (2.70-25.93, P = 0.0002). In addition, alcohol intake was reported to affect the mortality of HBV-related liver disease in a study by Ribes et al., in which 2352 HBsAg-positive patients were followed up for 20 years, and lifetime chronic consumption of alcohol more than 60 g/d was associated with a 6-fold increase in the risk of death from liver cirrhosis and HCC. Moreover, patients with HCC caused by CHB and chronic alcohol consumption are approximately 10 years younger than patients with HCC caused by CHB alone, suggesting that heavy alcohol drinking increases both the mobility and mortality of HCC in CHB patients.

It is worth noting that, compared with heavy alcohol drinking, the influence of mild to moderate alcohol drinking on HBV-induced liver fibrosis, cirrhosis, and HCC among patients infected with HBV remains unclear. A cross-sectional study of CHB patients showed that the incidence of advanced liver fibrosis in those patients who reported drinking alcohol (1-20 g alcohol per day) was similar to that in those who abstained from alcohol; hence, alcohol consumption should be kept to a minimum in patients with HBV infection. A study of 1045 hepatitis B patients showed that the prevalence of advanced liver fibrosis among patients with mild to moderate alcohol intake (26, 18.8%) was comparable to that of non-drinkers (190, 21.0%) (P = 0.57). The large-scale, prospective cohort REVEAL-HBV study of more than 3500 patients (aged 30-65 years) in Taiwan showed that male sex, older age, seropositivity for HBeAg, and habitual alcohol consumption are significantly correlated with the development of HCC. Taken together, these studies suggest that light-to-moderate habitual alcohol consumption appears to have, at best, a modest correlation with the progression of HBV-induced liver disease; this effect was not always significant, particularly in studies with a relatively small sample size. In addition, more accurate epidemiological and pathophysiological data obtained from larger cohort studies are
Effects of alcohol on the progression of HCV-induced liver disease

Alcohol intake is an independent risk factor associated with the progression of HCV infection and its related liver disease\[83,84\]. Multiple lines of evidence have shown worsened outcome of patients with chronic HCV and heavy alcohol use, although the definition of heavy alcohol use is somewhat different. For example, alcohol intake (40 g ethanol per day or more) is associated with the more rapid progression of HCV-induced liver diseases, including HCV-induced liver fibrosis and cirrhosis, compared to patients who consumed lower levels of alcohol\[85\]. A meta-analysis showed that the RR of progression to liver cirrhosis was 2.33-fold (95%CI: 1.67-3.26) in patients with heavy alcohol intake (240-560 g per week) compared to those with less heavy alcohol intake among patients with chronic HCV infection\[86\]. Decompensated cirrhosis in patients with hepatitis C is independently correlated with AUD in Britain\[92\]. New South Wales (HR: 3.68, 95%CI: 3.38-4.00), and Scotland (HR: 3.88, 95%CI: 3.42-4.40)\[20\]. Heavy alcohol intake increases the risk of HCC in patients with HCV infection\[87,88\]. Studies from Japan noted an increased risk of developing HCC in HCV patients who drank more than 65 g alcohol daily for over 5 years (RR: 3.04, 95%CI: 1.31-7.09)\[89,90\]. Similar to the findings in HBV-infected patients, heavy alcohol abuse is associated with an increased risk of developing HCC at a younger age in patients with HCV infection. Among HCV-positive patients who reported drinking alcohol (> 46 g/d), HCC occurred in patients at an average of 26 ± 6 years, younger than 31 ± 9 years for those who consumed alcohol less than 46 g/d\[91\]. Moreover, comparative analysis of tumor characteristics of HCC patients revealed that the tumors of heavy alcohol drinkers were significantly more anaplastic (5% with well-differentiated HCC vs 45% of nondrinkers) with increased extracapsular, capsular, and portal vein invasion and intrahepatic metastases\[89\].

In summary, no safe level of alcohol intake has been established for patients with HCV. Even light-to-moderate alcohol use can exert a synergistic effect with viral hepatitis, leading to the rapid progression of liver disease.

**EFFECTS OF ALCOHOL ON CLINICAL EFFICACY OF ANTIVIRAL TREATMENT OF HBV/HCV INFECTION**

IFN-based therapy is less effective in alcohol drinkers than in control patients, even after abstinence from alcohol for a period of time. As such, it has been recommended that patients with chronic infection of HCV should restrict alcohol intake to < 10 g/d, and abstinence from alcohol should be encouraged in patients with presence of liver cirrhosis or prior to IFN therapy\[98\]. Direct-acting antivirals are highly effective for the treatment of HCV infection, and alcohol intake is unlikely to alter achievement of sustained virologic suppression among patients with direct-acting antivirals treatment \[99\].

In terms of effects of alcohol drinking on the clinical efficacy of anti-HBV treatment, relative studies are limited. Hosaka et al\[100\] showed that alcohol consumption (> 200 kg) is a risk factor for cumulative HCC incidence rates at 5 years in patients with CHB treated with entecavir (HR = 2.21, 95%CI: 1.18-4.16, P = 0.013).
In addition to the effects of alcohol intake on antiviral therapy, liver fibrosis, cirrhosis, and liver cancer, it has not been reported whether it can cause chronic acute liver failure and whether other pathogens could be involved in chronic hepatitis patients. At the same time, there is no detailed report on whether other related decompensation complications can occur more easily or earlier in patients with HBV infection and alcoholism compared to patients with HBV infection or alcoholism alone. Future research efforts should focus on addressing the above issues.

CONCLUSION

Taken together, the existing studies indicate that alcohol adversely affects HBV and HCV infections in the liver by promoting viral replication and oxidative stress and suppressing viral immune responses. Considering the findings that the interaction of alcohol with viral hepatitis (e.g., HBV, HCV) contributes to the increased risk of developing HBV- or HCV-induced liver fibrosis, end-stage cirrhosis, and even deadly liver cancer, such as HCC, it is highly recommended that individuals with HBV or HCV infection abstain from alcohol to slow disease progression. In addition, these findings may have broader implications that abstaining from alcohol is needed for all individuals to protect the liver (Figure 1).

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Figure 1 was created with BioRender.com.
REFERENCES


Alcohol consumption on viral hepatitis B and C


Effects of anti-diabetic drugs on sarcopenia: Best treatment options for elderly patients with type 2 diabetes mellitus and sarcopenia

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Abstract
Human life expectancy increases as society becomes more developed. This increased life expectancy poses challenges associated with the rapid aging of the population. Sarcopenia, an age-related disease, has become a worldwide health issue. Patients with sarcopenia experience decreases in muscle mass and function, becoming frail and eventually bedridden. Type 2 diabetes mellitus (T2DM) is also a major health issue; the incidence of T2DM increases with aging. T2DM is associated with reduced muscle strength and poor muscle quality and may contribute to acceleration of the aging process, augmenting age-related sarcopenia. Recent studies indicate that elderly patients with diabetes are at an increased risk for sarcopenia. Therefore, these older diabetic patients with sarcopenia need specific anti-diabetic therapies targeting not only glycemic control but also sarcopenia, with the goal of preventing sarcopenia in pre-sarcopenic patients. Presently, various types of hypoglycemic drugs are available, but which hypoglycemic drugs are better suited for geriatric T2DM patients with sarcopenia remains undetermined. In this review, we discuss the association between diabetes and sarcopenia in geriatric patients, and how anti-diabetic drugs may influence sarcopenia outcomes. This review will guide clinical workers in the selection of drugs best suited for this patient population.

Key Words: Type 2 diabetes mellitus; Sarcopenia; Anti-diabetic drugs; Geriatric

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Core Tip: Elderly patients with diabetes are at an increased risk for sarcopenia. Therefore, these older diabetic patients with sarcopenia need specific anti-diabetic therapies targeting not only glycemic control but also sarcopenia, with the goal of
preventing sarcopenia in pre-sarcopenic patients. We herein discuss the association between diabetes and sarcopenia in geriatric patients, and how anti-diabetic drugs may influence sarcopenia outcomes.

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INTRODUCTION
Diabetes mellitus (DM), a chronic metabolic disease, has reached epidemic status and is considered one of the major threats to human health in the 21st century. In 2017, the International Diabetes Federation estimated that 425 million individuals worldwide have DM; this number is expected to increase to 629 million by 2045[1,2]. Approximately 90% of these individuals have type 2 DM (T2DM)[3], with the highest prevalence of T2DM observed in older adults[4]. Sarcopenia, which, in addition to the traditional microvascular and macrovascular complications, has emerged as a third category of T2DM-associated complications in geriatric individuals with diabetic syndromes, results in considerable disability[5]. Sarcopenia manifests primarily as decreased skeletal muscle mass. Combined with decreased bone mineral content and deteriorating bone quality, sarcopenia causes physical frailty and increases the risk for complications, which decrease quality of life and increase mortality[6]. A progressive decrease in muscle mass occurs at an annual rate of 1%-2% after 30 years of age, accelerates to 1.5%-3% per year after 60 years of age, and progresses even more rapidly after 75 years of age[7]. Because muscle is the main site of glucose consumption, reduced muscle mass leads to increased insulin resistance. Sarcopenia causes insulin resistance, which, in turn, exacerbates the loss of skeletal muscle[8]. Because sarcopenia is multifactorial, the diabetic geriatric population needs specific treatment parameters for both the initial and maintenance therapy using anti-diabetic agents. Therefore, prescribing anti-diabetic agents in such individuals should be conducted to lower not only hyperglycemic levels but also to treat and possibly prevent sarcopenia in pre-sarcopenic patients. In this review, we evaluate the relationship between diabetes and sarcopenia in elderly patients and discuss how certain anti-diabetic agents may play specific roles in influencing disease outcomes.

AGING AND SARCOPENIA
In 1989, Rosenberg first introduced the term “sarcopenia” in reference to age-related loss of skeletal muscle mass and volume[9]. Currently, sarcopenia is defined as an involuntary loss of skeletal muscle and used as a predictor of physical disability/mortality. Muscle mass accounts for 75% of body-cell mass and 45% of body mass[10]. Once people reach 60 years of age, they lose 1.5%-3% of their muscle mass per year. Therefore, aging is associated with adverse changes in body composition. Sarcopenia, a common disorder in the elderly, contributes to functional decline, disability, frailty, and falls[11]. Because of the aging of the population, sarcopenia has become a worldwide health concern. In China, the prevalence of sarcopenia in people aged 60 years and older is 10.6% (11.3% in men and 9.8% in women)[12]. In Japan, the prevalence of sarcopenia among community-dwelling older adults aged 65-89 years is 21.8% in men and 22.1% in women[13]. Low muscle mass in the legs is associated with muscle weakness, poor lower-extremity performance, and loss of mobility in older adults[14-16]. In the United States, community-dwelling older adults diagnosed with sarcopenia have a 1.29-fold higher risk for all-cause mortality[17]. The pathogenesis of sarcopenia is poorly understood, although altered hypoxic signaling, oxidative stress, and adipokines may be involved in sarcopenic processes. Age-related, chronic, low-grade inflammation has also been recognized as an important causative factor in sarcopenia[18].
AGING AND T2DM

T2DM is a heterogeneous, multifactorial, polygenic, endocrine, metabolic, chronic, and age-related disease characterized by obesity, insulin resistance, and hyperglycemia [19]. Aging is characterized by a progressive loss of physiological integrity, leading to impaired function. This deterioration is the primary risk factor for major human pathologies including cancer, cardiovascular disorders, neurodegenerative diseases, and diabetes[20]. Nevertheless, our understanding of how cellular aging contributes to the pathogenesis of diabetes is incomplete, and currently, there are no therapies targeting cellular aging in diabetes. Insulin resistance has been shown to induce the expression of aging markers, suggesting that β-cell aging could accelerate progression toward diabetes[21-23]. Therefore, reversing cellular aging may be a potential approach in novel anti-T2DM therapies.

T2DM AND SARCOPENIA

Although the mechanisms underlying the association between T2DM and sarcopenia are currently unknown, mitochondrial dysfunction, muscle protein degradation, and autophagy may be associated with loss of skeletal muscle mass and strength in patients with diabetes[24]. Sarcopenia contributes to functional impairment, and elderly diabetic patients are two times more likely to develop sarcopenia than those without diabetes[25]. The Health, Aging, and Body Composition Study showed that annual decline in appendicular muscle mass in patients with diabetes is approximately 0.2 kg/year (1%/year), while decline in appendicular lean mass in non-diabetic persons is 0.15 kg/year (0.7%/year)[26]. A recent prospective study showed that poor glycemic control is associated with sarcopenia and that chronic inflammation combined with mitochondrial dysfunction and oxidative stress play important roles in muscle atrophy[27]. Interactions among these factors may involve several intracellular signaling pathways that affect the balance between protein synthesis and degradation and induction of apoptosis; these two aspects are involved in the primary pathology of significant muscle mass loss[28].

AGING, T2DM, AND SARCOPENIA

Sarcopenia, one of the most serious health-related problems among elderly adults with diabetes, impairs the activities of daily living, increasing the risk of mortality[29]. Recent studies have reported that elderly patients with diabetes are at an increased risk for sarcopenia[24,26]. Additionally, microinflammation and insulin resistance may be central in the sarcopenia pathogenesis[24]. Previous research has shown that older adults with T2DM have an accelerated loss of muscle mass and strength compared with those of adults without diabetes[26]. Diabetes, which is associated with reduced muscle strength and poor muscle quality, involves an accelerated aging process that intensifies age-related sarcopenia[30]. The results from the Korean Sarcopenic Obesity Study showed that the prevalence of sarcopenia in patients with diabetes is considerably higher than in non-diabetic individuals. In patients older than 60 years, individuals with and without diabetes demonstrated a significant difference in the prevalence of sarcopenia; this was observed for both sexes[9] and agreed with findings obtained in another study[31]. In the general population, studies have shown that with aging, men lose more skeletal muscle mass than do women, even though men have a higher starting skeletal muscle mass compared with that of women[32]; however, women with diabetes are at a particularly high risk for the loss of skeletal muscle mass[26]. The relationship among aging, T2DM, and sarcopenia is illustrated in Figure 1.

ANTI-DIABETIC DRUGS AND SARCOPENIA

Evaluating the use of anti-diabetic agents in older T2DM patients with sarcopenia is important in order to determine which anti-diabetic drugs may alleviate sarcopenia or pose a decreased risk for the progression of sarcopenia. Currently available anti-diabetic agents include biguanides (metformin), insulin secretagogues (sulfonylureas and glinides), alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-
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TF2DM: Type 2 diabetes mellitus.

While all of these agents have shown beneficial hypoglycemic effects, we will discuss their potential utility in geriatric patients with sarcopenia (Table 1).

**Biguanides and sarcopenia**

Metformin (1,1-dimethylbiguanide hydrochloride) lowers blood glucose levels by sensitizing the liver to the effects of insulin, thereby suppressing hepatic glucose output. According to updated guidelines, metformin is considered a first-line treatment for T2DM, especially in elderly diabetic patients. In a study conducted in Iran, 51 individuals newly diagnosed with T2DM (21 men and 30 women) were treated using 1000 mg metformin twice daily for 6 mo; 41 participants (80.4%) completed the study. The results obtained in that study indicated that by week 24, the lean-to-fat ratio increased in the participants, with men showing significantly greater changes compared with those of women. The administration of metformin for 3 mo showed favorable effects on body composition, insulin sensitivity, and glucose homeostasis. This finding suggests that a metformin-based therapy may postpone the development of sarcopenia and may be particularly effective in women with T2DM, who are at an increased risk for the loss of skeletal muscle mass[31]. A two-site, randomized, double-blind, placebo-controlled clinical trial investigating the effects of metformin, combined with a progressive resistance-training program, showed that individuals aged 65 and older, treated using 1700 mg metformin per day for 16 wk, showed increased muscle hypertrophy and strength gains, thereby maintaining functional independence[33]. Another study showed that participants with risk factors for T2DM, treated using 850 mg metformin twice a day for 2 mo, showed a decrease in fat weight and increase in lean weight[34]. In the osteoporotic fractures in men study, 151 diabetic men were treated with insulin sensitizers, and 111 diabetic men were treated without insulin sensitizers, with a follow-up of 3.5 ± 0.7 years. Analysis of specific insulin sensitizers revealed that diabetic men treated using metformin, or using metformin coupled with thiazolidinediones, had significantly reduced total and appendicular lean mass loss compared with that of men with untreated diabetes, or that of diabetic men treated without insulin sensitizers[35]. Metformin increases the activity of adenosine monophosphate-activated protein kinase, which inhibits the glucose cotransporter-2 inhibitor (SGLT2i), and insulin.
mechanistic target of rapamycin (mTOR)\textsuperscript{36}, a key factor in muscle growth\textsuperscript{37}. Notably, metformin is currently being evaluated in clinical trials for the improvement of muscle function in patients with Duchenne muscular dystrophy\textsuperscript{38,39}.

Metformin-mediated mechanisms are also being evaluated in animal models. One study has shown that the percentage of centronucleated myofibers in metformin-treated mice is lower than that in control mice at 4 d post-injury. Moreover, at 7 d post-injury, control myofibers show a larger cross-sectional area (500 ha) than that obtained from metformin-conditioned mice. These data suggest that metformin-treated mice were fully regenerated at 7 d post-injury, indicating that metformin may be used for the maintenance of muscle stem cells during repeated regeneration cycles in disease and aging\textsuperscript{40}. However, other studies have suggested that metformin is ineffective in the recovery of muscle mass and strength\textsuperscript{41-44}. One study evaluated aged (23 mo) and young (3 mo) male mice fed a low-fat diet without or with the addition of 0.5% metformin for up to 8 wk. The results of that study showed that in aged mice, long-term treatment with metformin does not alter the decreased relative muscle mass that exhibits hyperactive mTORC1 signaling during the fasted state. However, the same treatment paradigm using metformin reduced fasted muscle mTORC1 signaling in young mouse muscle\textsuperscript{41}. Consistent with the results obtained in this study, another study demonstrated that 0.5% metformin administered for 6 wk shows limited effects on restoring normal metabolic and growth signaling in aged adipose tissue and muscle, respectively\textsuperscript{42}. Other studies have suggested that metformin may negatively impact the mitochondrial function in skeletal muscle\textsuperscript{43,44}. Thus, it is unclear whether metformin exerts positive, negative, or negligible effects on muscle mass and strength.

**Insulin secretagogues (sulfonylureas and glinides) and sarcopenia**

Sulfonylureas are insulin secretagogues that are typically divided into first- and second-generation drugs. Glinides possess a mechanism-of-action that is similar to that of sulfonylureas, but act in a plasma-glucose concentration-dependent manner with a shorter circulating half-life than that of sulfonylureas. Sulfonylureas and glinides, which are ATP-sensitive potassium channel blockers, stimulate insulin release from pancreatic beta cells\textsuperscript{45}. Several studies have shown that drugs in this class may be associated with muscle atrophy because they induce a muscle type-dependent atrophy in mice\textsuperscript{46}. Additionally, from October 6, 2011 through June 29, 2012, the Food and Drug Administration Adverse Event Reporting System received 1697582 reports of adverse events in human patients. Muscle atrophy was reported in 0.27% of reports on glibenclamide/glyburide. A data-mining analysis, performed by calculating the proportional reporting ratio, revealed a significant association between muscle atrophic events and the use of glyburide\textsuperscript{46}. This may occur because hypoglycemia can induce “in vitro” apoptosis and autophagic cell death, and high rates of hypoglycemia characterizing glibenclamide use are a precipitating factor in inducing atrophy “in vivo” in human patients\textsuperscript{47,48}. These findings indicate that insulin secretagogues should not be used as first-line therapy in older T2DM patients with sarcopenia.

**Alpha-glucosidase inhibitors and sarcopenia**

Alpha-glucosidase inhibitors are known to lower postprandial glucose by inhibiting the breakdown of complex carbohydrates in the intestine. However, at present, no studies have been used to examine the relationship between alpha-glucosidase...
inhibitors and sarcopenia.

**Thiazolidinediones and sarcopenia**

Thiazolidinediones (pioglitazone and rosiglitazone) can improve insulin sensitivity by enhancing insulin-mediated glucose disposal via activation of peroxisome proliferator-activated receptor gamma. In 2010, the European Medicines Agency suspended the use of rosiglitazone because of cardiotoxicity; thus, it is not commonly used in China, especially in elderly patients. Recent studies have shown that insulin resistance and mitochondrial dysfunction play an important role in loss of muscle mass, and thus, T2DM and aging-related sarcopenia are characterized by fatty muscle. One study showed that human satellite cells possess adipogenic potential, which may explain the origin of mature adipocytes within myofibers or within the intermuscular space. Treatment with rosiglitazone does not induce fat conversion in human satellite cells but does considerably enhance the adipogenic potential of these cells, which is triggered by the addition of a specific medium permissive of adipogenesis. Thus, thiazolidinediones, which can increase fatty acid disposal and oxidation in skeletal muscle, can reduce increases in intramyocellular triglyceride content and prevent the development of fat cells within muscle fibers. Several studies have shown that peroxisome proliferator-activated receptor gamma agonists exert beneficial effects on muscle performance in older diabetic patients. However, elderly individuals may have numerous common conditions affecting their health, complicated by coronary heart disease and cardiac insufficiency; thus, prescribing these types of drugs to elderly patients should be undertaken with caution.

**DPP4 inhibitors and sarcopenia**

DPP4 inhibitors, which are second-line treatment for T2DM, are widely employed because of their safety and effectiveness in glycemic control. Rizzo et al. reported in a cross-sectional study that elderly diabetic patients treated with DPP4 inhibitors show low levels of inflammatory parameters, high GLP-1 activity during the postprandial state, and high skeletal muscle mass and strength compared with those of patients treated with sulfonylurea. Another study showed that changes in the skeletal muscle index (SMI) of patients treated and not treated using DPP4 inhibitors were 0.04 ± 0.03 and -0.12 ± 0.03, respectively, and that this difference was clinically significant. The findings obtained in this study indicate that DPP4 inhibitors can protect against the loss of muscle mass in Japanese patients with T2DM. Moreover, these 20 patients (11 men and 9 women) with DPP4 inhibitors coupled with sitagliptin for 24 wk significantly reduced total body-fat mass (FM) but not fat-free mass (FFM). Numerous factors may account for this protective effect. The soluble form of DPP4 induces inflammation, and inflammation can be prevented by DPP4 inhibition, which is the presumed cause of sarcopenia. Also, inhibitors of DPP4, a GLP-1 degradation enzyme, are associated with alleviation in the reduction of muscle mass in diabetic and elderly diabetic patients. However, another study showed that neither FM nor SMM changed following a 6-mo treatment with teneligliptin in 21 T2DM patients on hemodialysis. Therefore, the effect of DPP4 inhibition on sarcopenia is likely protective or neutral, indicating that DPP4 inhibitors are safe to use in elderly T2DM patients with sarcopenia.

**GLP-1RA and sarcopenia**

GLP-1 is a 30-amino acid peptide incretin hormone synthesized and secreted by intestinal endocrine L-cells in the small intestine in response to eating. GLP-1 performs numerous physiological actions via its receptor, GLP-1R; these actions include promoting glucose-induced insulin secretion, increasing β-cell survival, inhibiting glucagon production, delaying gastric emptying, and regulating appetite. GLP-1R expression in muscle tissues and cells is controversial. GLP-1 can also induce insulin-independent vasodilation and may stimulate nitric oxide synthase phosphorylation in endothelial cells. GLP-1RA may exert anti-sarcopenic effects. A previous study has shown that the GLP-1RA, Ex-4, attenuates muscle atrophy in dexamethasone-induced mouse model of muscle atrophy and in chronic renal disease-derived model of muscle atrophy. Additionally, a long-acting GLP-1RA, dulaglutide, shows a therapeutic effect in DBA/2J-mdx mice, which are used to model Duchenne muscular dystrophy.

GLP-1RA have revolutionized the management of T2DM in elderly adults with T2DM who tend to develop sarcopenia and frailty as a result of poor energy intake. Increases in GLP-1 expression may represent a compensatory response to FFM loss, intended to enhance vascular/metabolic coupling in muscle via synergistic effect on
nitric oxide and insulin signaling pathways. GLP-1 expression is the strongest predictor of FFM loss, as was shown using the multivariate model[63]. This finding indicates that targeting GLP-1 may potentially be used to reduce FFM loss under hypoxic conditions. This can be achieved using DPP-4 inhibitors or GLP-1RA such as exendin-4; this pharmacological approach is now commonly used in the treatment of diabetes[66]. Inflammation can induce muscle atrophy by regulating the nuclear factor kappa B signaling pathway[67,68], while suppression of inflammation reverses muscle atrophy[68,69]. Indeed, GLP-1RA have shown anti-inflammatory effects in numerous different diseases that involve inflammation[70]. A 24-wk treatment using 3.0 mg liraglutide in overweight and obese elderly patients with T2DM was shown as safe, and none of the patients receiving this treatment became sarcopenic[71]. Unexpectedly, 5 patients showed an improvement in SMI, which was mainly due to an increase in fat-free mass of the legs and arms. Liraglutide reduces body weight and shows particular efficaciousness in reducing fat mass while supporting the stability of trophic SMM. This observation suggests that liraglutide affects muscle by preventing the breakdown of muscle proteins[71]. In another study, however, 6-mo treatment using dulaglutide combined with insulin therapy in T2DM patients on hemodialysis significantly reduced FM and SMM but did achieve significantly improved glycemic control and decreased the insulin dose. Therefore, dulaglutide should be used with caution in these patients because it may promote sarcopenia[62]. In conclusion, it is unclear whether GLP-1RA exert positive or negative effects on muscle mass and strength in patients with T2DM.

**SGLT2i and sarcopenia**

SGLT2i is a new type of anti-diabetic drug for the treatment of individuals with T2DM. Because of its protective effects on the cardiovascular system and kidneys, it is currently widely prescribed in this patient population. In a previous study, the effects of SGLT2i luseogliflozin on muscle atrophy were investigated in Db/Db mice using cross-sectional areas of the soleus and plantaris muscles. After 8 wk of treatment with luseogliflozin, the cross-sectional areas of the soleus muscle obtained from Db/Db mice not treated with SGLT-2i were significantly smaller than those obtained from Db/Db mice that were treated with SGLT-2i. This may have occurred because of suppression of increased foxo1 expression, which is associated with muscle atrophy in the skeletal muscle of Db/Db mice[72]. However, SGLT-2i shows the opposite effects in humans. A study conducted in Japan showed that the SMI of 37 obese T2DM patients treated with SGLT2 (tofogliflozin) was significantly reduced in both men and women. Although skeletal muscle was significantly decreased, SMI, assessed after such reductions, was sufficiently high and far enough from the cutoff values used in the Asian criteria for sarcopenia[73]. Another report from Japan showed that in T2DM patients treated with luseogliflozin for 52 wk, SMI decreased over the course of the treatment; these changes, however, did not reach the level of statistical significance[6]. These two studies included young obese patients, suggesting that it may not be advantageous to administer SGLT2 inhibitors to older T2DM patients at risk for sarcopenia. SGLT2i should also be used with caution in elderly adults with diabetes because these drugs can increase the risk for both dehydration and sarcopenia[74]. Currently, it is unclear whether SGLT2i exert positive or negative effects on sarcopenia. Further investigations are required in order to maintain adequate levels of skeletal muscle mass during treatment with SGLT2-i in T2DM patients.

**Insulin and sarcopenia**

Insulin, a powerful anabolic signal in proteins, may prevent sarcopenia in patients with T2DM. Insulin is known to stimulate muscle-protein synthesis in young adults, but not in older individuals or animals[75]. However, the beneficial effects of insulin on sarcopenia have not been yet confirmed in clinical settings.

Anti-diabetic drugs and resistance exercise also exert beneficial effects in T2DM patients with sarcopenia. One study assessed the effects of modified plant-based Mediterranean diet, circuit resistance training, and empagliflozin, separately and in combination, on the body composition and physical function of older individuals with T2DM. The results of that study showed that these interventions were effective in delaying the progression from diabetes to sarcopenia and/or frailty[76]. Another study showed that a combined exercise-metformin intervention therapy benefitted older individuals by promoting muscle hypertrophy and strength gains, thereby maintaining functional independence[33].
CONCLUSION

Sarcopenia is an increasingly common problem in the elderly, especially in geriatric patients with T2DM and in those receiving treatment with anti-diabetic agents. Therefore, it is important to assess appropriately a patient's condition before administering anti-diabetic drugs. Elderly patients are at a much higher risk than younger patients for the side effects of anti-diabetic drugs. This review will aid clinicians in their selection of appropriate anti-diabetic drugs for the treatment of geriatric T2DM patients with, or at risk for, sarcopenia.

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Retrospective Cohort Study

Utility of cooling patches to prevent hand-foot syndrome caused by pegylated liposomal doxorubicin in breast cancer patients

Yan-Fu Zheng, Xin Fu, Xiao-Xu Wang, Xiao-Jing Sun, Xiao-Dan He

Abstract

BACKGROUND
Pegylated liposomal doxorubicin (PLD) uses the hydrophilic layer of liposomes to reach the sweat on the skin surface or accumulate in the sweat glands, producing toxic free radicals and oxidative damage, resulting in hand-foot syndrome (HFS). Regional cooling can induce vasoconstriction to reduce the release of drugs in the limbs and reduce the accumulation of drugs in sweat glands; thus, decreasing the incidence and severity of HFS.

AIM
To study the efficacy of cooling patches to prevent HFS caused by PLD in the short-term.

METHODS
This is a retrospective cohort study. Female breast cancer patients (n = 101) who were treated with PLD in two breast wards at our department from February 2020 to February 2021 were enrolled in the study and were randomly divided into the cooling group (51 patients) and the control group (50 patients). Patients in the control group only received routine care, while the patients in the cooling group applied cooling patches, based on routine care, to the palm and back of the hands 15 min before chemotherapy infusion for 10 h. All patients took a corresponding dose of dexamethasone orally one day before chemotherapy, on the day of chemotherapy, and one day after chemotherapy. SPSS23.0 version was used to analyze the data in this study. The occurrence and severity of HFS was analyzed by the Mann-Whitney U test, and scores were analyzed by the Student’s t test or Wilcoxon rank-sum test. A P value < 0.05 was regarded as statistically significant.
Results

In this study, neither group of patients developed Grade 3 HFS. In the control group, the incidence of Grade 1 HFS and Grade 2 HFS was 38% and 2%, respectively. However, in the cooling group, only one person developed Grade 1 HFS (2%), and none of the patients developed Grade 2 HFS. These findings showed that cooling patches can effectively reduce the frequency and severity of HFS \((P < 0.0001)\) in the short-term. Before the fourth chemotherapy cycle, although general self-efficacy scale scores in the cooling group were low, they were still significantly higher than those in the control group \((17.22 \pm 5.16 \text{ vs } 19.63 \pm 6.42, P = 0.041)\). Compared with the control group, the mean Hand-Foot Skin Reaction and Quality of Life Questionnaire score in the cooling group was significantly lower \((18.08 \pm 7.01 \text{ vs } 14.20 \pm 7.39, P = 0.008)\).

Conclusion

Cooling patches can effectively reduce the frequency and severity of HFS caused by PLD in the short-term. In addition, it may help delay the decline in patients’ self-efficacy.

Key Words: The cooling patch; Hand-foot syndrome; Pegylated liposomal doxorubicin; Breast cancer; Self-efficacy; Quality of life

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Core Tip: The significance of cooling patches to prevent hand-foot syndrome (HFS) caused by pegylated liposomal doxorubicin (PLD) in breast cancer patients was evaluated. We retrospectively analyzed 101 breast cancer patients treated with PLD. Fifty-one patients applied cooling patches to their hands (the cooling group), and fifty patients did not apply cooling patches (the control group). We observed and recorded the occurrence of HFS. In the short-term, patients in the cooling group had a lower incidence of HFS than those in the control group \((40\% \text{ vs } 2\%)\), and patients’ self-efficacy in the cooling group decreased more slowly than that in the control group, and the difference was statistically significant.

Introduction

Breast cancer has been a major factor that threatens the lives and health of women worldwide[1]. Pegylated liposomal doxorubicin (PLD) is an effective chemotherapeutic drug commonly used in the treatment of breast cancer, ovarian cancer, lymphoma, and other malignant tumors. Hand-Foot Sydrome (HFS) and mucositis are the most common side effects of PLD treatment[2]. PLD is often administered in combination with other drugs, and patients may develop HFS after the treatment for 1-21 d or a few months, depending on the dose used[3].

HFS, also known as palmar–plantar erythrodysesthesia[4], and its symptoms vary due to different drugs used. For example, the characteristic symptoms of HFS caused by doxorubicin are mainly erythema and swelling[5]. Patients experience paresthesia initially, such as numbness, tingling, burning, and erythema. The affected area includes hands, feet, buttocks, groin, sagging breasts, armpits, etc. (especially hands and feet)[6]. As the disease progresses, HFS will lead to reduced quality of life (QOL) [7]. When patients develop HFS, they may not only risk dose adjustment or withdrawal due to physical pain but also limitation of their social activities as a result of psychological disorders[8].
The mechanism of PLD-induced HFS is not yet clear. Doxorubicin can penetrate the capillary wall and interact with metallic Cu (II) ions in the skin tissue to generate reactive oxygen species that can promote the release of chemokines and inflammatory cytokines and induce specific apoptosis of keratinocytes, triggering skin symptoms.[9] PLD may use the hydrophilic coating of liposomes to reach the skin surface via sweat, and the circulation time of PLD in the body is also long, which makes the above situation worse.[10] Local cooling plays a vasoconstricting role in the blood vessels alleviating pain, and acts as an antiperspirant, without adverse reactions.[11] Although cold therapy has prevented HFS to some extent in previous studies, there is still room for improvement.[12-14] The purpose of this study was to evaluate the efficacy of a local cooling patch on the prevention of HFS caused by PLD chemotherapy in breast cancer patients.

MATERIALS AND METHODS

Study design
We aimed to evaluate the short-term preventive effect of local cooling using cooling patches on HFS caused by chemotherapy with PLD. Female breast cancer patients (n = 101) were selected who underwent PLD in two breast wards at our department from February 2020 to February 2021. The patients were randomly divided into the cooling group (51 patients) and the control group (50 patients).

Patients, intervention and assessments
Patients enrolled in the experiment met the following eligibility criteria: (1) Patients who had been diagnosed with breast cancer by pathology or cytology; (2) Patients aged between 20 and 75 years, and who could cooperate with investigators and complete the scale by themselves; (3) At least 4 cycles of PLD were administered; and (4) Patients agreed to sign the informed consent. Patients with the following conditions were excluded: (1) Breast cancer patients suffering from other serious heart, brain, kidney, or serious metabolic diseases; (2) Those with local bleeding, ulcers, and infection tendency; (3) Those with impaired consciousness, unable to communicate normally; (4) Patients who do not understand the meaning of the terms of the scale; and (5) Patients who refused to participate in the study. Two chemotherapy regimens were administered in this study, including chemotherapy plan 1 (PLD + 0.6 mg/m² cyclophosphamide) and chemotherapy plan 2 (PLD + 0.6 mg/m² cyclophosphamide and sequential 80-100 mg/m² docetaxel treatment). Most patients received 30-35 mg/m² PLD. Briefly, chemotherapy plan 1 included 4 cycles, chemotherapy plan 2 also included 4 cycles of sequential docetaxel treatment based on chemotherapy plan 1. We only discussed the effect of the use of cooling patches on HFS during the first 4 cycles of chemotherapy.

In the control group, patients received routine care, including: (1) Wearing loose shoes, socks, and gloves to avoid frequent friction and excessive pressure on the hands and feet, and they avoided heavy physical labor and intense exercise; (2) Sun protection was advised to avoid direct sunlight on the skin; (3) Sitting or lying on a soft surface with legs as high as possible; and (4) For patients with abnormal skin sensations, contact with too cold, hot, sharp, and irritating objects was avoided. In the cooling group, patients applied cooling patches based on routine care. In addition, all patients received the corresponding dose of dexamethasone orally one day before, on the day of chemotherapy, and one day after chemotherapy, according to the doctor’s advice. Supportive therapy was given when necessary.

We explained the purpose and method of the investigation to the patients. The survey method was face-to-face data collection. The patients voluntarily participated in the research and completed the questionnaire according to the actual situation. We only explained unclear points but did not interfere with the patient’s selection. The questionnaire was handed out before each chemotherapy cycle. A higher score of the Hand-Foot Skin Reaction and Quality of Life Questionnaire (HF-QOL) indicates poorer QOL or worsening symptoms.[15] Self-efficacy plays a positive role in the psychological resilience of breast cancer patients after surgery.[16], which positively correlated with QOL.[17] To understand QOL and self-efficacy of the patients, we also conducted scale assessments, including HF-QOL and the general self-efficacy scale (GSES).

The main components of the cooling patch (50 mm × 110 mm) were pure water (77%), hydrophilic polymer gel, and mint extract (Japan DIA Pharmaceutical Co., Ltd). The cooling patch absorbs the heat from the skin through the polymer hydrogel layer
and uses vaporization to dissipate heat so that the local skin is continuously cooled. Cooling patches were applied to the palm and back (avoiding the needle hole for intravenous infusion) of the hands 15 min before infusion of chemotherapy, and the cooling effect was maintained for 10 h. Routine care was applied to the feet without cooling treatment. Each patient used four cooling patches per chemotherapy cycle. If skin ulcers or symptoms were too severe to apply the cooling patches during treatment, local cold therapy was terminated.

When symptoms first appeared on the hands, we evaluated the symptoms and classified HFS before each chemotherapy cycle (starting from the second chemotherapy cycle). Patients with corresponding symptoms in one or both hands were classified as HFS. Evaluation of the occurrence of HFS continued until 2 or 3 cycles after the 4th cycle due to the medicinal properties of PLD.

Statistical analysis
SPSS version 23.0 was used for statistical analysis of the data in this study. The occurrence and severity of HFS were analyzed by the Mann-Whitney U test, and the Student’s t test was used to analyze the scores of the scales. A P value < 0.05 was regarded as statistically significant.

RESULTS

Patient characteristics
One hundred and one female patients who met the criteria were enrolled, and all of them were treated with intravenous PLD in our department. None of these patients had received previous chemotherapy, and all followed the research protocol. Moreover, there were no significant differences between the two groups of patients in terms of some baseline. However, there were significant differences between the two groups in terms of character traits, such as facing major events in life, and attitudes to suffering from breast cancer (Table 1). However, multivariate analysis of variance indicated that these three items were not independent influencing factors on the occurrence of HFS, and their main effects and interaction effects did not affect the HF-QOL and GSES scores (P > 0.05) (Table 2).

Treatment efficacy and toxicity
The incidence of HFS was 40% in the control group and 2% in the cooling group, with a statistically significant difference (P < 0.0001) (Table 3). In the control group, the incidence of Grade 1 and Grade 2 HFS was 38% and 2%, respectively. However, up to the end of the 5th course of treatment, only one patient in the cooling group developed Grade 1 HFS. None of the patients developed Grade 3 HFS in either group. Most patients developed HFS after the 3rd or 4th course of treatment, and two patients developed HFS after the 5th course of treatment.

GSES and HF-QOL scores
The GSES and HF-QOL scores are shown in Figure 1A and B, respectively. We also performed intra-group comparisons (Table 4). In the third assessment in the control group, the GSES score was significantly different to the baseline score (the first evaluation). Several subsequent scores were also significantly different from the baseline. In the cooling group, the GSES score was significantly different from the baseline score in the second evaluation, and the difference persisted until the fourth evaluation. Compared with the baseline scores, the GSES scores showed a difference in the fourth evaluation in both the control group (19.48 ± 5.88 vs 17.22 ± 5.16, P = 0.012) and the cooling group (21.61 ± 6.13 vs 19.63 ± 6.42, P = 0.008), and the mean value of both groups was low, indicating that most patients had a lower sense of self-efficacy (the total score was 40 points, and below 24 points was regarded as low self-efficacy). A comparison between the two groups was then performed (Table 5). No significant difference in GSES scores between the two groups in the first assessment (19.48 ± 5.88 vs 21.61 ± 6.13, P = 0.078) was observed. And 78% of patients had low self-efficacy in the control group, and 64.7% of patients had low self-efficacy in the cooling group. In the third evaluation, there were no significant differences in GSES scores between the two groups. In the fourth assessment, although mean GSES scores were low in the cooling group, they were still significantly higher than those in the control group (17.22 ± 5.16 vs 19.63 ± 6.42, P = 0.041). Low self-efficacy was observed in 94% of patients in the control group, and in 78.4% of patients in the cooling group.
Table 1 Clinical characteristics of the study population at baseline

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Cooling group</th>
<th>F</th>
<th>Z</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.18 ± 9.27 yr</td>
<td>51.24 ± 10.16 yr</td>
<td>0.863</td>
<td>0.977</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>64.20 ± 10.29 kg</td>
<td>65.37 ± 9.74 kg</td>
<td>0.404</td>
<td>0.558</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>24.50 ± 3.60 kg/m²</td>
<td>24.98 ± 3.66 kg/m²</td>
<td>0.042</td>
<td>0.503</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>162 (158-165) cm</td>
<td>162 (160-165) cm</td>
<td>-0.044</td>
<td>0.965</td>
<td></td>
</tr>
<tr>
<td>Body surface area</td>
<td>1.6975 (1.6005-1.799) m²</td>
<td>1.723 (1.646-1.802) m²</td>
<td>-0.802</td>
<td>0.423</td>
<td></td>
</tr>
<tr>
<td>PLD dose</td>
<td>60 (54.25-60) mg</td>
<td>60 (60-60) mg</td>
<td>-1.53</td>
<td>0.126</td>
<td></td>
</tr>
<tr>
<td>Total PLD dose</td>
<td>240 (220-240) mg</td>
<td>240 (240-240) mg</td>
<td>-1.04</td>
<td>0.299</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy cycle</td>
<td>4 cycles, 21 d/cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytes</td>
<td>5.66 (4.48-7.0875)</td>
<td>6.02 (4.92-7.47)</td>
<td>-0.971</td>
<td>0.331</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>249.5 (225.5-301.25)</td>
<td>233 (203-270)</td>
<td>-1.96</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>47.59 (43.375-49.025)</td>
<td>46.5 (44.8-48.424)</td>
<td>-0.194</td>
<td>0.846</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>21 (13.5-33.525)</td>
<td>17 (12.47-24)</td>
<td>-1.502</td>
<td>0.133</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>21.9 (17-27.5)</td>
<td>20 (17-22.03)</td>
<td>-1.251</td>
<td>0.211</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>12.715 (7.9225-14.9)</td>
<td>10.58 (8.25-13.78)</td>
<td>-1.274</td>
<td>0.203</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>45.6 (41.465-48.8)</td>
<td>45.4 (42.8-49.5)</td>
<td>-0.234</td>
<td>0.815</td>
<td></td>
</tr>
<tr>
<td>Urea Nitrogen</td>
<td>4.69 (4.3-5.1218)</td>
<td>5.1 (4.12-5.9)</td>
<td>-1.485</td>
<td>0.138</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>-1.400</td>
<td>0.161</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td>-0.323</td>
<td>0.747</td>
<td></td>
</tr>
<tr>
<td>Profession</td>
<td></td>
<td></td>
<td>-0.999</td>
<td>0.318</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>-0.467</td>
<td>0.640</td>
<td></td>
</tr>
<tr>
<td>Household income level (in recent year)</td>
<td></td>
<td></td>
<td>-0.050</td>
<td>0.960</td>
<td></td>
</tr>
<tr>
<td>Resident population (in recent year)</td>
<td></td>
<td></td>
<td>-1.272</td>
<td>0.203</td>
<td></td>
</tr>
<tr>
<td>Medical procedures</td>
<td></td>
<td></td>
<td>-0.475</td>
<td>0.635</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has hypertension</td>
<td></td>
<td></td>
<td>-0.499</td>
<td>0.618</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has diabetes</td>
<td></td>
<td></td>
<td>-0.988</td>
<td>0.323</td>
<td></td>
</tr>
<tr>
<td>Whether the patient ever had heart disease</td>
<td></td>
<td></td>
<td>-0.020</td>
<td>0.984</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has other tumors</td>
<td></td>
<td></td>
<td>-0.566</td>
<td>0.571</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has a long-term medication history</td>
<td></td>
<td></td>
<td>-0.823</td>
<td>0.410</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has a smoking history</td>
<td></td>
<td></td>
<td>-1.010</td>
<td>0.313</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has a drinking history</td>
<td></td>
<td></td>
<td>0.000</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has the habit of taking health products</td>
<td></td>
<td></td>
<td>-1.036</td>
<td>0.300</td>
<td></td>
</tr>
<tr>
<td>Attitude</td>
<td></td>
<td></td>
<td>-1.203</td>
<td>0.196</td>
<td></td>
</tr>
<tr>
<td>Character traits</td>
<td></td>
<td></td>
<td>-2.479</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Facing major events in life</td>
<td></td>
<td></td>
<td>-3.258</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Attitude to this matter (suffering from breast cancer)</td>
<td></td>
<td></td>
<td>-2.654</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has undergone surgery</td>
<td></td>
<td></td>
<td>-1.364</td>
<td>0.172</td>
<td></td>
</tr>
<tr>
<td>Surgical approach</td>
<td></td>
<td></td>
<td>-0.543</td>
<td>0.587</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy administration</td>
<td></td>
<td></td>
<td>-1.344</td>
<td>0.179</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td></td>
<td></td>
<td>-1.143</td>
<td>0.253</td>
<td></td>
</tr>
</tbody>
</table>

PLD: Pegylated liposomal doxorubicin; BMI: Body mass index.
Zheng YF et al. Cooling patch to prevent HFS caused by PLD

Table 2 Intersubjective effect test

<table>
<thead>
<tr>
<th></th>
<th>HF-QOL 2nd</th>
<th>HF-QOL 3rd</th>
<th>HF-QOL 4th</th>
<th>GSES 2nd</th>
<th>GSES 3rd</th>
<th>GSES 4th</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>0.621</td>
<td>0.644</td>
<td>0.996</td>
<td>0.781</td>
<td>0.614</td>
<td>0.950</td>
</tr>
<tr>
<td>P value</td>
<td>0.102</td>
<td>0.677</td>
<td>0.965</td>
<td>0.997</td>
<td>0.704</td>
<td>0.734</td>
</tr>
<tr>
<td>P value</td>
<td>0.716</td>
<td>0.714</td>
<td>0.900</td>
<td>0.916</td>
<td>0.833</td>
<td>0.701</td>
</tr>
<tr>
<td>P value</td>
<td>0.443</td>
<td>0.670</td>
<td>0.532</td>
<td>0.850</td>
<td>0.832</td>
<td>0.960</td>
</tr>
</tbody>
</table>

1 The significance level of whether "Character traits" affect the scores.
2 The significance level of whether "Facing major events in life" affect the scores.
3 The significance level of whether "Attitude to this matter (suffering from breast cancer)" affect the scores.
4 The significance level of whether the above three affect the scores. HF-QOL: Hand-Foot Skin Reaction and Quality of Life Questionnaire; GSES: General self-efficacy scale.

Table 3 The incidence of hand-foot syndrome, n (%)

<table>
<thead>
<tr>
<th></th>
<th>HF occurrence</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No HFS</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Z</td>
</tr>
<tr>
<td>Control group</td>
<td>30 (60.0)</td>
<td>19 (38.0)</td>
<td>1 (2.0)</td>
<td>4.686</td>
<td>0.000005</td>
</tr>
<tr>
<td>Cooling group</td>
<td>50 (98.0)</td>
<td>1 (2.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HFS: Hand-foot syndrome.

Table 4 Intra-group comparisons of the general self-efficacy scale score

<table>
<thead>
<tr>
<th>GSES score</th>
<th>2nd and 1st</th>
<th>3rd and 1st</th>
<th>4th and 1st</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>-1.982</td>
<td>-2.373</td>
<td>-2.604</td>
</tr>
<tr>
<td>P value</td>
<td>0.053</td>
<td>0.022</td>
<td>0.012</td>
</tr>
<tr>
<td>Cooling group</td>
<td>-2.047</td>
<td>-2.385</td>
<td>-2.773</td>
</tr>
<tr>
<td>P value</td>
<td>0.046</td>
<td>0.021</td>
<td>0.008</td>
</tr>
</tbody>
</table>

GSES: General self-efficacy scale.

Table 5 Comparison of the general self-efficacy scale score between the two groups

<table>
<thead>
<tr>
<th>GSES score</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>19.48 ± 5.88</td>
<td>18.40 ± 5.55</td>
<td>17.52 ± 4.82</td>
<td>17.22 ± 5.16</td>
</tr>
<tr>
<td>Cooling group</td>
<td>21.61 ± 6.13</td>
<td>20.67 ± 6.08</td>
<td>19.94 ± 5.81</td>
<td>19.63 ± 6.42</td>
</tr>
<tr>
<td>F</td>
<td>0.021</td>
<td>0.479</td>
<td>0.552</td>
<td>1.647</td>
</tr>
<tr>
<td>P value</td>
<td>0.078</td>
<td>0.053</td>
<td>0.025</td>
<td>0.041</td>
</tr>
</tbody>
</table>

GSES: General self-efficacy scale.

At baseline, there were no significant differences in HF-QOL scores between the two groups (39.14 ± 10.29 vs 39.06 ± 8.56, P = 0.966) (Table 6). From the second evaluation, the HF-QOL scores in the two groups were significantly different, and this difference persisted until the fourth evaluation. In the fourth evaluation, the HF-QOL scores showed very significant differences (18.08 ± 7.01 vs 14.20 ± 7.39, P = 0.008) between the two groups, and compared with the control group, the median HF-QOL score in the cooling group was significantly lower. In the intra-group comparisons (Table 7), in both groups in the second evaluation, the HF-QOL score was significantly different
Table 6 Comparison of the Hand-Foot Skin Reaction and Quality of Life Questionnaire score between the two groups

<table>
<thead>
<tr>
<th>HF-QOL score</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>39.14 ± 10.29</td>
<td>21.80 ± 10.10</td>
<td>18.02 ± 5.96</td>
<td>18.08 ± 7.01</td>
</tr>
<tr>
<td>Cooling group</td>
<td>39.06 ± 8.56</td>
<td>16.65 ± 10.46</td>
<td>14.22 ± 6.01</td>
<td>14.20 ± 7.39</td>
</tr>
<tr>
<td>F</td>
<td>4.559</td>
<td>0.061</td>
<td>0.192</td>
<td>0.025</td>
</tr>
<tr>
<td>P value</td>
<td>0.966</td>
<td>0.013</td>
<td>0.002</td>
<td>0.008</td>
</tr>
</tbody>
</table>

HF-QOL: Hand-Foot Skin Reaction and Quality of Life Questionnaire.

Table 7 Intra-group comparisons of the Hand-Foot Skin Reaction and Quality of Life Questionnaire score

<table>
<thead>
<tr>
<th>HF-QOL score</th>
<th>2nd and 1st</th>
<th>3rd and 1st</th>
<th>4th and 1st</th>
</tr>
</thead>
<tbody>
<tr>
<td>The control group</td>
<td>t</td>
<td>-10.224</td>
<td>20.226</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>The cooling group</td>
<td>t</td>
<td>-14.500</td>
<td>4.781</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
</tbody>
</table>

HF-QOL: Hand-Foot Skin Reaction and Quality of Life Questionnaire.

Figure 1 Box plots of raw data for Hand-Foot Skin Reaction and Quality of Life Questionnaire and general self-efficacy scale score before the 1st, 2nd, 3rd and 4th cycle of chemotherapy. A: Hand-Foot Skin Reaction and Quality of Life Questionnaire scores; B: General self-efficacy scale scores. Data are outliers (dots), adjacent values (whiskers), median (central line), and interquartile range (box margins). HF-QOL: Hand-Foot Skin Reaction and Quality of Life Questionnaire; GSES: General self-efficacy scale.

Possible risk factors

In order to identify the factors that may have caused HFS, univariate analysis of the factors that may affect the occurrence of HFS was performed (Table 4). The results showed that occupation, albumin level, and whether the patient had a long-term medication history were the factors that may have caused HFS. However, after binary logistic regression analysis, none of these factors were found to be associated with the occurrence of HFS. Moreover, character traits, such as facing major events in life, attitudes toward cancer, body mass index (BMI), age, PLD dose, and body surface area were not significantly associated with the incidence of HFS (Table 8).
Table 8 Factors that may be related to the occurrence of hand-foot syndrome

<table>
<thead>
<tr>
<th>Possible risk factors</th>
<th>F</th>
<th>Z</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3.354</td>
<td>0.387</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.088</td>
<td>0.581</td>
<td></td>
</tr>
<tr>
<td>Body surface area</td>
<td>-0.649</td>
<td>0.517</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>-0.2</td>
<td>0.842</td>
<td></td>
</tr>
<tr>
<td>Profession</td>
<td>-3.023</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>-0.597</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has hypertension</td>
<td>-0.887</td>
<td>0.375</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has diabetes</td>
<td>-1.008</td>
<td>0.313</td>
<td></td>
</tr>
<tr>
<td>Whether the patient ever had heart disease</td>
<td>-1.04</td>
<td>0.298</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has other tumors</td>
<td>-0.896</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has a long-term medication history</td>
<td>-2.083</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has a smoking history</td>
<td>-0.512</td>
<td>0.608</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has a drinking history</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has the habit of taking health products</td>
<td>-1.04</td>
<td>0.298</td>
<td></td>
</tr>
<tr>
<td>Attitude</td>
<td>-0.363</td>
<td>0.717</td>
<td></td>
</tr>
<tr>
<td>Character traits</td>
<td>-1.459</td>
<td>0.145</td>
<td></td>
</tr>
<tr>
<td>Facing major events in life</td>
<td>-1.229</td>
<td>0.219</td>
<td></td>
</tr>
<tr>
<td>Attitude to this matter (suffering from breast cancer)</td>
<td>-1.26</td>
<td>0.208</td>
<td></td>
</tr>
<tr>
<td>Whether the patient has undergone surgery</td>
<td>-0.127</td>
<td>0.899</td>
<td></td>
</tr>
<tr>
<td>Surgical approach</td>
<td>-1.137</td>
<td>0.255</td>
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</tr>
<tr>
<td>Chemotherapy administration</td>
<td>-0.182</td>
<td>0.856</td>
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</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>-1.398</td>
<td>0.162</td>
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</tr>
<tr>
<td>Total PDL dose</td>
<td>-0.289</td>
<td>0.773</td>
<td></td>
</tr>
<tr>
<td>Leukocytes</td>
<td>-0.816</td>
<td>0.415</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>-1.712</td>
<td>0.087</td>
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</tr>
<tr>
<td>Albumin</td>
<td>-2.428</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>-1.177</td>
<td>0.239</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>-1.517</td>
<td>0.129</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>-0.833</td>
<td>0.405</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>-0.448</td>
<td>0.654</td>
<td></td>
</tr>
<tr>
<td>Urea Nitrogen</td>
<td>-0.088</td>
<td>0.93</td>
<td></td>
</tr>
</tbody>
</table>

PLD: Pegylated liposomal doxorubicin; BMI: Body mass index.

DISCUSSION

PLD is the most common cause of HFS. Approximately 83.7% of female cancer patients who received PLD developed HFS and the incidence of Grade 3 HFS was 52.9%.[18]. The management of HFS involves preventive measures, health education, symptom management, and dose adjustment[19]. Here we only discuss preventive measures for HFS caused by chemotherapy.

Plasma filtration can safely and effectively remove circulating PLD and decrease the incidence of HFS and mucositis[20]. However, the success rate depends on the technical equipment and experience of the operator in the therapeutic plasma filtration [2]. Topical antiperspirants (containing aluminum chlorohydrate) seemed to reduce the incidence of HFS, but the effect of preventing Grade 2 or Grade 3 HFS was insigni-
Table 9 Comparison of different cooling methods and the incidence of hand-foot syndrome

<table>
<thead>
<tr>
<th>n</th>
<th>Tumor</th>
<th>Chemotherapy regimen</th>
<th>Dosage of PLD</th>
<th>Cold therapy equipment</th>
<th>Cooling parts of the body</th>
<th>Cooling time</th>
<th>Incidence of HFS</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Ovarian cancer</td>
<td>Monotherapy</td>
<td>30-50 mg/m²</td>
<td>Ice packs</td>
<td>Around the wrists and ankles</td>
<td>After chemotherapy for 24 h</td>
<td>1/17 (5.9%)</td>
<td>Molpus et al[12]</td>
</tr>
<tr>
<td>53</td>
<td>Ovarian cancer</td>
<td>Combination or monotherapy</td>
<td>30-50 mg/m²</td>
<td>Ice packs</td>
<td>Around the wrists and ankles</td>
<td>During chemotherapy infusion</td>
<td>2/28 (7.1%)</td>
<td>Mangili et al[13]</td>
</tr>
<tr>
<td>55</td>
<td>Ovarian cancer</td>
<td>Combination</td>
<td>30 mg/m²</td>
<td>FGS</td>
<td>Whole hands and feet</td>
<td>From 15 min before infusion to 15 min after infusion</td>
<td>≥ Grade 2 (31.70%)</td>
<td>Bun et al[14]</td>
</tr>
<tr>
<td>41</td>
<td>Monotherapy</td>
<td></td>
<td>50 mg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>Breast cancer</td>
<td>Combination</td>
<td>30-35 mg/m²</td>
<td>The cooling patches</td>
<td>Palm and back of hands</td>
<td>Start 15 min before infusion and lasted for 10 h</td>
<td>1/51 (2.0%)</td>
<td>Our study</td>
</tr>
</tbody>
</table>

PLD: Pegylated liposomal doxorubicin.

significant (58%) [21]. Jung et al [22] used high concentrations of topical antioxidants to neutralize free radicals in the skin and found that they were more effective in preventing Grade 3 HFS. Pyridoxine has been used to prevent HFS caused by chemotherapy, but the evidence for its related efficacy is still controversial [23].

It has been recognized that as a non-drug therapy, local cooling is an effective means of preventing HFS caused by chemotherapy [24]. However, local cooling has disadvantages such as high shedding rate and cumbersome cold therapy process (Table 9). The cooling patch can make up for the insufficiency of ice packs, ice gloves, and ice socks. For example, it can be cut into suitable shapes according to affected areas (some uneven parts, such as underarms and breasts [6]) and can reduce the risk of skin friction. The cooling patch can result in a 0.5-1 degree temperature decrease within 10 min and has the advantages of low price, safety, comfort, good adhesion, simple operation, and the cooling effect can last for 10h. It also has a moisturizing effect. Although some of the water in the cooling patch will evaporate, the higher water content can keep the skin moist and prevent sweating, reducing the possibility of PLD accumulating in sweat glands [10]. We studied the preventive effect of cooling patches on the hands that are mostly affected by HFS. In our study, the incidence of HFS was much lower than in the previous studies on local cold therapy, and the dropout value was 0. Moreover, compared with the control group, the HF-QOL score in the cooling group was significantly lower. Our study also showed that the use of cooling patches may help delay the decline in patients’ self-efficacy, which may be due to psychological factors.

Liang et al [25] found that BMI is an independent risk factor for moderate to severe HFS, and the two are directly proportional. Patients with high BMI seemed more likely to develop HFS in our study (Table 10), although this was statistically non-significant. Yamada et al [26] thought that the severity of HFS and mucositis caused by PLD may be a predictor of its efficacy. Jandu et al [27] believed that HFS was a biological marker of improved survival rate in cancer patients. Our data may provide another possible explanation for HFS being associated with a good prognosis. It was shown that HFS was more likely to occur in women who were healthier (fewer diseases) and who were optimistic in personality (Table 10), although this was statistically non-significant.

Our study also had limitations. The observation period was short, only the hands received the cooling treatment, and it is impossible to directly evaluate the difference in the cooling effect between this method and other methods. In the future, more randomized studies should be conducted to determine the optimal duration, optimal temperature, and effectiveness of local cooling.

CONCLUSION

The cooling patch can effectively reduce the frequency and severity of HFS caused by PLD in the short term. In addition, it may help to improve patients' quality of life and delay the decline of their self-efficacy.
### Table 10: Characteristics of patients with hand-foot syndrome (n=21)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>≤ 17</td>
<td>0</td>
</tr>
<tr>
<td>18-45</td>
<td>38.1</td>
</tr>
<tr>
<td>46-69</td>
<td>61.9</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt; 18.5)</td>
<td>0</td>
</tr>
<tr>
<td>Normal (18.5-24.9)</td>
<td>42.9</td>
</tr>
<tr>
<td>Overweight (25.0-29.9)</td>
<td>52.4</td>
</tr>
<tr>
<td>Obese class I (30.0-34.9)</td>
<td>4.8</td>
</tr>
<tr>
<td>Obese class II (35.0-39.9)</td>
<td>0</td>
</tr>
<tr>
<td>Obese class III (≥40.0)</td>
<td>0</td>
</tr>
<tr>
<td>Whether the patient ever had hypertension</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.5</td>
</tr>
<tr>
<td>No</td>
<td>90.5</td>
</tr>
<tr>
<td>Whether the patient has diabetes</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.8</td>
</tr>
<tr>
<td>No</td>
<td>95.2</td>
</tr>
<tr>
<td>Whether the patient ever had heart disease</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>100</td>
</tr>
<tr>
<td>Whether the patient has other tumors</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>100</td>
</tr>
<tr>
<td>Whether the patient has a long-term medication history</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.5</td>
</tr>
<tr>
<td>No</td>
<td>90.5</td>
</tr>
<tr>
<td>Whether the patient has a smoking history</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>100</td>
</tr>
<tr>
<td>Whether the patient has a drinking history</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>100</td>
</tr>
<tr>
<td>Whether the patient has the habit of taking health products</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>100</td>
</tr>
<tr>
<td>Attitude</td>
<td></td>
</tr>
<tr>
<td>Impatient</td>
<td>61.9</td>
</tr>
<tr>
<td>Slowcoach</td>
<td>4.8</td>
</tr>
<tr>
<td>Somewhere in between</td>
<td>33.3</td>
</tr>
<tr>
<td>Character traits</td>
<td></td>
</tr>
</tbody>
</table>
Zheng YF et al. Cooling patch to prevent HFS caused by PLD

<table>
<thead>
<tr>
<th>Attitude to this matter (suffering from breast cancer)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extroverted</td>
<td>38.1</td>
</tr>
<tr>
<td>Introverted</td>
<td>28.6</td>
</tr>
<tr>
<td>Somewhere in between</td>
<td>33.3</td>
</tr>
<tr>
<td>Facing major events in life</td>
<td></td>
</tr>
<tr>
<td>Accept frankly</td>
<td>90.5</td>
</tr>
<tr>
<td>Accept after enlightenment</td>
<td>9.5</td>
</tr>
<tr>
<td>Difficult to accept after enlightenment and rethinking</td>
<td>0</td>
</tr>
</tbody>
</table>

BME: Body mass index.

ARTICLE HIGHLIGHTS

Research background
Hand-foot syndrome (HFS) is one of the most common skin toxicities of pegylated liposomal doxorubicin (PLD). When patients develop HFS, they may be at risk for dose adjustment (or withdrawal) and limitation of activities of daily living due to physical pain, even lead to limited social activities due to psychological disorders. Although cold therapy as a non-drug therapy to prevent and treat HFS has been effective in previous studies, there is room for improvement. If local cold therapy has the advantages of good effect, easy operation, and low price, it will be a huge benefit for patients with HFS.

Research motivation
Current methods of preventing chemotherapy-induced HFS are mostly pharmacological prevention, and local cooling as a non-drug therapy is effective in previous studies, but has disadvantages such as cumbersome implementation steps, low patient tolerance, and high shedding rate.

Research objectives
The main goal is to study the efficacy of the cooling patch in preventing HFS caused by PLD in the short term (for the prevention of hand symptoms). Improve the current situation that patients face the risks of restricted activities of daily living due to physical pain caused by HFS and limited social activities due to psychological disorders. We apply a cooling patch originally used to reduce fever in infants and children to prevent HFS caused by PLD in breast cancer patients to make up for some of the shortcomings of ice packs, ice gloves, and ice socks.

Research methods
This study was a retrospective cohort study in which using purposive sampling to select the research objects. The research objects answered the questions in the scale regularly, and we distributed and collected the scale.

Research results
The cooling patch can effectively reduce the frequency and severity of HFS in the short-term. Before the fourth chemotherapy cycle, although general self-efficacy scale scores in the cooling group were low, they were still significantly higher than those in the control group. Compared with the control group, the mean Hand-Foot Skin Reaction and Quality of Life Questionnaire score in the cooling group was significantly lower. We have used the cooling patch to prevent PLD-induced HFS with good results with higher comfort of patients and a shedding rate of 0.
Zheng YF et al. Cooling patch to prevent HFS caused by PLD

Research conclusions
The cooling patch can effectively reduce the frequency and severity of HFS caused by PLD in the short term. In addition, it may help to improve patients' quality of life and delay the decline of their self-efficacy. The cooling patch is often applied to treat fever in infants and young children. We use it to prevent HFS caused by PLD chemotherapy in breast cancer patients.

Research perspectives
In the future, we will study whether the cooling patch also has a good effect on the feet, underarms, and other parts that may be affected and conduct more rigorous randomized controlled studies to clarify the optimal duration, temperature, and effectiveness of local cooling.

REFERENCES


Zheng YF et al. Cooling patch to prevent HFS caused by PLD


Retrospective Study

Clinicopathological features of small T1 colorectal cancers

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Abstract

BACKGROUND

Although small colorectal neoplasms (< 10 mm) are often easily resected endoscopically and are considered to have less malignant potential compared with large neoplasms (≥ 10 mm), some are invasive to the submucosa.

AIM

To clarify the clinicopathological features of small T1 colorectal cancers.

METHODS

Of 32025 colorectal lesions between April 2001 and March 2018, a total of 1152 T1 colorectal cancers resected endoscopically or surgically were included in this study and were divided into two groups by tumor size: a small group (< 10 mm) and a large group (≥ 10 mm). We compared clinicopathological factors including lymph node metastasis (LNM) between the two groups.

RESULTS

The incidence of small T1 cancers was 10.1% (116/1152). The percentage of initial...
INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cancer cause of death worldwide[1]. Lymph node metastasis (LNM) is present in approximately 10% of T1 CRCs that require surgical resection with lymph node dissection[2,3]. Therefore, risk stratification for LNM in T1 CRC is necessary. According to the current guidelines, the risk factors for LNM are lymphovascular invasion, histological differentiation, depth of submucosal invasion, and tumor budding. Surgical treatment is recommended if any of these factors are identified in the pathological diagnosis of endoscopically resected specimens[4-8], whereas follow-up by endoscopic resection alone would be acceptable when there are no risk factors. However, tumor size is not mentioned in these guidelines. Although tumor size was reported to be a risk factor for prognosis in advanced cancers, few reports have investigated the correlation between tumor size and clinicopathological features including the presence of LNM in T1 CRC[9,10]. Recently, the “resect and discard” strategy has emerged. In this approach, polyps smaller than 10 mm that are preoperatively diagnosed by magnifying narrow-band imaging do not need to be sent for pathological examination because of its high diagnostic performance despite the potential risk of small invasive cancer, which should be assessed to determine the additional surgical resection should be determined according to pathological findings, regardless of tumor size.
MATERIALS AND METHODS

Patients
A total of 32025 colorectal lesions (< 10 mm: 21620 lesions, ≥ 10 mm: 10405 lesions), excluding advanced cancers, were endoscopically or surgically resected at Showa University Northern Yokohama Hospital (Yokohama, Japan) between April 2001 and March 2018. Of these, 1272 were T1 CRCs. We excluded 45 patients who had synchronous advanced CRC, three patients with Lynch syndrome, six patients with inflammatory bowel disease, and 66 patients whose specimens were impossible to evaluate pathologically in detail because of damage or loss. In total, 1152 cases were included (Figure 1). Patient characteristics analyzed included age, sex, tumor location, tumor size, polypoid/non-polypoid growth, adenoma component, tumor morphology, initial treatment, depth of submucosal invasion, histological grade, vascular invasion, lymphatic invasion, tumor budding, and LNM. Surgical specimens were used as the gold standard for the presence of LNM. We classified tumor morphology into three types according to the Paris classification and Kudo’s classification: flat type (IIa, laterally spreading tumor), protruded type (Is, Ip, and Isp), and depressed type (Iic, Ila + Iic, Ilc + Ila, Is + Iic, and Ip + Iic)[12].

Histological examination
All resected specimens were retrieved and immediately fixed in 10% buffered formalin and were observed with a focus on the pit pattern using a stereomicroscope. They were then cut at the point where the deepest invasion area could be exposed on the cut end surface. The other histological specimens were cut into parallel 2- to 3-mm-thick sections and stained with hematoxylin and eosin (H&E). Tumor size was measured after formalin fixation. All specimens were diagnosed on the basis of the 2019 World Health Organization Classification of Tumors[13] and the current Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines[6]. Histological grade was classified in view of the World Health Organization criteria as follows: well-differentiated adenocarcinoma, moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma (Por), and mucinous carcinoma (Muc). In this study, a Por/Muc component was considered present if any part of the lesion contained any of these features. The depth of submucosal invasion was classified according to the JSCCR classification as < 1000 μm (T1a) and ≥ 1000 μm (T1b)[6]. Vascular invasion was diagnosed by double staining with H&E and Victoria blue (Muto Pure Chemicals Co., Ltd., Tokyo, Japan) and lymphatic invasion was diagnosed by H&E staining and immunostaining with D2-40 antibody (Dako North America Inc., Carpinteria, CA, United States). Tumor budding is defined as a cancer cell nest consisting of one or fewer than five cells that infiltrate the interstitium at the invasive margin of the cancer. On selecting the region where tumor budding is the greatest, the front of the tumor growth is observed at 200 x magnification to count the number of tumor buds: BD1, 0-4; BD2, 5-9; and BD3, ≥ 10[14].

Statistical analysis
Nominal and ordinal variables are expressed as frequencies and percentages. Continuous variables are reported as mean ± SD. Continuous variables were compared using Student t-tests, while dichotomous variables were compared using chi-squared or Fisher’s exact tests, as appropriate. All statistical analyses were performed using R for Windows 4.0.3. All P values were two sided, and P < 0.05 was considered statistically significant.

Ethical considerations
This study was approved by the institutional review board of Showa University Northern Yokohama Hospital (approval No. 19H057) and was registered with the University Hospital Medical Network Clinical Trials Registry (UMIN000043922). Written informed consent was obtained from all patients before treatment.

RESULTS

Patients’ characteristics
Patients’ characteristics are shown in Table 1. Of the included patients, 116 cases (10.1%) were included in the small group (tumors of less than 10 mm) and 1036 cases (89.9%) were included in the large group (tumors of 10 mm or larger). The mean age
was 66.4 years. Seven hundred twenty-nine patients (63.2%) were male, and 788 patients (68.4%) had left-sided CRC. The number of lesions that were initially selected for endoscopic treatment was 710 (61.6%). Seven hundred ninety-eight (69.3%) T1 CRCs were surgically resected. Vascular invasion was observed in 322 (28.0%) cases, and lymphatic invasion was observed in 342 (29.7%) cases. Among the operated cases, 11.0% (88/798) had LNM.

**Small vs large in total cohort**
Comparison of clinicopathological characteristics between < 10 mm and ≥ 10 mm tumors in total cohort T1 CRCs are shown in Table 2. Compared with T1 CRCs of ≥ 10 mm, T1 CRCs of < 10 mm had a significantly higher percentage of depressed type morphology (< 10 mm 51.7% vs ≥ 10 mm 21.2%, P < 0.01), a significantly lower percentage of polypoid growth (PG) (< 10 mm 43.1% vs ≥ 10 mm 64.1%, P < 0.01), and
Table 2 Comparison of clinicopathological characteristics between < 10 mm and ≥ 10 mm tumors in total cohort T1 colorectal cancers (n = 1152)

<table>
<thead>
<tr>
<th></th>
<th>&lt; 10 mm (n = 116)</th>
<th>≥ 10 mm (n = 1036)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>66.8 ± 11.5</td>
<td>66.4 ± 11.6</td>
<td>0.72</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>84 (72.4)/32 (27.6)</td>
<td>645 (62.3)/391 (37.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Location (left-sided/right-sided)</td>
<td>77 (66.4)/39 (33.6)</td>
<td>710 (68.5)/326 (31.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>7.5 ± 1.2</td>
<td>22.5 ± 12.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Polypoid/non-polypoid growth (polypoid/non-polypoid)</td>
<td>50 (43.1)/66 (56.9)</td>
<td>664 (64.1)/372 (35.9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Adenomatous component (%)</td>
<td>34 (29.3)/82 (70.7)</td>
<td>432 (41.7)/604 (58.3)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Morphology (flat/protruded/depressed)</td>
<td>10 (8.6)/46 (39.7)/60 (51.7)</td>
<td>387 (37.4)/429 (41.4)/220 (21.2)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Initial treatment (endoscopic/surgical)</td>
<td>86 (74.1)/30 (25.9)</td>
<td>624 (60.2)/412 (39.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Surgical resection1</td>
<td>73 (62.9)/43 (37.1)</td>
<td>725 (70.0)/311 (30.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Depth of invasion (T1b/T1a)</td>
<td>72 (62.1)/44 (37.9)</td>
<td>754 (72.8)/282 (27.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Histological grade (Por or Muc2/tub1 or tub2)</td>
<td>3 (2.6)/113 (97.4)</td>
<td>55 (5.3)/981 (94.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>Vascular invasion (%)</td>
<td>35 (30.2)/81 (69.8)</td>
<td>287 (27.7)/749 (72.3)</td>
<td>0.59</td>
</tr>
<tr>
<td>Lymphatic invasion (%)</td>
<td>38 (32.8)/78 (67.2)</td>
<td>304 (29.3)/732 (70.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>Tumor budding (BD 2 or 3/BD 1)</td>
<td>24 (20.7)/92 (79.3)</td>
<td>218 (21.0)/818 (79.0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

1Surgical resection: initial and additional surgical resection.
2Por or Muc, poorly differentiated adenocarcinoma or mucinous carcinoma. Results are expressed as mean ± SD or number of patients (%), as appropriate.

a significantly lower proportion of adenomatous component (< 10 mm 29.3% vs ≥ 10 mm 41.7%, P < 0.01). In terms of the initial treatment modality, the percentage of patients with T1 CRCs of less than 10 mm opting for endoscopic treatment was significantly higher (< 10 mm 74.1% vs ≥ 10 mm 60.2%, P < 0.01). Furthermore, the rate of T1b was higher in the large group than in the small group (< 10 mm 62.1% vs ≥ 10 mm 72.8%, P = 0.02). There were no significant differences in the rate of histological grade, vascular invasion, lymphatic invasion, or tumor budding.

Small vs large tumors in the surgery group
Comparison of clinicopathological characteristics between < 10 mm and ≥ 10 mm tumors in surgical resection cohort T1 CRCs are shown in Table 3. Of these 1152 Lesions, 798 T1 CRCs underwent initial or secondary surgical resection. There was no significant difference in the LNM rate between the two groups (< 10 mm 12.3% vs ≥ 10 mm 10.9%, P = 0.70). The small group showed a higher rate of depressed type morphology, a lower rate of polypoid growth, and a lower rate of smaller adenomatous component. However, there were also no significant differences in the rate of depth of invasion, histological grade, vascular invasion, lymphatic invasion, vascular invasion, or tumor budding.

A case of small T1 CRC with LNM positivity
We present a typical case of small T1 CRC with LNM positivity in Figure 2. An 8-mm lesion with depressed type morphology was identified in the sigmoid colon. According to the magnification endoscopy findings, we predicted that the depth of invasion was T1b. Therefore, we selected surgical resection with lymph node dissection as the first-line treatment for this lesion. The final pathological findings were well to moderately differentiated adenocarcinoma, positive lymphovascular invasion, positive vascular invasion, 3750-μm depth of invasion, grade 2 tumor budding, and positive LNM. Despite the small lesion, it had risk factors for LNM and showed LNM positivity, and thus required surgical resection to achieve a cure. Of course, pre-treatment endoscopic diagnosis was important; however, if endoscopic resection was selected for this type of lesion, we should resect it with a negative margin and properly stratify the risk for LNM on the basis of the histopathological diagnosis.
### Table 3 Comparison of clinicopathological characteristics between < 10 mm and ≥ 10 mm tumors in surgical resection cohort T1 colorectal cancers (n = 798)

<table>
<thead>
<tr>
<th></th>
<th>&lt; 10 mm (n = 73)</th>
<th>≥ 10 mm (n = 725)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>66.0 ± 11.8</td>
<td>65.5 ± 11.2</td>
<td>0.71</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>55 (75.3)/18 (24.7)</td>
<td>438 (60.4)/287 (39.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Location (left-sided/right-sided)</td>
<td>51 (69.9)/22 (30.1)</td>
<td>516 (71.2)/209 (28.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>7.6 ± 1.1</td>
<td>22.3 ± 12.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Polypoid/non-polypoid growth (polypoid/non-polypoid)</td>
<td>26 (35.6)/47 (64.4)</td>
<td>473 (65.2)/252 (34.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Adenoma component (±)</td>
<td>15 (20.5)/58 (79.5)</td>
<td>236 (32.6)/489 (67.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Morphology (flat/ protruded/ depressed)</td>
<td>4 (5.5)/ 24 (32.9)/ 45 (61.6)</td>
<td>307 (42.3)/214 (29.5)/204 (28.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Initial treatment (endoscopic/surgical)</td>
<td>43 (58.9)/30 (41.1)</td>
<td>316 (43.6)/409 (56.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Depth of invasion (T1b/T1a)</td>
<td>67 (91.8)/6 (8.2)</td>
<td>631 (87.0)/94 (13.0)</td>
<td>0.35</td>
</tr>
<tr>
<td>Histological grade (Por or Muc or tub1 or tub2)</td>
<td>3 (4.1)/70 (95.9)</td>
<td>47 (6.5)/678 (93.5)</td>
<td>0.61</td>
</tr>
<tr>
<td>Vascular invasion (±)</td>
<td>32 (43.8)/41 (56.2)</td>
<td>261 (36.0)/464 (64.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Lymphatic invasion (±)</td>
<td>34 (46.6)/39 (53.4)</td>
<td>270 (37.2)/455 (62.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Tumor budding (BD 2 or 3/BD 1)</td>
<td>21 (28.8)/52 (71.2)</td>
<td>193 (26.6)/532 (73.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Lymph node metastasis (±)</td>
<td>9 (12.3)/64 (87.7)</td>
<td>79 (10.9)/646 (89.1)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

1Por or Muc, poorly differentiated adenocarcinoma or mucinous carcinoma. Results are expressed as mean ± SD or number of patients (%), as appropriate.

### DISCUSSION

LNM is present in approximately 10% of T1 CRC cases in which surgical resection with lymph node dissection is required to achieve a cure[15-18]. Therefore, we determine the need for additional surgical resection after endoscopic resection of T1 CRC according to the risk of LNM on the basis of the pathological factors. Although a consensus has been reached for several risk factors, including lymphovascular invasion, tumor differentiation, or tumor budding, no consensus has been reached for tumor size. Several reports investigated the relationship between tumor size and the rate of LNM in T1 CRC[19-21] with differing conclusions. Several claimed that tumor size is unrelated to LNM, while others reported that tumor size is related to LNM[22-27]. In this study, we concluded that tumor size alone not a risk factor for LNM.

Our findings revealed that the small group had higher rate of depressed type morphology. Kudo et al[28] recently reported the malignant potential of depressed type lesions. In their research, depressed type lesions showed a higher rate of LNM, followed by vascular invasion and lymphatic invasion, than other types of morphology (flat and protruded type). They speculated that the difference in the molecular phenotype by whole-exome sequencing and RNA sequencing was a potential reason for this observation. The small group showed a significantly higher rate of depressed type morphology in this study. This is a potential reason for why there were no significant differences in LNM between small and large T1 CRCs. Information on tumor morphology obtained by endoscopy is important and we should take care when performing resections, especially for such lesions even though they are small.

The “resect and discard” strategy using optical diagnosis is an attractive approach for endoscopists, pathologists, and patients, and enables a major reduction in the cost of screening and surveillance colonoscopy[29,30]. However, it has the potential risk to discard small, advanced neoplasia, which are lesions of less than 10 mm with advanced histology (high grade dysplasia, villous component, and adenocarcinoma). Notably, in T1 CRC, additional surgical resection after endoscopic resection is required according to the risk of LNM on the basis of the pathological findings of resected specimens to achieve a cure. More than 60% of T1 CRCs are misdiagnosed as adenoma by endoscopists according to a recent prospective study in the Netherlands[31]. In our study, small lesions occupied approximately 10.1% of total T1 CRCs, which had equal potential for metastasis to lymph nodes compared with large lesions. Therefore, careful observation by endoscopy should be undertaken when adopting the “resect
Figure 2 A typical case of small T1 colorectal cancer with lymph node metastasis positivity. A: An 8-mm-sized lesion of erythematous color located in the sigmoid colon was detected by white light observation; B: Indigo carmine spray observation showed elevation in the center and a depression line at the edge, and was diagnosed as Ia + Ibc by morphology; C: By magnification observation with crystal violet staining, a non-structured area was identified around severe irregular pits diagnosed as V2 type pit pattern; D: Hematoxylin and eosin (H&E) staining showing well to moderately differentiated adenocarcinoma; E: Victoria blue staining. Vascular invasion was positive; F: Desmin staining. Depth of invasion was 3750 μm; G: D2-40 staining. Lymphatic invasion was positive; H: Dissected lymph nodes by H&E staining. Metastasis was positive.

This study had several limitations. First, it was a retrospective analysis of patients treated at a single institution. Second, when evaluating the incidence of LNM, only patients who had undergone surgery were included. Patients treated by endoscopic resection alone were excluded because the incidence of LNM this group was not precisely assessed.

CONCLUSION

In conclusion, we investigated the clinicopathological features of small T1 CRCs and revealed that there was no significant difference in the rate of LNM, followed by the rate of vascular invasion, lymphatic invasion, or histological grade, between the small and large tumor groups. Therefore, requirements for additional surgical resection after endoscopic resection of T1 CRC should be determined on the basis of a careful pathological diagnosis, even if it is a small lesion.
ARTICLE HIGHLIGHTS

Research background
Additional surgical resection of T1 colorectal cancer after endoscopic resection is determined according to the risk of lymph node metastasis (LNM) on the basis of the histopathological findings of resected specimens.

Research motivation
Clinicopathological features including the rate of LNM in small (< 10 mm) T1 colorectal cancer were unknown.

Research objectives
The purpose of this study was to clarify the clinicopathological characteristics of small (< 10 mm) T1 colorectal cancer compared with large (≥ 10 mm) tumors.

Research methods
We retrospectively analyzed clinicopathological features, including the rate of LNM, of 1152 T1 colorectal cancers divided into two groups: small (< 10 mm) and large (≥ 10 mm) tumors.

Research results
Small T1 colorectal cancer had a similar rate of LNM, followed by a positive rate of histological grade and lymphovascular invasion, compared with large tumors.

Research conclusions
Because there were no significant differences in the rate of LNM between small and large T1 colorectal cancers, the decision on whether to undertake secondary surgical resection should be determined according to pathological findings, regardless of tumor size.

Research perspectives
Because this was a single-center retrospective study, prospective multicenter studies are required to validate these findings.

ACKNOWLEDGEMENTS
The authors would like to express great appreciation to all members of the Digestive Disease Center and the Department of Diagnostic Pathology, Showa University Northern Yokohama Hospital for their excellent effort.

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[PMID: 32727186 DOI: 10.3760/cma.j.cn12139-20200518-00390]


Retrospective Study

Comparison of dental pulp periodontal therapy and conventional simple periodontal therapy as treatment modalities for severe periodontitis

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Author contributions: Wang T designed the research study; Li L performed the research; Chen HJ and Lian Y analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Affiliated Hospital of North Sichuan Medical College Institutional Review Board.

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: None.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

Abstract

BACKGROUND

Severe periodontitis is a major oral health concern today as it can lead to loss of teeth. Conventional periodontal therapy has numerous pitfalls as it does not address the pulp-periodontal complex in its entirety.

AIM

To investigate the effect of dental pulp periodontal therapy on the levels of interleukin-1β (IL-1β) and IL-10 in gingival crevicular fluid (GCF) in patients with severe periodontitis.

METHODS

Eighty-six patients with severe periodontitis were randomly divided into a research group ($n = 43$) and a control group ($n = 43$). The control group was treated with simple periodontal therapy, and the research group was treated with dental pulp periodontal therapy. The total effective rates of the treatments; periodontal status before and after treatment through the measurement of the periodontal pocket probing depth (PPD), gingival sulcus bleeding index (SBI), mobility (MD), and plaque index (PLI); the levels of inflammatory factors IL-1β and IL-10 in the GCF; and the incidence of complications were calculated for both groups and compared using the Student’s $t$ test and the $\chi^2$ test.

RESULTS
The total effective rate of treatment in the study group (93.02%) was higher than that in the control group (76.74%; \( P < 0.05 \)). While before treatment, there was no significant difference in the PLI, MD, SBI, or PPD between the two groups, the post-treatment values of PLI, MD, SBI, and PPD (4.71 ± 0.16 mm, 0.61 ± 0.09 mm, 0.96 ± 0.17 mm, and 0.76 ± 0.26 mm, respectively) were significantly lower \( (P < 0.05) \) in the research group than in the control group (5.35 ± 0.24 mm, 0.93 ± 0.15 mm, 1.35 ± 0.30 mm, and 1.04 ± 0.41 mm, respectively). There was no significant difference in the level of IL-1β or IL-10 in the GCF before treatment between the two groups; after treatment, the IL-1β level in the research group (139.04 ± 15.54 pg/mL) was significantly lower than that in the control group (156.35 ± 18.10 pg/mL), and the level of IL-10 in the research group (7.98 ± 1.01 ug/L) was higher than that in the control group (5.56 ± 0.96 ug/L) \( (P < 0.05) \). The incidence of complications in the study group (4.65%) was significantly lower than that of the control group (18.60%; \( P < 0.05 \)).

**CONCLUSION**

Endodontic therapy and periodontal treatment for patients with severe periodontitis can effectively reduce the levels of inflammatory factors in the GCF and the inflammatory reaction. In addition, it can improve the periodontal condition and the overall treatment effect, reduce the risk of complications, and ensure the safety of treatment.

**Key Words:** Severe periodontitis; Dental pulp and periodontal therapy; Interleukin-1β; Interleukin-10

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**Core Tip:** Dental pulp periodontal therapy can effectively avoid the shortcomings of simple periodontal therapy. In this study, the authors investigated the efficacy and safety of this treatment.

**INTRODUCTION**

Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by microorganisms, resulting in the progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession, or both. The incidence of periodontitis has continued to rise in recent years due to poor oral hygiene habits. It impacts oral health and quality of life and is an important cause of tooth loss in adults[1,2]. Severe periodontitis can not only affect periodontal tissues but also the dental pulp. Infection of the pulp can in turn adversely affect periodontal tissue healing[3,4].

At present, most patients with severe periodontitis are managed with simple periodontal therapy. While it can improve periodontal condition to an extent, it may result in damage to the gingiva. Additionally, the risk of pulpal infection exists because of the relationship between the pulp and periodontium. As a result, its clinical application is limited[5,6]. Dental pulp periodontal therapy can effectively avoid these shortcomings as it involves treatment of both dental pulp and periodontal lesions. Furthermore, it can reduce the re-occurrence of infection, and ensure the effectiveness and safety of treatment[7,8].

The present study aimed to evaluate the effectiveness of dental pulp periodontal therapy in comparison to simple periodontal therapy for the treatment of severe periodontitis. We compared the total effective rate of treatment; periodontal status indices, such as periodontal probing depth (PPD), gingival sulcus bleeding index (SBI),
tooth mobility (MD), and plaque index (PLI); the levels of interleukin-1β (IL-1β) and IL-10 in the gingival crevicular fluid (GCF); and the incidence of complications between the two treatment groups.

**MATERIALS AND METHODS**

**Patient selection criteria**

Patients who presented with severe periodontitis to our hospital from March 2019 to March 2020 were selected. The inclusion criteria were: A diagnosis of periodontitis, alveolar bone loss involving more than 2/3 of the root length without root tip exposure, tooth mobility less than grade III, knowledge about and consent for participation in this study, good compliance and communication skills, and no history of antimicrobial use in the month before the patient’s inclusion in the study. We excluded patients presenting with pulpal disease, acute or severe infections, an immunocompromised status, neurological diseases, and communication disorders; pregnant or lactating female patients; and those who underwent periodontal therapy in the year preceding the commencement of this study.

**Patient data**

A total of 86 patients were selected and randomly divided into a research group (n = 43) and a control group (n = 43). The research group comprised 24 men and 19 women in the age range of 34-56 years (mean ± SD: 44.91 ± 8.92 years), and the course of disease ranged from 1.1 to 3.9 years (mean ± SD: 2.51 ± 1.13 years). The control group comprised 26 men and 17 women in the age range of 32-59 years (mean ± SD: 46.04 ± 9.33 years), and the course of disease was 0.9-4.3 years (mean ± SD: 2.64 ± 1.08 years). The clinical data such as sex, age, and course of disease were balanced and comparable between the two groups (P > 0.05).

**Methods**

All patients of both groups received basic interventional measures, such as occlusal adjustments, splinting of mobile teeth, antimicrobial therapy, etc., on the basis of different treatment schemes that were adopted. The patients of the control group were treated with simple periodontal therapy, including supragingival scaling, root planing, subgingival curettage, and local administration of minocycline ointment into the periodontal pocket. The research group received endodontic treatment in the teeth exhibiting periodontitis. After local anesthesia administration, an access cavity was prepared, and the pulp was extirpated. Working length determination was done with an apex locator, biomechanical preparation with adequate irrigation using 17% ethylenediaminetetraacetic acid and 2.5% sodium hypochlorite solutions, air-drying treatment, and calcium hydroxide plugging of the root canal. Finally, the canal was obturated using gutta-percha and a root canal sealer after 7 d.

**Observation indexes**

The outcomes of the two interventions were measured in the following manner: (1) The treatment was considered significantly effective if occlusal function recovered markedly, the alveolar bone loss did not progress, and the clinical symptoms disappeared completely 12 mo after treatment. If the occlusal function recovered to some extent and the clinical symptoms improved but did not disappear completely, the treatment was considered effective. If there was no improvement in occlusal function or clinical symptoms, the treatment was regarded ineffective. The total effective rate was calculated as the percentage of significantly effective and effective outcomes; (2) The periodontal status of the two groups was assessed before and after treatment, including PLI, MD, gingival SBI, periodontal PPD; (3) The levels of inflammatory factors IL-1β and IL-10 in the GCF were measured before and after treatment. A filter paper strip was cut into a rectangle (10 mm × 2 mm) and loaded into a microcentrifuge tube (0.5 mL). Plaque and calculus deposits coronal to the observation point were removed. The patient was asked to gargle with water for 10 min and then the gingival sulcus was dried. The filter paper strip was inserted with tweezers into the mesial, central, and distal gingival sulci, and discontinued after resistance. After 30 s, 200 μL of buffer was added to the microcentrifuge to shake for 60 min. The filter paper was removed, frozen in the refrigerator at -70 °C, and subjected to an enzyme-linked immunosorbent assay; and (4) The incidence of complications in the two groups was calculated.
**Statistical analysis**
All continuous data are presented as the mean ± SD and analyzed using the Student’s $t$ test. The count data were analyzed using the $\chi^2$ test. All data were analyzed using the SPSS v22.0 software. A $P$ value of $<0.05$ indicated a significant difference.

**RESULTS**

**Therapeutic effects**
The total effective rate of the study group (93.02%) was higher than that of the control group (76.74%; $P < 0.05$) (Table 1).

**Periodontal status**
Before treatment, there was no significant difference in the observed values of PLI, MD, SBI, and PPD between the research group and the control group. After treatment, the observed values of PLI, MD, SBI, and PPD in the research group were significantly lower than those of the control group ($P < 0.05$) (Table 2).

**Inflammatory factors in GCF**
Before treatment, there was no significant difference in the level of IL-1$\beta$ or IL-10 in the GCF between the study group (212.59 ± 19.45 pg/mL and 2.83 ± 0.69 ug/L, respectively) and the control group (209.01 ± 22.31 pg/mL and 2.77 ± 0.72 ug/L, respectively). After treatment, the level of IL-1$\beta$ in the GCF in the study group (139.04 ± 15.54 pg/mL) was significantly lower than that of the control group (156.35 ± 18.10 pg/mL). The level of IL-10 (7.98 ± 1.01 ug/L) was significantly higher than that of the control group (5.56 ± 0.96 ug/L) ($P < 0.05$) (Table 3).

**Incidence of complications**
The incidence of complications in the study group (4.65%) was significantly lower than that of the control group (18.60%; $P < 0.05$) (Table 4).

**DISCUSSION**
Periodontitis is a chronic inflammatory disease of the periodontium mainly caused by microorganisms in plaque. Severe periodontitis is a complex condition that is difficult to treat[11,12]. It can lead to increased tooth mobility and pathologic migration, which may adversely affect masticatory function and esthetics[13,14]. The ideal treatment for severe periodontitis remains a topic of research.

The main treatment modality for severe periodontitis is simple periodontal treatment at present. It is necessary to detect dental pulp vitality before treatment to determine whether dental pulp treatment is necessary or for patients with obvious pulpsitis. However, the affected teeth still experience reactions when periodontal inflammation or even local necrosis occurs; therefore, simple periodontal therapy has obvious limitations[15]. In recent years, it has been found that the risk of dental pulp disease is significantly increased if alveolar bone loss involves two-thirds of the root surface. It has been found that periodontal therapy for such patients can easily trigger or aggravate dental pulp disease, which can in turn adversely affect the normal repair of the periodontal tissue[16,17]. The pulp-periodontal complex has great healing potential, and the implementation of systematic pulp periodontal therapy can effectively promote periodontal tissue healing and control inflammatory reactions. Frencken et al[18] showed that in patients with severe periodontitis, dental pulp periodontal therapy can effectively improve the SBI and PLI, reduce the depth of the periodontal pockets, and improve the overall treatment effect (91.89%). Kruk et al[19] demonstrated that in cases of severe periodontitis treated with dental pulp periodontal therapy, indices such as the PLI and MD improved, and the total effective rate was higher than in cases treated with simple periodontal therapy. In the current study, we observed that the periodontal status-related indices of the research group significantly improved compared to those of the control group, and the total effective rate (93.02%) was higher in the research group than in the control group (76.74%; $P < 0.05$). This finding is consistent with the results of previous studies, which confirms that dental pulp periodontal therapy is more valuable in patients with severe periodontitis and can effectively improve the periodontal condition of patients and the overall treatment effect. The main reason is that although periodontal therapy alone can remove...
Table 1 Comparison of therapeutic effects between the two groups, n (%)  

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Significantly effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research</td>
<td>43</td>
<td>26 (60.47)</td>
<td>14 (32.56)</td>
<td>3 (6.98)</td>
<td>40 (93.02)</td>
</tr>
<tr>
<td>Control</td>
<td>43</td>
<td>17 (39.53)</td>
<td>16 (37.21)</td>
<td>10 (23.26)</td>
<td>33 (76.74)</td>
</tr>
</tbody>
</table>

χ²  
P value  

Table 2 Comparison of periodontal status between the two groups before and after treatment (mean ± SD)  

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>PLI</th>
<th>MD (mm)</th>
<th>SBI</th>
<th>PPD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td>42</td>
<td>7.88 ± 0.68</td>
<td>3.39 ± 0.39</td>
<td>6.45 ± 0.65</td>
<td>5.39 ± 0.63</td>
</tr>
<tr>
<td>Control</td>
<td>42</td>
<td>8.01 ± 0.73</td>
<td>3.45 ± 0.37</td>
<td>6.68 ± 0.61</td>
<td>5.54 ± 0.70</td>
</tr>
<tr>
<td>t</td>
<td>0.951</td>
<td>0.797</td>
<td>1.843</td>
<td>1.137</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.344</td>
<td>0.427</td>
<td>0.068</td>
<td>0.258</td>
<td></td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td>42</td>
<td>4.71 ± 0.16</td>
<td>0.61 ± 0.09</td>
<td>0.96 ± 0.17</td>
<td>0.76 ± 0.26</td>
</tr>
<tr>
<td>Control</td>
<td>42</td>
<td>5.35 ± 0.24</td>
<td>0.93 ± 0.15</td>
<td>1.35 ± 0.30</td>
<td>1.04 ± 0.41</td>
</tr>
<tr>
<td>t</td>
<td>15.845</td>
<td>13.064</td>
<td>8.077</td>
<td>4.119</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

PLI: Plaque index; MD: Mobility; SBI: Sulcus bleeding index; PPD: Pocket probing depth.

Table 3 Comparison of inflammatory factors in gingival crevicular fluid between the two groups before and after treatment (mean ± SD)  

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>IL-1β (pg/mL)</th>
<th>IL-10 (ug/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td>42</td>
<td>212.59 ± 19.45</td>
<td>2.83 ± 0.69</td>
</tr>
<tr>
<td>Control</td>
<td>42</td>
<td>209.01 ± 22.31</td>
<td>2.77 ± 0.72</td>
</tr>
<tr>
<td>t</td>
<td>0.864</td>
<td>0.430</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.390</td>
<td>0.668</td>
<td></td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td>42</td>
<td>139.04 ± 15.54</td>
<td>7.98 ± 1.01</td>
</tr>
<tr>
<td>Control</td>
<td>42</td>
<td>156.35 ± 18.10</td>
<td>5.56 ± 0.96</td>
</tr>
<tr>
<td>t</td>
<td>5.182</td>
<td>12.403</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

IL: Interleukin.

subgingival necrotic tissue, calculus, and plaque on the tooth surface, it is effectively a mechanical treatment. It can potentially affect periodontal tissue healing and may lead to infection after treatment. Further, dental pulp periodontal therapy can more effectively improve the healing of the periodontium, reduce pulp inflammation, and avoid pulp infection in the process of treatment. In addition, it can achieve a radical cure, eradicate existing pulpal infection, and establish a coordinated relationship to promote periodontal tissue healing and improve tooth mobility. Moreover, the injection of minocycline hydrochloride through the root canal approach can not only achieve the efficacy of traditional drugs for root canal disinfection but also peri-root
Table 4 Comparison of the incidence of complications between the two groups, n (%)  

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Poor healing</th>
<th>Periodontal infection</th>
<th>Dental pulp infection</th>
<th>Total incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research</td>
<td>43</td>
<td>1 (2.33)</td>
<td>1 (2.33)</td>
<td>0 (0.00)</td>
<td>2 (4.65)</td>
</tr>
<tr>
<td>Control</td>
<td>43</td>
<td>3 (6.98)</td>
<td>2 (4.65)</td>
<td>3 (6.98)</td>
<td>8 (18.60)</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.074</td>
</tr>
<tr>
<td>$P$ value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.044</td>
</tr>
</tbody>
</table>

and apical effects through the potential pathogenetic trafficking pathway in dental pulp and periodontal lesions and thus improve the therapeutic effect.

GCF, an exudate in the gingival sulcus, can accurately reflect the metabolic changes in the periodontium and thus, the degree of periodontitis. The evaluation of periodontitis by measuring the classic inflammatory factors in the GCF is non-invasive, convenient, and repeatable. IL-1β promotes the proliferation of T and B lymphocytes, induces host inflammatory response, and promotes the destruction of bone and cartilage[20]. IL-10 is a multifunctional cytokine, mainly secreted by Th1 cells, which can participate in the immune response and inflammatory reactions, and has antiallergic and anti-inflammatory effects; it also inhibits eosinophils and accelerates their apoptosis. IL-10 levels have been reported to continuously decrease with increasing periodontal loss[21]. In the present study, the level of IL-1β in the GCF in the research group was lower than that of the control group, and the level of IL-10 in the research group was higher than that of the control group ($P < 0.05$). Serum microscopic analysis further confirmed that the effect of dental pulp periodontal treatment is better, which can improve oral inflammation and periodontal condition. In addition, this study also found that the incidence of complications in the study group (4.65%) was lower than that of the control group (18.60%; $P < 0.05$). This result indicated that dental pulp periodontal therapy can also reduce the risk of complications in patients with severe periodontitis.

CONCLUSION

In conclusion, dental pulp periodontal treatment for patients with severe periodontitis can effectively reduce the levels of inflammatory factors in the GCF and reduce inflammatory reactions. In addition, dental pulp periodontal treatment can improve periodontal condition and the overall treatment effect, and reduce the risk of complications to ensure the safety of treatment.

ARTICLE HIGHLIGHTS

Research background
Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by microorganisms, resulting in the progressive destruction of the periodontal ligament.

Research motivation
Periodontitis impacts oral health and quality of life and is an important cause of tooth loss in adults.

Research objectives
We wanted to evaluate the effectiveness of dental pulp periodontal therapy in comparison to simple periodontal therapy for the treatment of severe periodontitis.

Research methods
We selected patients with severe periodontitis at our hospital who met the inclusion and exclusion criteria.

Research results
After treatment, the interleukin-1β (IL-1β) level of the study group was significantly
lower than that of the control group, and the IL-10 level was significantly higher than that of the control group.

**Research conclusions**
Dental pulp periodontal treatment can improve periodontal condition and the overall treatment effect, and reduce the risk of complications to ensure the safety of treatment.

**Research perspectives**
The level of inflammatory factors reflects the prognosis of periodontitis treatment.

**REFERENCES**
17. Manresa C, Sanz-Miralles EC, Twigg J, Bravo M. Supportive periodontal therapy (SPT) for


Retrospective Study

Tripartite intensive intervention for prevention of rebleeding in elderly patients with hypertensive cerebral hemorrhage

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Author contributions: Li CX and Li L designed the experiment; Zhang JF drafted the manuscript, Zhang QH and Jin XH collected the data; Li CX and Cai GJ analyzed and interpreted data, Li CX and Cai GJ wrote the article.

Institutional review board statement: This study was approved by the Affiliated Hangzhou First People’s Hospital Ethics Committee.

Informed consent statement: Patients were not required to give informed consent 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 conflicting interests.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

Specialty type: Nursing

Abstract

BACKGROUND

Hypertensive cerebral hemorrhage (HICH) is the rupture and bleeding of vessels of the cerebral parenchyma caused by continuously elevated or violently fluctuating blood pressure. The condition is characterized by high disability and high mortality. Hematoma formation and resulting space-occupying effects following intracerebral hemorrhage are among the key causes of impaired neurological function and disability. Consequently, minimally invasive clearance of the hematoma is undertaken for the treatment of HICH because it can effectively relieve intracranial hypertension. Therefore, special attention should be given to the quality of medical and nursing interventions in the convalescent period after minimally invasive hematoma clearance.

AIM

The study aim was to determine the value of intensive intervention, including doctors, nurses, and patient families, for the prevention of rebleeding in elderly patients with HICH during the first hospitalization for rehabilitation after the ictal event

METHODS

A total of 150 elderly HICH patients with minimally invasive hematoma evacuation in our hospital between May 2018 and May 2020 were selected and equally divided into two groups of 75 each by their planned intervention. The control group was given conventional nursing intervention and the observation group was given tripartite intensive intervention. The length of hospital stay, cost, complication rate, satisfaction rate, and rebleeding rate during hospitalization were recorded. Changes in cerebral blood flow indicators were recorded in both
Core Tip: We evaluated the value of tripartite intensive intervention in elderly patients with hypertensive intracerebral hemorrhage (HICH) during their first rehabilitation hospitalization after onset. A tripartite intensive intervention strategy in elderly HICH patients during the convalescent period shortened their hospitalization duration, reduced hospitalization costs, and lowered the rate of rebleeding during hospitalization as well as the overall incidence of complications, including pulmonary infection, pressure sores, central high fever, and deep venous thrombosis.
INTRODUCTION

Hypertensive intracerebral hemorrhage (HICH) is a common clinical cerebrovascular event\(^1\)-\(^3\). Rupture of blood vessels and formation of hematoma for various reasons will compress the surrounding brain tissue, leading to secondary brain injury and neurological impairment\(^4\)-\(^7\). Because of the sudden onset and rapid progress of HICH, it usually manifests with lasting limb hemiplegia, language impairment, dysphagia, and other sequelae\(^8\)-\(^12\). Patients in the convalescent period are prone to emotional excitement, which is not conducive to the rehabilitation process\(^13\)-\(^16\). On the other hand, severe emotional fluctuations can induce recurrent bleeding, which has a negative impact on prognosis. Therefore, nursing intervention should be emphasized during the rehabilitation for elderly patients hospitalized after first onset HICH, so as to reduce the risk of recurrent bleeding.

The nursing staff is currently the primary source of clinical nursing for HICH patients during convalescence, and the overall nursing effectiveness needs to be improved beyond just mechanically follow the doctor’s advice\(^17\). Tripartite intensive intervention refers to a novel approach to medical care jointly delivered doctors, nursing staff, and the patient’s family. It can provide patients with timely, comprehensive, and professional medical care services that enhance rehabilitation, and it has already been applied in a variety of medical fields\(^18\). This study explored the value of tripartite intensive intervention for elderly patients with HICH to prevent rebleeding during hospitalization for rehabilitation subsequent to ictus.

MATERIALS AND METHODS

General information

Elderly HICH patients who were treated at our hospital between May 2018 and May 2020 and underwent minimally invasive hematoma evacuation were recruited for this study. The inclusion criteria were (1) HICH that satisfied the criteria of the Guidelines for Diagnosis and Treatment of Intracerebral Hemorrhage in China (2014), and documented by imaging; (2) between 60 and 75 years of age, without restriction based on gender; (3) prior minimally invasive hematoma evacuation; (4) first onset of HICH; and (5) with complete clinical data. The exclusion criteria were (1) time from onset to initial physician assessment of more than 12 h; (2) accompanying circulatory and respiratory dysfunction; (3) a past medical history of mental illness; (4) accompanying neurological diseases; (5) accompanying severe diseases such as of the heart, liver, or kidney; and (6) not understanding the study procedures. A total of 150 patients, 78 men and 72 women with an average age of 68.21 ± 5.23 years were included in the study and were divided into two groups of 75 patients each. The control group was provided conventional nursing intervention. The observation group was provided with intensive tripartite intervention. There were no significant differences in the general data between the two groups \((P > 0.05)\), as shown in Table 1.

Methods

The control group was provided with conventional nursing intervention and close monitoring of the vital signs, administration of drugs per doctor’s advice, guiding the patients toward a reasonable diet, maintaining emotional stability, and implementing rehabilitation exercise as planned. The observation group was given tripartite intensive intervention by doctors, nurses, and the patient’s family. A trinity of nursing group doctors, nursing staff, and family members was established. Trinity nursing knowledge training was provided to all team members. Ward rounds were jointly conducted by the medical staff. Prior to ward rounds, the nursing staff were tasked to evaluate the patient’s vital signs, disease dynamics, emotional state, and the effect of rehabilitation exercise. The findings were reported to the doctor. During ward rounds, the nursing staff were expected to ask the doctors about the priorities for nursing care and the details of each patient, for continuous improvement of nursing quality. The nursing staff were also expected to inform the patient’s family about the key points of focus in the daily care process. For patients with obvious adverse emotions, doctors, nursing staff, and family members were expected to cooperate for psychological counseling. Doctors were expected to clearly inform the patients that minimally invasive hematoma removal has satisfactory effects so as to reduce their anxiety and accordingly communicate the prognosis of similar patients to bolster confidence on the road to recovery. The nursing staff were expected to explain the importance of postoperative rehabilitation exercises to the patients and guide them as to the correct...
Table 1 General participant characteristics in the two groups, $n$ (%)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group, $n = 75$</th>
<th>Observation group, $n = 75$</th>
<th>$\chi^2/t$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.107</td>
<td>0.744</td>
</tr>
<tr>
<td>Male</td>
<td>40 (53.33)</td>
<td>38 (50.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35 (46.67)</td>
<td>37 (49.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in yr</td>
<td>67.96 ± 6.11</td>
<td>68.45 ± 5.89</td>
<td>0.500</td>
<td>0.618</td>
</tr>
<tr>
<td>Hypertension course in yr</td>
<td>8.56 ± 2.17</td>
<td>8.41 ± 2.23</td>
<td>0.417</td>
<td>0.677</td>
</tr>
<tr>
<td>Time of onset in h</td>
<td>6.45 ± 2.13</td>
<td>6.51 ± 2.28</td>
<td>0.167</td>
<td>0.868</td>
</tr>
<tr>
<td>Bleeding in mL</td>
<td>36.58 ± 5.45</td>
<td>37.12 ± 5.08</td>
<td>0.628</td>
<td>0.531</td>
</tr>
<tr>
<td>Cerebral hemorrhage site</td>
<td></td>
<td></td>
<td>1.841</td>
<td>0.398</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>48 (64.00)</td>
<td>41 (54.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The hypothalamus</td>
<td>19 (25.33)</td>
<td>21 (28.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral lobe</td>
<td>8 (10.67)</td>
<td>13 (17.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td>0.435</td>
<td>0.805</td>
</tr>
<tr>
<td>Primary or lower secondary</td>
<td>12 (16.00)</td>
<td>11 (14.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school, or secondary school,</td>
<td>38 (50.67)</td>
<td>42 (56.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College or above</td>
<td>25 (33.33)</td>
<td>22 (29.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>27 (36.00)</td>
<td>33 (44.00)</td>
<td>1.000</td>
<td>0.317</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>22 (29.33)</td>
<td>15 (20.00)</td>
<td>1.758</td>
<td>0.185</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (21.33)</td>
<td>20 (26.67)</td>
<td>0.585</td>
<td>0.444</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>36 (48.00)</td>
<td>38 (50.67)</td>
<td>0.107</td>
<td>0.744</td>
</tr>
</tbody>
</table>

way of performing the exercises. Families were expected to help patients relax and facilitate treatment adherence through encouraging words and actions. Family members were expected to accompany the patients during rehabilitation and exercise, and to provide prompt reports on any problem to their doctors and nursing staff to guide changes to the plan of rehabilitation and exercise programs. The period of intervention in both groups lasted included the duration of hospitalization for rehabilitation.

**Observation indicators and evaluation criteria**

The hospitalization duration, cost, complication rate, satisfaction rate, and rebleeding rate during hospitalization were recorded for each patient. The rebleeding criteria were established on the basis of clinical deterioration within 24 h following surgery (with rebleeding from the original site of the lesion), recurrence of hematoma upon clinical deterioration beyond 24 h following surgery, or increase in hematoma volume by more than 50% or more than 20 mL despite satisfactory clinical outcomes. Health behavior scores included five key aspects, emotional control (10 points), adherence to medications ordered by the doctor (15 points), dietary management (20 points), exercise management (20 points) and self-monitoring (10 points). Higher scores corresponded to better health behaviors.

The National Institutes of Health Stroke Scale (NIHSS) and Quality of Life Index (QLI) scores\cite{19} were used to evaluate neurological function and quality of life. The total score of the NIHSS is 42 points, and higher scores correspond with worsening neurological function. The QLI has a maximum score of 10 points, and lower scores correspond to worsening quality of life. Patient satisfaction was evaluated using an in-house scoring system. The total score consisted of 100 points. Ninety to 100 were very satisfactory, 75–89 points were satisfactory; and scores below 75 were unsatisfactory.

**Detection methods**

Cerebrovascular function indicators such as mean flow rate ($Q_{mean}$) and mean velocity, ($V_{mean}$) dynamic resistance, and peripheral vascular resistance were measured in both
groups at the time of hospitalization prior to intervention and following intervention (at the time of discharge). The instrument used in the examination was an AD-7 cerebrovascular hemodynamic analyzer (Beduz, Germany).

**Statistical analysis**
The data were processed with SPSS ver. 19.0. The measurement indices were reported as means ± SD, and t-tests were used for comparison. Count data were reported as the number and percentage (%) of cases. Comparisons were performed by $\chi^2$ tests. The level of significance was set at $P = 0.05$.

**RESULTS**

*Comparison of duration of stay, cost, and rebleeding between the two groups*
The duration of hospitalization was shorter, the cost of hospitalization was less, and the rebleeding rate during hospitalization was lower in the intervention group than in the control group, with statistical significance (all $P < 0.05$; Table 2).

*Comparison of cerebral blood flow indicators between the two groups*
Before intervention, there was no significant difference in cerebral blood flow between the two groups ($P > 0.05$). After intervention, the $Q_{mean}$ and $V_{mean}$ values increased in both groups ($P < 0.05$), and the dynamic resistance and peripheral vascular resistance decreased in both ($P < 0.05$). The $Q_{mean}$ and $V_{mean}$ values were higher in the intervention group than in the control group ($P < 0.05$), and the dynamic resistance and peripheral vascular resistance were lower than those in the control group ($P < 0.05$; Table 3).

*Comparison of health behavior scores between the two groups*
Before intervention, there was no significant difference in the health behavior scores between the two groups ($P > 0.05$). After intervention, the health behavior scores, including emotional control, medication adherence, dietary management, exercise management, and self-monitoring increased in the two groups compared with those prior to intervention ($P < 0.05$). Health behavior scores in the observation group were higher than those in the control group ($P < 0.05$; Table 4).

*Comparison of NIHSS and QLI scores between the two groups*
Prior to intervention, the NIHSS and QLI scores between the two groups were not statistically significant (both $P > 0.05$). Following intervention, the QLI scores of both groups accordingly increased ($P < 0.05$); the NIHSS score decreased ($P < 0.05$); and the QLI score of the observation group was higher than that of the control group ($P < 0.05$). Moreover, the NIHSS score in the treatment group was lower than that of the control group ($P < 0.05$; Table 5).

*Complications during hospitalization of the two groups*
The total incidence of complications such as pulmonary infection, pressure sores, central hyperpyrexia, and deep vein thrombosis was significantly lower in the intervention group than that in the control group ($P < 0.05$; Table 6).

*Comparison of satisfaction between the two groups*
The satisfaction rate was higher in the observation group significantly higher than in the control group ($P < 0.05$; Table 7).

**DISCUSSION**
Tripartite intensive intervention is a novel approach to medical care that is different from the conventional nursing interventions delivered in the past. The model attributes great importance to the participation of doctors and the patient’s family members so that doctors can better grasp the specific situations of each patient during rehabilitation. It allows due consideration of the initiative of the patient’s family so that the patient can obtain better care[20]. Some previous care givers applied the trinity nursing model in interventions for patients with transient ischemic attack, and found that the short-term efficacy of treatment and the quality of life of patients improved. However, no relevant studies have reported on the use of the intervention
Table 2 Hospital stay, cost, and rebleeding rate in the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Hospital stay in d</th>
<th>Hospitalization costs, 10000 yuan</th>
<th>Rebleeding rate during hospitalization, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>75</td>
<td>16.89 ± 2.45</td>
<td>2.76 ± 0.32</td>
<td>10 (13.33)</td>
</tr>
<tr>
<td>Observation Group</td>
<td>75</td>
<td>15.21 ± 2.34</td>
<td>2.58 ± 0.28</td>
<td>3 (4.00)</td>
</tr>
</tbody>
</table>

$\chi^2$  
$P$ value  
0.000  
0.000  
4.127

Table 3 Cerebral blood flow indexes in the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>$Q_{mean}$ in mL/s</th>
<th>$V_{mean}$ in cm/s</th>
<th>Dynamic resistance in kPa·s/m</th>
<th>Peripheral vascular resistance in kPa·s/m</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-intervention</td>
<td>After intervention</td>
<td></td>
<td>Pre-intervention</td>
<td>After intervention</td>
</tr>
<tr>
<td>Control group</td>
<td>75</td>
<td>8.64 ± 0.64</td>
<td>10.35 ± 0.71$^a$</td>
<td>12.52 ± 1.36</td>
<td>16.36 ± 1.42$^a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42.02$^a$</td>
<td></td>
</tr>
<tr>
<td>Observation Group</td>
<td>75</td>
<td>8.69 ± 0.72</td>
<td>11.56 ± 0.57$^a$</td>
<td>12.43 ± 1.82</td>
<td>18.21 ± 1.53$^a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28.47$^a$</td>
<td></td>
</tr>
</tbody>
</table>

$t$  
P value  
0.449  
0.000  
11.509  
0.000  
0.343  
0.732  
7.675  
0.000  
0.986  
0.000  
4.728  
0.000  
0.161  
3.798

*P < 0.05 vs the same group before intervention.

Table 4 Health behavior scores in the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time</th>
<th>Control group, n = 75</th>
<th>Observation group, n = 75</th>
<th>$t$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional control</td>
<td>Pre-intervention</td>
<td>5.74 ± 0.96</td>
<td>5.69 ± 1.02</td>
<td>0.309</td>
<td>0.758</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>7.32 ± 0.67$^a$</td>
<td>8.51 ± 0.88$^a$</td>
<td>9.318</td>
<td>0.000</td>
</tr>
<tr>
<td>Compliance with medication</td>
<td>Pre-intervention</td>
<td>7.65 ± 1.12</td>
<td>7.59 ± 1.08</td>
<td>0.334</td>
<td>0.739</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>12.33 ± 1.54$^a$</td>
<td>12.54 ± 1.26$^a$</td>
<td>0.914</td>
<td>0.362</td>
</tr>
<tr>
<td>Catering management</td>
<td>Pre-intervention</td>
<td>10.23 ± 1.35</td>
<td>10.08 ± 1.27</td>
<td>0.701</td>
<td>0.484</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>14.12 ± 1.24$^a$</td>
<td>16.35 ± 1.41$^a$</td>
<td>10.285</td>
<td>0.000</td>
</tr>
<tr>
<td>Movement management</td>
<td>Pre-intervention</td>
<td>10.45 ± 1.08</td>
<td>10.29 ± 1.13</td>
<td>0.886</td>
<td>0.377</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>14.03 ± 1.51$^a$</td>
<td>16.65 ± 1.32$^a$</td>
<td>11.313</td>
<td>0.000</td>
</tr>
<tr>
<td>Self-monitoring</td>
<td>Pre-intervention</td>
<td>6.52 ± 0.38</td>
<td>6.61 ± 0.67</td>
<td>0.880</td>
<td>0.381</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>7.89 ± 0.64$^a$</td>
<td>8.78 ± 0.69$^a$</td>
<td>8.190</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*P < 0.05 vs the same group before intervention.

model during the convalescence of elderly HICH patients.

Tripartite intensive intervention was applied in this study of the management of elderly HICH patients in the convalescent period. It was found to shorten the duration of hospitalization, reduce hospitalization costs, lower the rate of rebleeding during hospitalization, reducing the overall incidence of complications such as respiratory infection, pressure sores, central hyperpyrexia, and deep venous thrombosis. With the trinity nursing model, medical staff can undertake joint ward rounds, and the nursing staff can provide feedback on the patient’s vital signs, dynamic conditions, emotional state, response to rehabilitation exercises, and other information. The feedback can be communicated to the doctor in a more detailed and timely manner to facilitate the doctor’s formulation of the treatment plan and the implementation of improvements in the rehabilitation process. During ward rounds, doctor may remind nurses of the priorities and minutiae of care, which facilitates continuous improvement in the
Table 5 National Institutes of Health Stroke Scale and Quality of Life Index scores between the two groups (mean ± SD, subdivision)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>NIHSS score</th>
<th>QLI score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-intervention</td>
<td>After intervention</td>
</tr>
<tr>
<td>Control group</td>
<td>75</td>
<td>13.23 ± 3.26</td>
<td>7.45 ± 2.66&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Observation Group</td>
<td>75</td>
<td>14.02 ± 3.41</td>
<td>6.27 ± 2.13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>t</td>
<td>1.450</td>
<td>2.999</td>
<td>0.358</td>
</tr>
<tr>
<td>P value</td>
<td>0.149</td>
<td>0.003</td>
<td>0.721</td>
</tr>
</tbody>
</table>

<sup>a</sup>P < 0.05 vs the same group before intervention.

NIHSS: National Institutes of Health Stroke Scale; QLI: Quality of Life Index.

Table 6 Complications during hospitalization in both groups, n (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Pulmonary infection</th>
<th>Pressure sore</th>
<th>Central hyperthermia</th>
<th>Deep venous thrombosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>75</td>
<td>2 (2.67)</td>
<td>3 (4.00)</td>
<td>5 (6.67)</td>
<td>2 (2.67)</td>
<td>12 (16.00)</td>
</tr>
<tr>
<td>Observation group</td>
<td>75</td>
<td>0 (0.00)</td>
<td>1 (1.33)</td>
<td>2 (2.67)</td>
<td>0 (0.00)</td>
<td>3 (4.00)</td>
</tr>
<tr>
<td>χ&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.000</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.014</td>
</tr>
</tbody>
</table>

Table 7 Satisfaction in the two groups, n (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Very pleased</th>
<th>Satisfactory</th>
<th>Not satisfied</th>
<th>Satisfaction rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>75</td>
<td>29 (38.67)</td>
<td>33 (44.00)</td>
<td>13 (17.33)</td>
<td>62 (82.67)</td>
</tr>
<tr>
<td>Observation group</td>
<td>75</td>
<td>42 (56.00)</td>
<td>28 (37.33)</td>
<td>5 (6.67)</td>
<td>70 (93.33)</td>
</tr>
<tr>
<td>χ&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>4.040</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.044</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

quality of care. Through the process, family members learned of key points for attention to care that allowed better implementation of daily nursing operations, reduced complications, and ultimately promoted recovery.

In this study, emotional control, medication adherence, dietary management, exercise management, self-monitoring, and other health behavior scores before and after nursing intervention were evaluated. It was found that the tripartite intensive intervention improved the health-seeking behavior of these elderly HICH patients. Furthermore, the NIHSS score was used to evaluate the degree of neurological impairment, and the QLI score was used to evaluate quality of life. It was found that intensive intervention could better reduce neurological impairment and improve patient quality of life. With the tripartite intensive intervention model, all parties cooperate to relieve the patient’s adverse emotions. The doctor is responsible for providing patients with information on the good effect of the operation and the prognosis of similar patients so that the patient can build confidence for recovery. The nursing staff serves as the main performers of the intervention, and during the nursing interval, they explain the importance of postoperative rehabilitation exercises and the correct methods for performing the program to the patients; they may help patients to overcome difficulties and fear and adhere to the rehabilitation plan until its completion. Nurses can also teach patients to count their heart rate, and can provide timely information to physicians if the patients experience discomfort upon rehabilitation training, to ensure patient safety. Family members can help foster calmness through their emotions and enhance treatment adherence through encouraging language and actions. In addition, family members can carefully prepare the patient’s meals, frequently change their clothes, and provide good life care. The joint efforts from the three parties can greatly reduce the negative emotions of the patients. During the rehabilitation exercises, the patient is accompanied by his/her family member. When patients encounter discomfort, they are helped to sit down and are asked about
the situation. If any problems are found, they promptly reported to the doctor and nursing staff so that the doctor can promptly tailor the rehabilitation exercise plan to achieve maximum rehabilitation with the least effort, minimizing patient disability [21].

Increased cerebrovascular resistance and decreased blood perfusion are risk factors for poor prognosis in elderly HICH patients. In this study, measurement of cerebral blood flow indices before and after the intervention found that intensive intervention by doctors, nurses and family members increased $Q_{\text{mean}}$ and $V_{\text{mean}}$ and reduced dynamic resistance and peripheral vascular resistance. It was related to enhanced emotional control, treatment adherence, dietary management, exercise management, self-monitoring and other health behaviors following intervention.

CONCLUSION

In conclusion, intensive intervention by doctors, nurses, and family members reduced the rebleeding rate during hospitalization and the incidence of complications, promoted rehabilitation, and improved quality of life, neurological function, and patient satisfaction and health-seeking behavior.

ARTICLE HIGHLIGHTS

Research background
Hypertensive cerebral hemorrhage (HICH) is the rupture and bleeding of vessels of the cerebral parenchyma caused by continuously elevated or violently fluctuating blood pressure. The condition is characterized by high disability and high mortality. Hematoma formation and the resulting space-occupying effects following intracerebral hemorrhage are among the key causes of impaired neurological function and disability. Minimally invasive clearance of the hematomata effectively relieves intracranial hypertension. Therefore, special attention should be given to the quality of medical and nursing interventions during convalescence after minimally invasive hematoma clearance.

Research motivation
This study confirmed the value of intensive intervention including doctors, nurses, and patient families, for the prevention of rebleeding among elderly patients with HICH during the first hospitalization for rehabilitation after the ictal event.

Research objectives
This study aimed to determine the value of intensive intervention with tripartite care in preventing rebleeding in elderly HICH patients with HICH during their first hospitalization after the onset.

Research methods
A total of 150 elderly HICH patients who underwent minimally invasive hematoma evacuation were selected and divided equally to two groups of 75 each according to their intervention plan. The control group was given conventional nursing intervention and the observation group was given intensive tripartite intervention. The length of hospital stay, cost, complication rate, satisfaction rate, and rebleeding rate during hospitalization were recorded; changes in cerebral blood flow indicators were recorded.

Research results
The hospital stay was shorter, the hospitalization cost was lower, and the rate of rebleeding during hospitalization was lower in the observation group than in the control group. There were no significant differences in the patient characteristics and health behavior scores between the two groups before treatment. The scores for healthy behaviors such as emotion control, medication adherence, dietary management, exercise management, and self-monitoring in both groups were higher after treatment than before treatment, and the of healthy-behavior scores in the intervention group were higher than those in the control group.
Li CX et al. Hypertensive intracerebral hemorrhage and rebleeding prevention

Research conclusions
Intensive intervention by doctors, nurses, and families of elderly patients with HICH can reduce the rate of rebleeding during hospitalization, reduce the incidence of complications, promote rehabilitation, improve the quality of life, and enhance nerve function.

Research perspectives
Intensive intervention can improve the quality of treatment and care for the elderly with HICH.

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Retrospective Study

Clinical and electroencephalogram characteristics and treatment outcomes in children with benign epilepsy and centrotemporal spikes

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Author contributions: Chen RH and Li BF designed this retrospective study; Chen RH wrote the paper; Chen RH, Li BF, Wen JH, Zhong CL, and Ji MM were responsible for sorting the data.

Institutional review board statement: This study was approved by the Ganzhou Maternal and Child Health Hospital Medical Ethics Committee.

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

Conflict-of-interest statement: This is no conflict of interest to disclose.

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Country/Territory of origin: China

Specialty type: Clinical neurology

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Abstract

BACKGROUND
Epilepsy is a syndrome characterized by transient, rigid, paroxysmal, and repetitive central nervous system dysfunction. Prevention, control, and improvement of cognitive and behavioral dysfunction are of great significance for improving the patients’ intellectual development and quality of life. Electroencephalograms (EEG) can predict an accelerated decline in cognitive function.

AIM
To determine the clinical and EEG characteristics and treatment results of benign epilepsy in spiking children.

METHODS
A total of 106 cases of benign epilepsy in children with myocardial spines treated at our hospital from January 2017 to January 2020 were selected. Differences in clinical data and EEG characteristics between treatment-effective/-ineffective patients were analyzed, and children’s intellectual development before and after treatment evaluated using the Gesell Development Diagnostic Scale.

RESULTS
EEG showed that the discharge proportion in the awake and sleep periods was 66.04%, and the peak/peak discharge was mainly single-sided, accounting for 81.13%, while the discharge generalization accounted for 31.13%. There was no
Epilepsy is a syndrome characterized by transient, rigid, paroxysmal, and repetitive central nervous system dysfunction, generally caused by excessive neuron synchronization in the brain and self-limited abnormal discharge caused by various etiological factors. As a common disease among children, the incidence rate of epilepsy has shown an increasing trend in recent years. Benign epilepsy in children with centrotemporal spike waves is an age-dependent epileptic syndrome, which generally peaks between 6–8 years old, with normal mental and motor development[1,2]. At present, the primary goal of antiepileptic treatments is to completely control epileptic seizures, while simultaneously considering prevention, control, and improvement of cognitive and behavioral dysfunction is of great significance for improving the patients' intellectual development and quality of life. Electroencephalogram (EEG) is an important external validator of normal brain structure and function and useful to detect some brain alterations. Cognitive function, an important aspect of brain function, is also based on brain morphology and/or function. Studies have shown that abnormal EEG can predict an accelerated decline in cognitive function[3,4]. In this study, the clinical and EEG characteristics of children with benign epilepsy and centrotemporal spikes were analyzed, and the children’s treatment and outcomes also discussed.
MATERIALS AND METHODS

Patients
A total of 106 cases of benign epilepsy, including 66 males and 40 females, in children with spinous waves in the central temporal region were treated at our hospital from January 2017 to January 2020. Their ages ranged from 3 to 12 years old, and their average age was 7.15 ± 1.82 years old. The inclusion criteria were: (1) The diagnosis met the criteria for the epilepsy diagnosis and treatment guidelines of the International League Against Epilepsy; (2) First-time treatment; (3) Aged 3–12 years old; (4) Complete clinical, EEG, and follow-up data; (5) Had intelligence tests; and (6) Informed consent from the child’s guardian. The exclusion criteria were: (1) A history of encephalitis, meningitis, brain developmental malformation, and other brain diseases; (2) Other diseases such as connective tissue disease, nephrotic syndrome, and immunodeficiency; and (3) Patients with a history of glucocorticoid and other treatments within 6 mo before treatment in our hospital.

Treatment and follow-up
The children were treated with levetiracetam and lamotrigine. The levetiracetam dose was 10 mg/kg/d, and the final therapeutic dose was 10-30 mg/kg/d. Lamotrigine was administered at doses from 0.3-0.6 mg/kg/d, gradually increasing to 3-6 mg/kg/d. Each child was followed for 1 year after treatment, and the treatment was considered ineffective if there were clinical epileptic seizures during the follow-up period, and effective if there were no clinical epileptic seizures.

EEG examination
We employed an EEG-1200C manufactured by Japan Optoelectronics Co., Ltd with the following parameters: Gain, 50 µV; high-pass filtering conducted at 45 Hz; time constant, 0.3 s; accuracy, 16 bit; frequency, 200 Hz; and scalp resistance, ≤ 5000 MΩ. Reference electrodes were placed on the bilateral earlobes and we used 16 recording electrodes in total. EEG signals were recorded in a quiet and eye-closed state for 5 min, and the complexity was calculated. The human electroencephalogram frequency was (0.5-30) Hz, including β (13.5-30.0) Hz, α (8.0–13.0) Hz, θ (4.0-7.5) Hz, and δ (1.0-3.5) Hz.

Intelligence development test
The development of children’s intelligence was assessed using the Gesell Development Diagnostic Scale, which included five domains, namely, gross motor, fine motor, adaptability, language, and personal-social ability. The test result of each domain is expressed as development quotient (DQ), and a DQ > 85 was considered normal.

Statistical analysis
SPSS22.0 software was used for data analyses. Measurement data with a normal distribution are expressed as the mean ± SD, and t test was used for comparison between groups. Count data are expressed as n (%), and inter-group comparisons were performed by the chi-square test. Pearson correlation analysis for correlation, and logistic regression analysis for multivariate analysis were also performed. P values < 0.05 were considered statistically significant.

RESULTS

Children’s EEG characteristics
Among the 106 children, the EEG showed a discharge proportion in the awake and sleep periods of 66.04%, a spike/sharp wave discharge rate of 81.13% (mainly unilateral discharge), and a discharge generalization rate of 31.13%, as shown in Table 1.

Comparison of children’s EEG characteristics with respect to sex and age
There was no significant difference in the proportion of discharge, spike/sharp wave unilateral discharge, and discharge generalization between the sexes and among all age groups either during the awake or asleep period (P > 0.05), as shown in Table 2.
Table 1 Electroencephalogram characteristics of children

<table>
<thead>
<tr>
<th>Electroencephalogram characteristic</th>
<th>Number of cases</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awake and sleep periods</td>
<td>70</td>
<td>66.04</td>
</tr>
<tr>
<td>Sleep period</td>
<td>36</td>
<td>33.96</td>
</tr>
<tr>
<td>Spine/spike discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>86</td>
<td>81.13</td>
</tr>
<tr>
<td>Bilateral</td>
<td>20</td>
<td>18.87</td>
</tr>
<tr>
<td>Discharge generalization</td>
<td>33</td>
<td>31.13</td>
</tr>
</tbody>
</table>

Table 2 Comparison of electroencephalogram characteristics of children of different sexes and ages

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Awake and sleep discharge (%)</th>
<th>Spike/sharp wave unilateral discharge (%)</th>
<th>Discharge generalization (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>66</td>
<td>42 (63.64)</td>
<td>55 (83.33)</td>
<td>19 (28.79)</td>
</tr>
<tr>
<td>Woman</td>
<td>40</td>
<td>28 (70.00)</td>
<td>31 (77.50)</td>
<td>14 (35.00)</td>
</tr>
<tr>
<td>χ²</td>
<td>0.450</td>
<td>0.554</td>
<td>0.448</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.502</td>
<td>0.457</td>
<td>0.503</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 7 yr</td>
<td>34</td>
<td>25 (73.53)</td>
<td>26 (76.47)</td>
<td>11 (32.35)</td>
</tr>
<tr>
<td>&gt; 7 yr</td>
<td>72</td>
<td>45 (62.50)</td>
<td>60 (83.33)</td>
<td>22 (30.56)</td>
</tr>
<tr>
<td>χ²</td>
<td>1.253</td>
<td>0.711</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.263</td>
<td>0.399</td>
<td>0.852</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of clinical data of treatment responsive/unresponsive children

The proportion of children with young-age onset (< 5 years old) and attack frequency > 3 times/half a year in the treatment unresponsive group was significantly higher than that in the treatment responsive group (P < 0.05), and the discharge index significantly lower (P < 0.05). There was no significant difference in sex, age, or discharge period between the treatment responsive/unresponsive groups (P > 0.05, Table 3).

Correlation between discharge index and Gesell scale

Pearson correlation analysis showed a negative correlation between the discharge index and fine motor skills and the language development quotient (r = -0.274 and -0.247, respectively; P < 0.05), but no significant correlation was observed in any other parameters (P > 0.05), as shown in Table 4 and Figure 1.

Results of multivariate analysis

Logistic regression analysis was performed using the above statistically significant indicators as independent variables and treatment effectiveness as the dependent variable. The results showed that low age (< 5 years old) and seizure frequency were the factors affecting the lack of treatment response in children with benign epilepsy and centrotemporal spike wave (Odds ratio = 11.304 and 5.784, respectively; P < 0.05), as shown in Table 5.

Comparison of discharge index and Gesell scale between treatment responsive/unresponsive children before and after treatment

The discharge index after treatment in the treatment responsive group was 34.47 ± 10.02%, significantly lower than that in the unresponsive group (P < 0.05). In the treatment responsive group, fine motor skills, adaptability, and language development quotient improved after treatment (P < 0.05). There was no significant difference in gross and fine motor skills, adaptability, language, or personal-social ability.
Table 3 Comparison of clinical data of children with and without effective treatment, n (%)

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Treatment ineffective (n = 20)</th>
<th>Treatment effective (n = 86)</th>
<th>χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>11 (55.00)</td>
<td>55 (63.95)</td>
<td>0.554</td>
<td>0.457</td>
</tr>
<tr>
<td>Woman</td>
<td>9 (45.00)</td>
<td>31 (36.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>7.15 ± 1.98</td>
<td>7.15 ± 1.80</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Discharge period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awake and sleep periods</td>
<td>15 (75.00)</td>
<td>55 (63.95)</td>
<td>0.883</td>
<td>0.347</td>
</tr>
<tr>
<td>Sleep period</td>
<td>5 (25.00)</td>
<td>31 (36.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spike/sharp wave discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>19 (95.00)</td>
<td>67 (77.91)</td>
<td>2.081</td>
<td>0.149</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1 (5.00)</td>
<td>19 (22.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge generalization</td>
<td>8 (40.00)</td>
<td>25 (29.07)</td>
<td>0.904</td>
<td>0.342</td>
</tr>
<tr>
<td>Low age onset (&lt; 5 yr)</td>
<td>8 (40.00)</td>
<td>6 (6.98)</td>
<td>12.690</td>
<td>0.000</td>
</tr>
<tr>
<td>Seizure frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3 times/half a year</td>
<td>12 (60.00)</td>
<td>21 (24.42)</td>
<td>9.582</td>
<td>0.002</td>
</tr>
<tr>
<td>≤ 3 times/half a year</td>
<td>8 (40.00)</td>
<td>65 (75.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge index (%)</td>
<td>65.05 ± 7.74</td>
<td>73.28 ± 9.17</td>
<td>-3.714</td>
<td>0.000</td>
</tr>
<tr>
<td>Gesell scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross motor (points)</td>
<td>85.70 ± 6.62</td>
<td>85.28 ± 7.29</td>
<td>0.236</td>
<td>0.814</td>
</tr>
<tr>
<td>Fine motor (points)</td>
<td>88.60 ± 5.99</td>
<td>86.62 ± 8.00</td>
<td>1.040</td>
<td>0.301</td>
</tr>
<tr>
<td>Adaptability (points)</td>
<td>87.60 ± 7.02</td>
<td>86.08 ± 7.20</td>
<td>0.854</td>
<td>0.395</td>
</tr>
<tr>
<td>Language (points)</td>
<td>88.15 ± 7.13</td>
<td>86.33 ± 7.92</td>
<td>0.942</td>
<td>0.348</td>
</tr>
<tr>
<td>Individual-social ability (points)</td>
<td>85.40 ± 8.61</td>
<td>85.99 ± 8.22</td>
<td>-0.287</td>
<td>0.775</td>
</tr>
</tbody>
</table>

Table 4 Results of correlation analysis

<table>
<thead>
<tr>
<th>Gesell scale</th>
<th>Discharge index</th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross motor</td>
<td></td>
<td>-0.014</td>
<td>0.887</td>
</tr>
<tr>
<td>Fine motor</td>
<td></td>
<td>-0.274</td>
<td>0.005</td>
</tr>
<tr>
<td>Adaptability</td>
<td></td>
<td>-0.068</td>
<td>0.488</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td>-0.247</td>
<td>0.011</td>
</tr>
<tr>
<td>Individual-social ability</td>
<td></td>
<td>0.098</td>
<td>0.316</td>
</tr>
</tbody>
</table>

development quotient between the treatment responsive/unresponsive group after treatment (P > 0.05, Table 6).

DISCUSSION

Epilepsy is a brain disease mainly characterized by transient central nervous system dysfunction caused by abnormal neuron discharge. Repeated epileptic seizures are often accompanied by a variety of neurobiological, cognitive, psychological, and social dysfunctions. Benign epilepsy with spinous waves in the central temporal region is the most common partial epilepsy in childhood, with an onset age between 3-13 years and accounting for 15%-24% of all kinds of epilepsy in children[3]. Several studies have shown that children with epilepsy and centrotemporal spikes have various degrees of
Table 5 Results of multivariate analysis

<table>
<thead>
<tr>
<th>Index</th>
<th>β</th>
<th>SE</th>
<th>Wals</th>
<th>P value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence at a young age (&lt; 5 yr)</td>
<td>2.425</td>
<td>0.696</td>
<td>12.131</td>
<td>0.000</td>
<td>11.304 (2.888-44.251)</td>
</tr>
<tr>
<td>Attack frequency</td>
<td>1.755</td>
<td>0.593</td>
<td>8.760</td>
<td>0.003</td>
<td>5.784 (1.809-18.490)</td>
</tr>
<tr>
<td>Constant term</td>
<td>-2.686</td>
<td>0.480</td>
<td>31.254</td>
<td>0.000</td>
<td>-</td>
</tr>
</tbody>
</table>

OR: Odds ratio.

cognitive and behavioral damage[6,7], while other reports have found that the cognitive impairment in these children is not caused by seizures but related to frequent clinical discharge. Neuropsychological and sociological problems exist in half of these children after adulthood[8,9]. Although the primary goal of antiepileptic treatment is to completely control epileptic seizures, prevention, control, and improvement of cognitive and behavioral dysfunction must be simultaneously considered. Therefore, clinicians must achieve a balance between controlling the epileptic seizures as much as possible and preserving cognitive and behavioral functions[10]. Long-term outbreaks of spike-and-slow wave rhythm and bilateral asynchronous spike-and-slow wave distribution cause more severe cognitive impairment than single spike waves[11]. EEG monitoring, a common modern auxiliary examination method for the clinical diagnosis of mild cognitive impairment diseases, induces no physical trauma and has confirmed value in the diagnosis of brain diseases. However, comprehensive analyses, as well as other experimental and auxiliary examinations, need to be conducted based on specific symptoms and signs; therefore, it is of great clinical significance to explore chemical markers of brain damage[12]. EEG represents the waveforms formed by the brain spontaneous potential; these waveforms can be divided into α, β, γ, θ, and δ waves according to their frequencies, with different waveforms being shown at different ages, in various consciousness states, and at various brain function levels[13,14]. Some studies have shown that abnormal EEGs can predict an accelerated decline in cognitive function. In children with epilepsy, EEGs accompanied by spinous waves in the central temporal region during the attack stage are often characterized by tonic-clonic seizures, where the initial fast wave activity of low amplitude in the central or middle temporal region on one side gradually increases in amplitude and decreases in frequency, gradually evolving into the alternating appearance of spinous and slow waves, which can be generalized to the ipsilateral hemisphere or even spread to the contralateral one[15]. At present, EEGs are considered to be highly related to epilepsy with spinous waves in the central temporal region. And compared with those of healthy peers, an increase in extremely high-amplitude spinous and slow waves in the high Rolandic region can be observed in the awake period, along with a widespread rhythmic outbreak of 2-3 Hz high-amplitude spinous and slow waves in the awake period. However, the discharge is significantly increased in the sleep period, and the spinous and slow wave discharge index is > 50% during the non-rapid-eye-movement sleep period[16]. In epilepsy accompanied by centrotemporal spikes, the presence of a status epilepticus EEG during sleep is known to cause nerve damage and cognitive changes; the higher the abnormal discharge index in the EEG, the more severe the cognitive damage in children. Therefore, we should actively diagnose, treat, and observe the therapeutic effects in children with epilepsy accompanied by centrotemporal spikes[17,18]. In this study, correlation analysis revealed that the discharge index was negatively correlated with fine motor performance and the language development quotient. Logistic regression analysis showed that an early age of onset (< 5 years old) and seizure frequency were influencing factors for the unresponsive treatment of benign epilepsy with centrotemporal spikes in children, indicating that monitoring the EEG discharge index could be used to preliminarily determine the children's fine motor skills and language development quotient. During treatment, great attention should be given to children with early-onset and frequent seizures in whom clinical treatment has a poor effect. Frequent attacks can lead to delayed reaction time or even reaction loss in children, suggesting that abnormal discharges may be accompanied by transient cognitive function changes under clinical conditions, which reminds us that seizure control should not be the target of clinical treatment but the inhibition of clinical discharge and subsequent improvement in patients’ cognitive function[19,20]. An early age of onset is an important factor leading to poor treatment effect in children with benign epilepsy and centrotemporal spikes. Given the lack of clear clinical data
Table 6 Comparison of discharge index and Gesell scale scores between treatment-effective and treatment-ineffective children before and after treatment

<table>
<thead>
<tr>
<th>Index</th>
<th>Treatment ineffective (n = 20)</th>
<th>Treatment effective (n = 86)</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge index (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>65.05 ± 7.74</td>
<td>73.28 ± 9.17</td>
<td>-3.714</td>
<td>0.000</td>
</tr>
<tr>
<td>After treatment</td>
<td>40.15 ± 5.36</td>
<td>34.47 ± 10.02</td>
<td>2.449</td>
<td>0.016</td>
</tr>
<tr>
<td>t</td>
<td>11.828</td>
<td>26.498</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross motor (points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>85.70 ± 6.62</td>
<td>85.28 ± 7.29</td>
<td>0.236</td>
<td>0.814</td>
</tr>
<tr>
<td>After treatment</td>
<td>85.90 ± 5.47</td>
<td>86.20 ± 6.47</td>
<td>-0.192</td>
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</tr>
<tr>
<td>t</td>
<td>-0.104</td>
<td>-0.875</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
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<td>0.383</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine motor (points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>88.60 ± 5.99</td>
<td>86.62 ± 8.00</td>
<td>1.040</td>
<td>0.301</td>
</tr>
<tr>
<td>After treatment</td>
<td>91.20 ± 2.69</td>
<td>89.24 ± 5.29</td>
<td>1.605</td>
<td>0.111</td>
</tr>
<tr>
<td>t</td>
<td>-1.771</td>
<td>-2.533</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.085</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adaptability (points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>87.60 ± 7.02</td>
<td>86.08 ± 7.20</td>
<td>0.854</td>
<td>0.395</td>
</tr>
<tr>
<td>After treatment</td>
<td>88.50 ± 5.04</td>
<td>88.26 ± 5.38</td>
<td>0.182</td>
<td>0.856</td>
</tr>
<tr>
<td>t</td>
<td>-0.466</td>
<td>-2.249</td>
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<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.644</td>
<td>0.026</td>
<td></td>
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</tr>
<tr>
<td>Language (points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>88.15 ± 7.13</td>
<td>86.33 ± 7.92</td>
<td>0.942</td>
<td>0.348</td>
</tr>
<tr>
<td>After treatment</td>
<td>89.35 ± 6.02</td>
<td>88.55 ± 5.99</td>
<td>0.537</td>
<td>0.592</td>
</tr>
<tr>
<td>t</td>
<td>-0.575</td>
<td>-2.073</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.569</td>
<td>0.040</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal-social ability (points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>85.40 ± 8.61</td>
<td>85.99 ± 8.22</td>
<td>-0.287</td>
<td>0.775</td>
</tr>
<tr>
<td>After treatment</td>
<td>86.95 ± 6.78</td>
<td>87.91 ± 6.27</td>
<td>-0.607</td>
<td>0.545</td>
</tr>
<tr>
<td>t</td>
<td>-0.633</td>
<td>-1.722</td>
<td></td>
<td></td>
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<tr>
<td>P value</td>
<td>0.531</td>
<td>0.087</td>
<td></td>
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</tr>
</tbody>
</table>

on the specific scope of early-onset benign epilepsy with centrottemporal spikes, an early age at onset can be used as a relevant factor to predict treatment prognosis in these children. In this study, early age of onset was < 5 years old.

The analysis of the results of this study showed that the two antiepileptic drugs levetiracetam and lamotrigine could effectively control epileptic seizures and inhibit epileptic discharge, thus improving children’s cognitive function. However, this study has various limitations. Due to the limited number of enrolled children, there may be some deviation and error in the evaluation of discharge index, which may lead to a lack of generalizability. Therefore, further research expanding the sample size and extending follow-up time is needed.
CONCLUSION

In summary, the EEG of children with benign epilepsy and centrotemporal spikes has characteristic changes, and therapeutic effects are affected by the age and attack frequency at the time of onset.

ARTICLE HIGHLIGHTS

Research background
The primary goal of antiepileptic treatments is to completely control epileptic seizures, while simultaneously considering prevention, control, and improvement of cognitive and behavioral dysfunction is of great significance for improving the patients' intellectual development and quality of life.

Research motivation
In this study, the clinical and electroencephalograms (EEG) characteristics of children with benign epilepsy and centrotemporal spikes were analyzed, and the children’s treatment and outcomes also discussed.

Research objectives
This study aimed to determine the clinical and EEG characteristics and treatment results of benign epilepsy in spiking children.

Research methods
A total of 106 benign epilepsy children with myocardial spines were included. Differences in clinical data and EEG characteristics between treatment-effective/-ineffective patients were analyzed, and children’s intellectual development before and after treatment evaluated using the Gesell Development Diagnostic Scale.

Research results
EEG showed that the discharge proportion in the awake and sleep periods was 66.04%, and the peak/peak discharge was mainly single-sided, accounting for 81.13%, while the discharge generalization accounted for 31.13%. The discharge index was negatively correlated with fine motor skill and language development, but not with the rest. The discharge index of the responsive group after treatment was significantly lower than that of the unresponsive group.

Research conclusions
The EEG of children with benign epilepsy and centrotemporal spikes has charac-
teristic changes, and therapeutic effects are affected by the age and attack frequency at the time of onset.

Research perspectives

Further research expanding the sample size and extending follow-up time is needed.

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Chen RH et al. EEG characteristics and treatment outcomes in BEC

Retrospective Study

Endoscopic ultrasonography diagnosis of gastric glomus tumors

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Author contributions: Bai B, Mao CS, Li Z and Kuang SL contributed equally to this work; Bai B designed the research study; Mao CS performed the case search; Li Z analyzed the data; Kuang SL wrote the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Henan Provincial People's Hospital.

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

Conflict-of-interest statement: We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

Specialty type: Gastroenterology

Abstract

BACKGROUND
A gastric glomus tumor is relatively rare, and there is little knowledge on its endoscopic ultrasound findings.

AIM
To assess the accuracy of endoscopic ultrasonography (EUS) in the diagnosis of gastric glomus tumor and to discuss its value by reviewing the literature.

METHODS
A retrospective analysis of the EUS characteristics of gastric glomus tumor (such as tumor location, shape, size, echogenicity, homogeneity, margins, layer of origin, and so on) was performed. The study included 12 cases of gastric glomus tumor confirmed by surgery and pathology (7 females and 5 males, age range 36-74 years, average age was 58.2 years).

RESULTS
All the lesions were located in the gastric antrum (12 cases), protruding into the cavity, with a diameter between 1 and 3.5 cm. Glomus tumor of the stomach manifested as a circumscribed and slightly hypoechoic mass in the fourth layer, with an internal heterogeneous echo mixed with hyperechogenic spots and a marginal more hypoechoic halo. Smooth muscle actin, h-caldesmon and vimentin were shown to be positive by immunohistochemistry.

CONCLUSION
Although glomus tumor of the stomach is relatively rare, a typical glomus tumor of the stomach has characteristic changes under EUS.
Key Words: Glomus tumor; Endoscopic ultrasonography; Computed tomography; Pathology

Core Tip: Gastric glomus tumor is a rare non-epithelial benign vascular tumor and is difficult to diagnose with upper gastrointestinal endoscopy. We summarized the characteristics of endoscopic ultrasonography (EUS), computed tomography (CT) and pathology of 12 cases of gastric glomus tumor confirmed by pathology. The EUS characteristics of a gastric glomus tumor include a hypoechogenic lesion originating from the fourth layer with a peripheral acoustic halo. Clinically, the diagnosis can be confirmed by the EUS characteristics combined with CT imaging findings.

INTRODUCTION
Glomus tumor is a rare non-epithelial benign vascular tumor occurring at the site of arteriovenous anastomoses. Tumor cells are derived from smooth muscle cells with vascular spheroid degeneration. Glomus tumors often occur under the nail bed at the end of the extremities, and can also occur in other parts, such as soft tissue, mediastinal lung, nose, pharynx, sacrococcygeal region etc. Glomus tumors of the gastrointestinal tract are relatively rare and more common in the stomach. Most gastric glomus tumors are benign and are occasionally found as subepithelial lesions [1,2]. Endoscopic ultrasound is currently more and more widely used in clinical practice, but there is little understanding of the endoscopic ultrasound manifestations of gastric glomus tumors, and their characteristics. This study summarized the endoscopic ultrasound manifestations and related pathological characteristics of 12 cases of gastric glomus tumors confirmed by surgery and pathology, combined with a review of relevant literature, to improve the diagnosis and understanding of the disease under endoscopic ultrasound.

MATERIALS AND METHODS

Patient and case selection.
This study was a retrospective observational study. We retrospectively collected data from medical records and endoscopic reports at Henan Provincial People’s Hospital (Zhengzhou China). Twelve cases of gastric glomus tumor confirmed by surgery and pathology in our hospital from January 2013 to October 2020 were enrolled, including 7 females and 5 males, aged 36-74 years, with an average age of 58.2 years. Six cases experienced epigastric pain and discomfort with acid reflux and heartburn, 1 case had nausea, 2 cases had a positive stool occult blood test and 3 cases were normal following physical examination. Of the 12 patients, 9 underwent endoscopic submucosal dissection (ESD) and 3 underwent surgical procedures. All patients underwent endoscopic ultrasound and abdominal contrast-enhanced CT scanning before treatment.

Endoscopic equipment and methods
Endoscopic ultrasound examination included the use of the EU-ME2 PP ultrasound host (Olympus Japan), MAJ-935 or MAJ-1720 ultrasound probe driver, UM-2R, UM-3R ultrasound microprobe, or the GF-UE160-AL5 radial array scanning endoscope. Ultrasound scanning was performed by the water injection method. The liquid and gas in the gastric cavity were first removed, and the target lesions of ultrasonic scanning were displayed and confirmed. Then, water was slowly injected at a low flow rate to enhance the echogenicity and acoustic characteristics of the lesion.
rate, and the lesion was completely immersed in degassed water following suction of gastric air. The micro-probe was taken out of the endoscopic channel for ultrasound scanning, and for larger lesions, a radial scanning ultrasound was used for ultrasound scanning. The following features were recorded: location, size, the presence of mucosal ulceration, shape, original layer, echogenicity, echo uniformity, the presence of marginal halos, cystic change, and calcification.

**Histopathologic examination**

All specimens were fixed in 10% buffered formalin and routinely processed, followed by routine hematoxylin and eosin immunohistochemical staining. The immunohistochemical staining process was carried out according to the instructions. The pathology results were independently interpreted by 2 experienced pathologists. Under a light microscope, tumor cells were seen growing around blood vessels. Diagnosis was confirmed when immunohistochemistry showed positive smooth muscle actin (SMA), h-caldesmon and vimentin[3].

**RESULTS**

**Endoscopic ultrasound**

During gastroscopy, all lesions were located in the gastric antrum, and presented as a submucosal tumor that protruded into the lumen in a small semi-spherical shape (Figure 1A). Ten cases had smooth hemispherical bulges of the mucosa, the same color as the surrounding mucosa, and 2 cases had small concave ulcers on the mucosa surface, leading to hemorrhage. The lesions were located in the anterior wall of the gastric antrum in 3 cases and in the lesser curvature of the gastric antrum in 9 cases. Endoscopic ultrasonography (EUS) showed that the lesions were round, ranging in maximum diameter from 10 mm to 35 mm with a mean diameter of 20 mm. The echo was slightly hypoechoic, and was uniform, accompanied by small hyperechoic spots. There were small anechoic areas in the larger lesions, and halos with a lower echo. The outer boundary of the halo was clear, and the inner boundary was fuzzy. All lesions originated from the fourth layer, that is, the muscularis propria (Figure 1B). The clinical and endoscopic ultrasound features of the 12 cases of gastric glomus tumor are summarized in Table 1.

**Computed tomography features**

Enhanced CT examination was as follows: A Philips ingenuity 64 slice multi-slice spiral CT scanner was used, 1 mm thick, 5 mm reconstruction, whole abdomen plain scan and enhanced scan. The non-ionic contrast agent ioversol (100 mL; 320 mg I/mL) was injected with a Medrad Vistron CT high-pressure syringe at a rate of 3.0 mL/s via the elbow vein. The first phase (arterial phase) abdominal scan was started 30 s after injection, and the second phase (portal phase) abdominal scan was started 80 s after injection. CT showed well-defined subepithelial masses with homogeneous soft tissue densities with clear margins and perigastric adipose tissue. Dynamic contrast-enhanced CT showed strong peripheral nodular or homogeneous enhancement in the arterial and portal phases and prolonged enhancement in the delayed phase. The capsule of the tumor was slightly enhanced on CT scan, and no enlarged lymph nodes were observed (Figure 2).

**Pathological features**

Gross examination showed the following: In 9 cases of ESD resection of tumor and 3 cases of partial gastric wall and tumor, the lesions were round, with clear boundaries, no obvious capsule, grayish-red, or grayish-white in color, and a tough texture. Histologically, the tumors were located in the gastric muscularis propria and composed of glomus cells surrounding capillaries. The tumor cells were small, uniform in size, arranged in nests, and round without nuclear pleomorphism, mitotic figures, or necrosis, and grew around blood vessels. The tumors had abundant blood supply; dilated blood vessels were visible in the surrounding muscularis along with clear or light red cytoplasm, and no atypia or mitosis (Figure 3A). Immunohistochemically, tumor cells showed diffuse immunostaining for SMA, h-caldesmon, and vimentin in 12 cases (figure 3B-D), and all tumors were negative for CD117, CD34, S-100, dog-1, desmin, and CD31.
Table 1 Clinical and endoscopic ultrasound features of 12 cases of gastric glomus tumor

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Treatment method</th>
<th>Location</th>
<th>Symptom</th>
<th>Diameter (cm)</th>
<th>Endoscopic ultrasound features</th>
<th>Ulceration</th>
<th>Follow-up time (yr)</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>36</td>
<td>ESD</td>
<td>Anterior wall of the gastric antrum</td>
<td>Normal</td>
<td>1</td>
<td>The fourth layer, round, hypoechoic, halos</td>
<td>N</td>
<td>3</td>
<td>N</td>
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<tr>
<td>2</td>
<td>Female</td>
<td>47</td>
<td>ESD</td>
<td>Lesser curvature of the gastric antrum</td>
<td>Normal</td>
<td>1.2</td>
<td>The fourth layer, round, hypoechoic, halos</td>
<td>N</td>
<td>4</td>
<td>N</td>
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<tr>
<td>3</td>
<td>Female</td>
<td>56</td>
<td>Operation</td>
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<td>Positive OBT</td>
<td>3.5</td>
<td>The fourth layer, round, hypoechoic, halos, with anechoic areas</td>
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<td>7</td>
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<tr>
<td>4</td>
<td>Male</td>
<td>63</td>
<td>ESD</td>
<td>Anterior wall of the gastric antrum</td>
<td>Epigastric pain, heartburn</td>
<td>1.5</td>
<td>The fourth layer, round, hypoechoic, halos</td>
<td>N</td>
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<td>N</td>
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<tr>
<td>5</td>
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<td>65</td>
<td>ESD</td>
<td>Lesser curvature of the gastric antrum</td>
<td>Epigastric pain, heartburn</td>
<td>1.8</td>
<td>The fourth layer, round, hypoechoic, halos</td>
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<td>2</td>
<td>N</td>
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<tr>
<td>6</td>
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<td>58</td>
<td>ESD</td>
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<td>Heartburn</td>
<td>2.3</td>
<td>The fourth layer, round, hypoechoic, halos, small hyperechoic spots</td>
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<td>4</td>
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<tr>
<td>7</td>
<td>Female</td>
<td>54</td>
<td>ESD</td>
<td>Lesser curvature of the gastric antrum</td>
<td>Heartburn</td>
<td>2.1</td>
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<td>64</td>
<td>ESD</td>
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<td>2.2</td>
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<tr>
<td>9</td>
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<td>70</td>
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<td>1.3</td>
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<tr>
<td>10</td>
<td>Female</td>
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<td>Epigastric pain, heartburn</td>
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<td>The fourth layer, round, hypoechoic, halos</td>
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<tr>
<td>11</td>
<td>Female</td>
<td>55</td>
<td>Operation</td>
<td>Lesser curvature of the gastric antrum</td>
<td>Positive OBT</td>
<td>3.2</td>
<td>The fourth layer, round, hypoechoic, halos, with anechoic areas</td>
<td>Y</td>
<td>1</td>
<td>N</td>
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<tr>
<td>12</td>
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<td>74</td>
<td>Operation</td>
<td>Lesser curvature of the gastric antrum</td>
<td>Nausea</td>
<td>2.8</td>
<td>The fourth layer, round, hypoechoic, halos, with anechoic areas</td>
<td>N</td>
<td>0.5</td>
<td>N</td>
</tr>
</tbody>
</table>

ESD: Endoscopic submucosal dissection; OBT: Occult blood test; N: No; Y: Yes.

DISCUSSION

A gastric glomus tumor is an organ-like tumor composed of glomus cells. The glomus is a network of capillaries connecting arteries and veins. The terminal organ-like tumor is composed of a small entering artery, anastomotic vessel/original collecting vein, endovascular reticular structure and a capsule. According to its contraction mechanism, it regulates and controls the peripheral blood flow, so as to control blood pressure and body temperature[4]. The glomus cells are covered by thin-walled vessels rich in normal endothelial cells. Most of the tumor cells of the gastric glomus tumor have no atypia, occasionally some tumor cells have atypia, and even invade blood vessels. A few cases have metastasis, but most of them are benign. The recommended criteria for malignant gastric glomus tumor proposed by Folpe et al[5].
Figure 1 Endoscopic view of a well-circumscribed elevated lesion with normal overlying mucosa at the stomach antrum (arrow). A: Endoscopic ultrasound (EUS) characteristics of glomus tumors; B: Tumor originates from the fourth EUS layer (muscularis propria) and shows slight hypoechogenicity and a characteristic marginal halo around the tumor.

Figure 2 Computed tomography features of glomus tumors. Contrast-enhanced computed tomography image obtained during the plain scan, arterial phase, portal phase; homogeneous strong enhancement is seen in the gastric antrum lesion (arrow).

are: (1) Deep tumor location; (2) Tumor diameter more than 2 cm; (3) Moderate or high nuclear grade with mitotic image, ≥ 5 mitotic figures/50 hpf; and (4) Pathological mitosis. Tumor size, cell atypia, mitotic number and pathological mitosis were prognostic factors. Zhang reported a case of gastric glomus tumor with the largest diameter of 10 cm. Although the tumor was deeply located and the diameter was much larger than 2 cm, the tumor cells did not show mitosis, and it was a benign lesion[6]. In our study, the diameter of the gastric glomus tumors was less than or equal to 3.5 cm, the boundary was clear, there was no atypia and mitosis, and all were benign lesions.

Miettinen et al[7] reported 32 cases of gastrointestinal glomus tumor. Among them, 31 cases originated from the stomach and 1 case from the cecum. Gastric glomus tumors account for 1% of gastric mesenchymal tumors. A gastric glomus tumor is usually located in the muscularis propria or submucosa of the stomach. Patients usually have no specific symptoms, abdominal discomfort, upper abdominal pain, and/or upper gastrointestinal bleeding are relatively common clinical manifestations. The lesion is more common in people over 60 years old, and more common in women than in men. The average age in our group was 58.2 years. Seven patients mainly had epigastric discomfort, acid reflux and heartburn. The lesion was found by gastroscopy examination in 3 patients, and by fecal occult blood in 2 patients. The data showed slightly more female patients than male patients, and the lesions were located in the gastric antrum, which was basically consistent with the literature reports.

All cases in this study were identified by endoscopy, and endoscopic ultrasound was then performed. The common endoscopic manifestations are subepithelial lesions, regular shape of the mucosa bulge, smooth surface mucosa, color is the same as the surrounding mucosa[8]. Endoscopic ultrasound of a gastric glomus tumor is characterized by a hypoechogenic tumor, located in the third or fourth layer of the gastric wall, with an uneven internal echo and high echo spots. An acoustic halo at the edge can be seen[9]. We found that the lesions were round and hypoechogenic, with a lower echoic halo around them, and some with small hyperechoic spots, which were consistent with previous reports. However, the echo was slightly hypoechogenic, and all of them originated from the fourth layer, the muscularis propria. A slightly hypoechogenic echo
Figure 3 Photomicrograph of the tumor cells. A: Clusters of uniform, round cells around dilated blood vessels, cytoplasm was transparent or reddish, and the cells had no atypia or mitotic appearance; B: Positive smooth muscle actin staining of tumor cells, which shows a brown cytoplasmic stain; C: Positive h-caldesmon staining of tumor cells, which shows a brown cytoplasmic stain; D: Positive vimentin staining of tumor cells, which shows a brown cytoplasmic stain. Hematoxylin-eosin; original magnification: 200 ×.

was observed compared with the echogenicity of gastrointestinal stromal tumors. The gastrointestinal stromal tumor is the most common interstitial tumor in the stomach. Gastrointestinal stromal tumors are characterized by subepithelial lesions, which is one of the most important features in the differential diagnosis of gastric glomus tumors. Typical endoscopic ultrasound features are clear boundary, low echogenicity and even relative echogenicity, which originate from the fourth layer, mostly at the fundus of the stomach. The echo intensity of a gastric glomus tumor is generally higher than that of a gastrointestinal stromal tumor. Of course, a more accurate method is to measure the gray value or relative gray value (compared with the intrinsic muscular layer beside the lesion). It is difficult to distinguish gastric glomus tumor or gastrointestinal stromal tumor under endoscopy, which is characterized by subepithelial lesions with a mucosal bulge. A gastric glomus tumor is usually isolated, located in the antrum or the lower part of the stomach. Gastrointestinal stromal tumor is single, occasionally multiple, mostly found in the stomach body or fundus.

A contrast-enhanced CT scan of gastric glomus tumors shows significant enhancement in the arterial, portal, and delayed phases, nodular or homogeneous enhancement may be seen around the mass in the arterial phase, and there is still significant enhancement in the portal and delayed phases, indicating that the lesion enhances substantially and simultaneously with the abdominal aorta at the same level [2,8,10]. Histopathologically, there are many thin-walled and tortuous vessels within the tumor tissue with an abundant blood supply. This internal structure of the tumor determines the pathologic basis for the apparent enhancement seen on the contrast-enhanced CT scan, which is significantly higher than that of other benign tumors.

Microscopically, a gastric glomus tumor is composed of a vascular lumen surrounded by small round cells of a single morphology with centrally placed nuclei and inconspicuous nucleoli. Pleomorphism, atypia, mitosis and necrosis are rare in gastric glomus tumors[8,11]. Immunohistochemically, the tumor is positive for SMA, vimentin, actin, collagen IV, and laminin, and negative for CD117, dog-1, S100, CD34, desmin and negative for neuroendocrine markers such as chromogranin, synaptophysin, CD56, and CD57[11]. Most gastrointestinal stromal tumors are strongly positive for CD117 and dog-1, and immunohistochemistry of gastric glomus tumors show negative CD117 and dog-1 as a means of differential diagnosis. The morphology
and immunohistochemical features of the patients’ lesions in our group were consistent with those in the literature.

Gastric glomus tumors are mostly benign and most do not require treatment, so their preoperative diagnosis is especially important. Endoscopic ultrasound combined with abdominal enhanced CT can diagnose gastric glomus tumors, but the final definitive diagnosis requires immunohistochemistry of the pathology. In this case group, 7 patients were diagnosed with gastric glomus tumors by endoscopic ultrasound, which shows that with the accumulation of endoscopic ultrasound experience, the endoscopic ultrasound characteristics of gastric glomus tumors can increase the understanding of the disease and make the diagnosis less difficult.

**CONCLUSION**

Although gastric glomus tumors are relatively rare, typical gastric glomus tumors have characteristic changes on endoscopic ultrasound. These characteristic changes include gastric antrum location, originate from the fourth layer, solitary, round and slightly hypoechoic lesions with halos at the margins are typical manifestations. The diagnosis of a gastric glomus tumor can be made clinically based on the endoscopic ultrasound features and contrast-enhanced CT findings; however, confirmatory diagnosis is always by pathological examination.

**ARTICLE HIGHLIGHTS**

**Research background**
Gastric glomus tumors are relatively rare, and there is little knowledge regarding their endoscopic ultrasound findings.

**Research motivation**
Knowledge of the endoscopic characteristics of gastric glomus tumor is helpful in the diagnosis and differential diagnosis, and avoiding unnecessary surgery.

**Research objectives**
To summarize the endoscopic ultrasound characteristics of gastric glomus tumors confirmed by histopathology, and to verify the effectiveness of these characteristics in clinical cases.

**Research methods**
The records of 12 consecutive patients undergoing endoscopic ultrasonography (EUS) examination, surgery and pathology analysis for gastric glomus tumors in one institution from 2013-2020 were reviewed. Analysis of the EUS characteristics of gastric glomus tumors (such as tumor location, shape, size, echogenicity, homogeneity, margins, layer of origin, and so on) was carried out.

**Research results**
Ten cases had smooth hemispherical bulges of the mucosa, the same color as the surrounding mucosa, and 2 cases had small concave ulcers on the mucosa surface, leading to hemorrhage. The lesions were located in the anterior wall of the gastric antrum in 3 cases and in the lesser curvature of the gastric antrum in 9 cases. EUS showed that the lesions were round, ranging in maximum diameter from 10 mm to 35 mm with a mean diameter of 20 mm. The echo was slightly hypoechoic, and uniform, accompanied by small hyperechoic spots in some. There were small anechoic areas in the larger lesions, and halos with a lower echo. The outer boundary of the halo was clear, and the inner boundary was fuzzy. All of the lesions originated from the muscularis propria.

**Research conclusions**
Typical manifestations of gastric glomus tumors include gastric antrum location, originate from the fourth layer, solitary, round and slightly hypoechoic lesions with halos at the margins.
Research perspectives
A multi-center study, with an expanded sample size and prospective verification is required.

REFERENCES


Retrospective Study

Learning curves of robot-assisted pedicle screw fixations based on the cumulative sum test

Jie Yu, Qi Zhang, Ming-Xing Fan, Xiao-Guang Han, Bo Liu, Wei Tian

Abstract

BACKGROUND
In robot-assisted (RA) spine surgery, the relationship between the surgical outcome and the learning curve remains to be evaluated.

AIM
To analyze the learning curve of RA pedicle screw fixation (PSF) through fitting the operation time curve based on the cumulative summation method.

METHODS
RA PSFs that were initially completed by two surgeons at the Beijing Jishuitan Hospital from July 2016 to March 2019 were analyzed retrospectively. Based on the cumulative sum of the operation time, the learning curves of the two surgeons were drawn and fit to polynomial curves. The learning curve was divided into the early and late stages according to the shape of the fitted curve. The operation time and screw accuracy were compared between the stages.

RESULTS
The turning point of the learning curves from Surgeons A and B appeared in the 18th and 17th cases, respectively. The operation time [150 (128, 188) min vs 120 (105, 150) min, \( P = 0.002 \)] and the screw accuracy (87.50% vs 96.30%, \( P = 0.026 \)) of RA surgeries performed by Surgeon A were significantly improved after he completed 18 cases. In the case of Surgeon B, the operation time (177.35 ± 28.18 min vs 150.00 ± 34.64 min, \( P = 0.024 \)) was significantly reduced, and the screw accuracy (91.18% vs 96.15%, \( P = 0.475 \)) was slightly improved after the surgeon completed 17 RA surgeries.

CONCLUSION
After completing 17 to 18 cases of RA PSFs, surgeons can pass the learning phase of RA technology. The operation time is reduced afterward, and the screw accuracy shows a trend of improvement.
INTRODUCTION
Because spine surgeons cannot see deep tissues, they cannot directly apply preoperative designs to the operation[1]. In addition, their hand stability is often insufficient. Due to the special anatomical structure of the spine, the accuracy of freehand pedicle screw fixation (PSF) is not very high[2,5]. Inaccurate screw positions can cause serious complications, such as damage to blood vessels and nerves[4]. It is also sometimes necessary to repeatedly adjust the screw trajectory, which reduces fixation strength.

Surgical robots have been successfully used in many surgeries[5-7], and robotic systems have been developed to improve the accuracy of screw placement in spine surgery[8-12]. The advantage of surgical robots is that they allow doctors to see deep tissues through three-dimensional real-time navigation, and direct positioning after intraoperative planning.

Every new surgical technique has a unique learning curve[13]. The relationship between the learning curve and the outcome is an important indicator for evaluating a new surgical technique. It takes a certain process for the surgeon to be familiar with and master surgical robot technology. In robot-assisted (RA) spine surgery, the relationship between the surgical outcome and the learning curve remains to be evaluated.

In this study, the cumulative summation method was used to analyze the learning curve of RA PSF through fitting the operation's time curve.

MATERIALS AND METHODS
Study design
This study is a retrospective case control study of clinical data. The data come from the medical record management and imaging system of the Beijing Jishuitan Hospital. The learning curve of RA lumbar PSF was analyzed by measuring the operation time and screw accuracy of two of the hospital's surgeons.

Study objective
Patient inclusion criteria were: (1) over 18 years old; (2) diagnosed as having lumbar spinal stenosis or lumbar spondylolisthesis; and (3) having undergone RA single-segment minimally invasive pedicle screw surgery. Patient exclusion criteria were: (1) having undergone multi-segment surgery; (2) severe preoperative comorbidities; (3) abnormal coagulation function; and (4) requiring revision surgery.

This study retrospectively analyzed the first 45 cases for Surgeon A and the first 30 cases for Surgeon B of RA single-segment minimally invasive PSF at the Department of Spine Surgery of Beijing Jishuitan Hospital from July 2016 to March 2019. Prior to the first RA operation, these two surgeons had independently completed more than 200 freehand pedicle screw internal fixations. Both surgeons had accepted formal
training before starting the operation. This study was approved by the ethics review committee of Beijing Jishuitan Hospital. RA procedures were performed according to the guideline for thoracolumbar pedicle screw placement assisted by the TiRobot Orthopedic Robotic System [14] (Beijing TINAIV Medical Technology Co. Ltd.).

Sample size
The estimate of sample size is based on the operation time in the early and late stages of the learning curve. The formula for calculating the sample size is 

\[ n = 2 \left[ \sigma ^2 \left( z_{1-\alpha/2} + z_{1-\beta} \right) \right] / (\mu_A - \mu_B)^2 \]

According to previous research, \( \mu_A \) (pre-operation time) was assumed to be 180 min, \( \mu_B \) (post-operation time) was assumed to be 150 min, \( \sigma \) was 25, \( \alpha \) was 0.05, and \( \beta \) was 0.20. Based on these calculations, each group required at least 12 cases; that is, each surgeon needed to include at least 24 cases.

Outcome measurement
A postoperative computed tomography (CT) scan was performed to evaluate the accuracy of the pedicle screws. One surgeon and one radiologist who were blind to this study independently assessed the accuracy of the pedicle screws through the lumbar CT multiplanar reconstruction images. If the ratings of the two were inconsistent, the evaluation was then conducted by a senior surgeon. The pedicle screw position was graded according to the Gertzbein and Robbins grading scale [15] (screw accuracy = number of grade A screws/total number of screws \times 100\%).

The operation time was recorded as the time from the installation of the patient tracer to completion of the suture. According to the intraoperative use of gauze and suction, the surgeon, anesthesiologist, and nurse calculated the amount of blood loss. Surgery-related complications included postoperative infection, cerebrospinal fluid leakage, vessel damage, and nerve damage.

Cumulative sum analysis of the learning curve
According to the method proposed by Bokhari et al [16] and Song et al [17], the cumulative sum (CUSUM) method was used to determine the learning curve based on the operation time.

The CUSUM value of the first case was the operation time (\( T_1 \)) minus the mean operation time (\( M_T \)); the CUSUM value of the second case was the operation time of the second case (\( T_2 \)) minus the \( M_T \), then plus the CUSUM value of the first case. A recursive process continued until the last case, and the CUSUM value was zero at the end. Polynomial curve fitting was performed on CUSUM to calculate the model’s fit.

According to the shape of the fitted curve, when the curve changes from rising to falling, it indicated that the learning curve had been successfully crossed. We chose this time point to divide the surgeries of one surgeon into early stage and late stage. We then compared the results of screw accuracy, operation time, blood loss, and complications in the early and late stages.

Statistical analysis
Statistical analysis was performed using IBM SPSS v 24.0 software). The categorical variables were expressed by frequencies (percentage), and the \( \chi^2 \) test or Fisher’s exact test was used for comparison between groups. The Shapiro-Wilk test was used to test the normalcy of continuous variables. Normally distributed continuous variables were represented by the mean ± SD, and non-normally distributed continuous variables were represented by the median (25% quantile, 75% quantile). The Student’s \( t \)-test was used to compare between groups of normally distributed data, and the Mann-Whitney U test was used to compare between groups of non-normally distributed data. A \( P \) value < 0.05 was considered statistically significant.

RESULTS

Learning curve for Surgeon A
Surgeon A completed 45 RA PSFs. Patients included 24 males and 21 females, with an average age of 60.38 years. Surgeon A placed a total of 180 pedicle screws. Postoperative CT showed that the accuracy of pedicle screws was 92.78%. The operation time was 130 (120, 165) min. The intraoperative blood loss was 100 (80, 200) mL. There were no perioperative complications related to the use of the robot. The operation time showed a downward trend as the number of surgical cases increased (Figure 1A).
The fitting model formula of Surgeon A’s learning curve was CUSUM\(_T\) = 0.014X^3 - 1.769X^2 + 51.305X + 45.437 (X represents the case order). The goodness of fit was \(R^2 = 0.935\). According to the shape of the learning curve for Surgeon A, the learning curve for RA surgery can be divided into two stages (Figure 2A). The first 18 cases were in the early stage (CUSUM\(_T\) fitting curve continued to rise, representing the learning of surgical technique), and the 19\(^{th}\) to 45\(^{th}\) cases in the late stage (CUSUM\(_T\) fitting curve continued to decline, representing the mastery of surgical technique).

The comparison of screw accuracy, operation time, and intraoperative blood loss in the two stages of Surgeon A’s learning curve is shown in Table 1. The operation time in the late stage was shorter than that in the early stage [150 (128, 188) min \(vs\) 120 (105, 150) min, \(P = 0.002\)]. The screw accuracy in the late stage was higher than that in the early stage (87.50% \(vs\) 96.30%, \(P = 0.026\)). There was no statistically significant difference in intraoperative blood loss between the two stages [100 (88, 200) mL \(vs\) 100 (80, 100) mL, \(P = 0.186\)].

**Learning curve for Surgeon B**

Surgeon B completed 30 RA PSFs. Patients included 14 males and 16 females, with an average age of 57.57 years. Surgeon B placed a total of 120 pedicle screws. Postoperative CT showed that the accuracy of pedicle screws was 93.33%. The operation time was 165.50 ± 33.54 min (Figure 1B). The intraoperative blood loss was 200 (100, 200) mL. There were no perioperative complications related to the use of the robot.

The fitting model formula of Surgeon B’s learning curve was CUSUM\(_T\) = -0.024X^3 + 0.405X^2 + 7.642X + 99.455 (X represents the case order). The goodness of fit was \(R^2 = 0.835\). According to the shape of the learning curve of Surgeon B, the learning curve of

![Figure 1](https://example.com/)
RA surgery can be divided into two stages (Figure 2B). The first 17 cases were in the early stage (CUSUM\textsubscript{T} fitting curve continued to rise, representing learning of the surgical technique), and the 18th to 30th cases in the late stage (CUSUM\textsubscript{T} fitting curve continued to decline, representing mastery of the surgical technique).

The comparison of the screw accuracy, operation time, and intraoperative blood loss in the two stages of Surgeon B’s learning curve is shown in Table 2. The operation time during the late stage was shorter than that during the early stage (177.35 ± 28.18 min vs 150.00 ± 34.64 min, \(P = 0.024\)). The screw accuracy in the late stage (96.15%) was slightly higher than that in the early stage (91.18%), but the difference was not statistically significant (\(P = 0.475\)). There was no statistically significant difference in intraoperative blood loss between the two stages [200 (100, 200) mL vs 100 (100, 200) mL, \(P = 0.095\)].

### Table 1 Comparison of the two stages in Surgeon A’s learning curve

<table>
<thead>
<tr>
<th>Variables</th>
<th>Early stage</th>
<th>Late stage</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of surgeries</td>
<td>18</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Number of screws</td>
<td>72</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Screw accuracy</td>
<td>87.50%</td>
<td>96.30%</td>
<td>0.026</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>150 (128, 188)</td>
<td>120 (105, 150)</td>
<td>0.002</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>100 (88, 200)</td>
<td>100 (80, 100)</td>
<td>0.186</td>
</tr>
</tbody>
</table>
Table 2 Comparison of the two stages in Surgeon B’s learning curve

<table>
<thead>
<tr>
<th>Variables</th>
<th>Early stage</th>
<th>Late stage</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of surgeries</td>
<td>17</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Number of screws</td>
<td>68</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Screw accuracy</td>
<td>91.18%</td>
<td>96.15%</td>
<td>0.475</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>177.35 ± 28.18</td>
<td>150.00 ± 34.64</td>
<td>0.024</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>200 (100, 200)</td>
<td>100 (100, 200)</td>
<td>0.095</td>
</tr>
</tbody>
</table>

DISCUSSION

Spine surgery requires surgeons to have sufficient professional knowledge, good planning ability, and meticulous surgical techniques. The training process for spine surgeons is usually long and arduous. Only after years of professional learning and clinical practice can spine surgeons accurately and efficiently complete preoperative planning, exposure, nerve decompression, internal fixation, and fusion[18]. Therefore, any techniques that can improve the safety, accuracy, and efficiency and shorten the learning curve of spine surgery will be welcome.

The use of surgical robots aims to make up for the surgeon’s physiological shortcomings in vision and operation. Their emergence has brought about significant improvements in spinal fixation. With the development of image navigation technology, a variety of surgical robot systems have been developed to deal with the problems encountered in spine surgery, especially for the accurate placement of internal fixation[8,12]. The positioning of surgical robots is accurate and stable, which can improve the accuracy and safety of PSF in minimally invasive spine surgery[9]. Studies have shown that the accuracy of pedicle screw placement in RA lumbar spine surgery can reach about 95%, which is much higher than the accuracy of freehand pedicle screw placement[19,20]. However, we still do not have enough knowledge on the learning curve of RA PSF.

Looking at RA surgery of other disciplines, we see that the learning curve of RA urological surgery is significantly shorter than that of freehand surgery[21]. Surgeons can master surgical techniques after completing 50 RA gynecological surgeries. Surgeons can also master surgical techniques after completing 16 to 32 cases of RA cholecystectomy. The learning stage of RA gastric bypass surgery can be passed after completing 14 cases[22,23].

As an emerging technology, RA spine surgery has a specific learning curve, which is mainly reflected in the operation time and screw accuracy[18,24-26]. This study included RA single-segment minimally invasive lumbar spine surgeries performed separately by two surgeons, and evaluated the learning curve of RA PSF. The turning points of the learning curve of surgeons A and B were in the 18th and 17th cases, respectively. The screw accuracy and operation time in the late stage of the learning curve were improved compared with the early stage, indicating that the surgeon can master the surgical technique of RA lumbar spine surgery after completing 17 to 18 cases. Therefore, problems such as long operation time and insufficient screw accuracy in the initial application of RA lumbar spine surgery would be gradually solved after surgeons completed a certain number of surgeries.

Hu et al[25] studied the learning curve for Mazor Robotics’ Renaissance RA pedicle screw placement. They analyzed the results of the first 150 RA pedicle screw placements performed by one surgeon. They divided 150 surgeries into five groups of 30. The success rate of RA surgery in groups 1 to 5 were 82%, 93%, 91%, 95%, and 93%, respectively. The inaccurate rate of screws in groups 1 to 5 were 0.8%, 0.3%, 1.4%, 0.8%, and 0%, respectively. Therefore, they defined the first 30 cases as the learning curve of RA spine surgery[25]. Siddiqui et al[24] analyzed the learning curve of the ExcelsiusGPS® RA spine surgery. After a clear learning curve of 30 screws being placed, the screw accuracy improved. The study of Kam et al[27] showed that the learning curve of RA pedicle screw placement is very short. The study of Urakov et al[18] showed that the operation time of RA surgery decreased with the increase in the number of cases. In addition, RA pedicle screw placement can reduce the technical training required for successful screw placement[18]. Schatlo et al[26] found that the inaccurate rate of screws was higher in the 10th to 20th cases in the SpineAssist RA spine surgery. Hyun et al[28] found that the average insertion time per screw was reduced from 5.5 min in the first 15 cases to 4.0 min in the subsequent 15 cases and that the...
average fluoroscopy time per screw was reduced from 4.1 s to 2.9 s. The study of Kim et al.\textsuperscript{29} showed that the screw insertion time was reduced from 14.9 min in the first eight cases to 9.3 min in the subsequent 29 cases and that the fluoroscopy time was reduced by 30\% after the eighth case.

The CUSUM method was originally used for quality control in the industrial field, and was subsequently introduced into the medical field to analyze a surgery’s learning curve\textsuperscript{30}. CUSUM analysis is currently widely used to evaluate the learning curve of new surgeries, such as RA rectal resection\textsuperscript{31}, laparoscopic hepatectomy\textsuperscript{32}, and laparoscopic pancreaticoduodenectomy\textsuperscript{33}. Kim et al.\textsuperscript{20} believe that the CUSUM method can be effective in studying the results of spine surgery. CUSUM analysis converts the original data into continuous cumulative data that deviate from the average value, which can display data trends that cannot be discerned by other methods. In this study, the turning point of the learning curve cannot be derived from the original data of the operation time. However, the CUSUM fitting curve of the operation time can be used to divide the learning process of RA surgery into two stages, according to the apex of the curve. The CUSUM\textsubscript{T} in the early stage of the curve showed an upward trend, which represents the learning of the surgical technique. The CUSUM\textsubscript{T} in the late stage of the curve showed a downward trend, which represents the mastery of the surgical technique. Through CUSUM analysis, it was found that the learning stages of Surgeons A and B were the first 18 cases and the first 17 cases, respectively.

This study has several limitations. First, the sample size of this study was limited to 75 surgeries performed by two surgeons. Secondly, these two surgeons came from the leading orthopedic hospital in China. Whether other surgeons with less experience can obtain the same learning curve remains to be seen.

**CONCLUSION**

This paper retrospectively studied the RA minimally invasive single-segment PSF performed by two surgeons, and analyzed the learning curve of RA PSF using the CUSUM method. After completing 17 to 18 cases of RA lumbar PSF, surgeons can pass the learning phase of RA technology. Operation time is reduced, and screw accuracy shows a trend of improvement.

**ARTICLE HIGHLIGHTS**

**Research background**

Every new surgical technique has a unique learning curve. The relationship between the learning curve and the outcome is an important indicator for evaluating a new surgical technique. It takes a certain process for the surgeon to be familiar with and master surgical robot technology.

**Research motivation**

In robot-assisted (RA) spine surgery, the relationship between the surgical outcome and the learning curve remains to be evaluated.

**Research objectives**

This study aimed to analyze the learning curve of RA pedicle screw fixation (PSF) through fitting the operation’s time curve.

**Research methods**

Based on the cumulative sum of the operation time, the learning curves of the two surgeons were drawn and fit to polynomial curves. The learning curve was divided into the early and late stages according to the shape of the fitted curve. The operation time and screw accuracy were compared between the stages.

**Research results**

The turning point of the learning curves from Surgeons A and B appeared in the 18\textsuperscript{th} and 17\textsuperscript{th} cases, respectively.
Research conclusions
After completing 17 to 18 cases of RA PSFs, surgeons can pass the learning phase of RA technology. The operation time is reduced afterward, and the screw accuracy shows a trend of improvement.

Research perspectives
These two surgeons came from the leading orthopedic hospital in China. Whether other surgeons with less experience can obtain the same learning curve remains to be seen.

REFERENCES


Retrospective Study

Value of GRACE and SYNTAX scores for predicting the prognosis of patients with non-ST elevation acute coronary syndrome

Xiao-Feng Wang, Ming Zhao, Fei Liu, Guo-Rong Sun

ORCID number: Xiao-Feng Wang 0000-0002-6652-606X; Ming Zhao 0000-0002-7007-3630; Fei Liu 0000-0003-1473-7567; Guo-Rong Sun 0000-0002-8348-7410.

Author contributions: Wang XF, Zhao M, Fei Liu F, and Sun GR contributed to the manuscript writing, revising; All authors confirmed the revised version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Cangzhou Central Hospital Institutional Review Board.

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: There is no conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

Specialty type: Cardiac and Cardiovascular Systems

Provenance and peer review: Unsolicited article; Externally peer reviewed

Abstract

BACKGROUND
GRACE and SYNTAX scores are important tools to assess prognosis in non-ST-elevation acute coronary syndrome (NSTE-ACS). However, there have been few studies on their value in patients receiving different types of therapies.

AIM
To explore the value of GRACE and SYNTAX scores in predicting the prognosis of patients with NSTE-ACS receiving different types of therapies.

METHODS
The data of 386 patients with NSTE-ACS were retrospectively analyzed and categorized into different groups. A total of 195 patients who received agents alone comprised the medication group, 156 who received medical therapy combined with stents comprised the stent group, and 35 patients who were given agents and underwent coronary artery bypass grafting (CABG) comprised the CABG group. General information was compared among the three groups. GRACE and SYNTAX scores were calculated. The association between GRACE and SYNTAX scores and the occurrence of major adverse cardiovascular events (MACEs) was analyzed. Pearson’s correlation analysis was used to determine the factors influencing prognosis in patients with NSTE-ACS. Univariate and multivariate analyses were conducted to analyze the predictive value of GRACE and SYNTAX scores for predicting prognosis in patients with NSTE-ACS using the Cox proportional-hazards model.

RESULTS
The incidence of MACE increased with the elevation of GRACE and SYNTAX scores (all P < 0.05). The incidence of MACE was 18.5%, 36.5%, and 42.9% in the medication group, stent group, and CABG group, respectively. By comparison, the incidence of MACE was significantly lower in the medication group than in the stent and CABG groups (all P < 0.05). The incidence of MACE was 6.2%, 28.0%...
Wang XF et al. Value of GRACE and SYNTAX scores in acute coronary syndrome

INTRODUCTION

Acute coronary syndrome (ACS), mainly comprising ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation acute coronary syndrome (NSTE-ACS), is a common cardiac disease. Usually these patients present as acute coronary insufficiency and unstable plaque caused by coronary atherosclerosis[1-3]. Rapid progression of NSTE-ACS may lead to serious complications. Thus, supplementary aids are needed to estimate the prognosis of patients with NSTE-ACS[3,4]. Definite diagnosis and accurate risk stratification are essential for the subsequent treatment of NSTE-ACS. Therapies vary in NSTE-ACS patients with different major adverse cardiovascular event (MACE) risk[5,6]. Currently, the risk assessment model GRACE score is used to predict the prognosis of patients with NSTE-ACS. However, it does not carry adequate weight in patients with NSTE-ACS.

GRACE and SYNTAX scores are widely used in clinical practice targeting different risk scores. However, it does not provide adequate weight in the risk stratification of NSTE-ACS patients. The presented study evaluated the predictive value of GRACE and SYNTAX scores for MACE incidence in NSTE-ACS patients. It is assumed that the results of this study can provide promising guidance for the management of NSTE-ACS patients.

Key Words: GRACE score; SYNTAX score; Non-ST elevation acute coronary syndrome; Prognosis

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DOI: https://dx.doi.org/10.12998/wjcc.v9.i33.10143
Wang XF et al. Value of GRACE and SYNTAX scores in acute coronary syndrome

not take the results of patients' coronary angiography into consideration[7-9]. Similarly, SYNTAX score is one of the most promising tools for assessment of coronary artery[10]. It is used to stratify risk of patients with NSTE-ACS based on the complexity of coronary artery lesions. To be specific, it can comprehensively assess anatomic features of coronary artery lesions ranging from site of lesion and complexity of severity to bifurcation, calcification, and compensation. This study discusses the value of GRACE and SYNTAX scores for predicting the prognosis of patients with NSTE-ACS.

MATERIALS AND METHODS

General information
A retrospective analysis was conducted in 386 patients with NSTE-ACS admitted to Cangzhou Central Hospital (Hebei Province, China) from March 2017 to December 2020. They were categorized into three groups based on the treatment they received. Of them, 195 patients receiving agents were enrolled in a medication group, 126 patients receiving agents plus stent treatment were enrolled in a stent group, and 35 patients who were administrated with agents and underwent coronary artery bypass grafting (CABG) were enrolled in a CABG group. Enrollment criteria were as follows: patients aged 18-years-old to 75-years-old, diagnosis of NSTE-ACS confirmed by clinical symptoms and relevant examination, and single- or multi-vessel stenosis > 50% validated by coronary angiography. Exclusion criteria included: patients with poor physical performance; patients with a previous history of myocardial infarction; patients with comorbidities of heart failure, myocardiitis, or myocardialpathy; patients with arrhythmia; patients with severe kidney, liver, and lung diseases; patients with an infection, malignant tumors, or severe anemia; and pregnant women. Baseline demographic and clinical characteristics data are summarized in Table 1.

Research methodology
Patients received treatment based on their angiographic features of coronary lesions. All patients were administered enteric aspirin oral 300 mg (Approval No. J20171021; Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA) and clopidogrel 300 mg (approval No. J20180029; Sanofi (Hangzhou) Pharmaceuticals Co. Ltd., Hangzhou, China) for secondary prevention of cardiovascular diseases. Patients in the stent group underwent coronary angiography and conventional stent implantation surgery. Patients in the CABG group were given medicine and CABG surgery.

Baseline data were collected from the three groups including gender, age, history of diseases (hypertension, diabetes, hyperlipidemia), unstable angina or acute non-ST-elevation myocardial infarction. GRACE and SYNTAX scores were calculated. Data on patient prognosis were obtained through telephone follow-up or clinical visits. Hospitalization and coronary angiography were advised for patients with symptoms such as typical chest pain or ischemia. The end points of follow-up were the occurrence of major adverse cardiovascular events (MACEs) after the treatments including cardiac death, non-fatal myocardial infarction, and target lesion revascularization. MACE was estimated. Patients were followed-up for 46 mo.

Evaluation criterion
The incidence of MACE was investigated in patients with different GRACE scores receiving different treatments. According to the GRACE score, patients were divided into tertiles as low- (0 to 88 points), intermediate- (89 to 117 points), and high (≥ 118 points)-risk groups. Also, the incidence of MACE was examined in patients with different SYNTAX scores receiving different treatments. According to the SYNTAX score, patients were sorted into tertiles as low- (0 to 22 points), intermediate- (23 to 32 points), and high (≥ 33 points)-risk groups. Factors influencing NSTE-ACS were analyzed.

Statistical analysis
SPSS18.0 software was used for the statistical analyses in this study. The logged data were rechecked and analyses were conducted after the outliers were deleted and removed. Measurement data are expressed as the mean ± SD, and inter-group differences were compared using the Student’s t-test. The statistical relationship between the two variables was determined using Spearman’s rank correlation coefficient. Count data are expressed as the frequency and percentage. Kruskal-Wallis
Table 1 Baseline characteristics of patients with non-ST-elevation acute coronary syndrome, n = 386

<table>
<thead>
<tr>
<th>Items</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Age in yr, mean ± SD</td>
<td>61.25 ± 4.09</td>
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<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>243 (63.0)</td>
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<tr>
<td>Female</td>
<td>143 (37.0)</td>
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<td>Unstable angina</td>
<td>327 (84.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>262 (69.4)</td>
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<tr>
<td>Diabetes</td>
<td>95 (24.6)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>62 (16.1)</td>
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<tr>
<td>Major adverse cardiovascular events</td>
<td>108 (28.0)</td>
</tr>
<tr>
<td>Recurrent angina</td>
<td>115 (29.8)</td>
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<tr>
<td>NYHA class I or above</td>
<td>17 (4.4)</td>
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<tr>
<td>Nonfatal recurrent myocardal infarction</td>
<td>8 (2.1)</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>22 (5.7)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Number of stents</td>
<td>247 (64.0)</td>
</tr>
<tr>
<td>CABG</td>
<td>35 (9.1)</td>
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test was used for multi-group comparisons. Cox proportional-hazards model was used for univariate and multivariate analyses. P < 0.05 was considered statistically significant. The two-tailed test was performed.

RESULTS

The incidence of MACE increased with the elevated scores of GRACE and SYNTAX (all P < 0.05; Table 2). The rates of MACE were 18.5%, 36.5%, and 42.9% in the medication group, stent group, and CABG group, respectively. The MACE rate was significantly lower in the medication group than in the stent and CABG groups (all P < 0.05). However, the difference in MACE rate between the stent group and CABG group was not significant (P > 0.05).

The rates of MACE were 6.2%, 28.0%, and 40.0% in patients receiving medication, stent, and CABG, respectively, in the low GRACE score tertile group (all P < 0.05; Table 3). The rates of MACE were 31.0%, 30.3%, and 42.9% in patients receiving medication, stent, and CABG, respectively, in the intermediate GRACE score tertile group (all P < 0.05). The rates of MACE were 16.9%, 46.2%, and 43.8% in patients receiving medication, stent, and CABG, respectively, in the high GRACE score tertile group (all P < 0.05).

The rates of MACE were 16.2%, 35.4%, and 60.0% in patients receiving medication, stent, and CABG, respectively, in the low SYNTAX score tertile group (all P < 0.05); 37.5%, 40.9%, and 41.7%, respectively, in the intermediate SYNTAX score tertile group (all P > 0.05); and 50.0%, 75.0%, and 25.0%, respectively, in the high SYNTAX score tertile group (all P < 0.05; Table 4).

Univariate Cox regression analyses showed that GRACE (hazard ratio [HR] = 1.212, 95% confidence interval [CI]: 1.083 to 1.176; P < 0.05) and SYNTAX (HR = 1.160, 95% CI: 1.104 to 1.192; P < 0.05) scores were factors contributing to the risk of MACE (all P < 0.05). Multivariate analyses of GRACE and SYNTAX scores revealed that GRACE (HR = 1.091, 95% CI: 1.015 to 1.037; P < 0.05) and SYNTAX (HR = 1.031, 95% CI: 1.076 to 1.143; P < 0.05) scores were independent factors influencing MACE (all P < 0.05).
Table 2 Incidence of major adverse cardiovascular events in patients with different GRACE and SYNTAX scores, n = 386

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>MACE, n</th>
<th>Incidence of MACE, %</th>
<th>Hc value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRACE scores (points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk group (0-88)</td>
<td>95</td>
<td>13</td>
<td>13.7</td>
<td>7.398</td>
<td>0.031</td>
</tr>
<tr>
<td>Intermediate risk group (89-117)</td>
<td>151</td>
<td>48</td>
<td>31.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk group (≥ 118)</td>
<td>140</td>
<td>47</td>
<td>33.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYNTAX scores (points)</td>
<td></td>
<td></td>
<td></td>
<td>4.381</td>
<td>0.042</td>
</tr>
<tr>
<td>Low risk group (0-22)</td>
<td>330</td>
<td>85</td>
<td>25.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk group (23-32)</td>
<td>42</td>
<td>17</td>
<td>40.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk group (≥ 33)</td>
<td>14</td>
<td>6</td>
<td>42.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td>8.123</td>
<td>0.021</td>
</tr>
<tr>
<td>Medication group</td>
<td>195</td>
<td>36</td>
<td>18.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent group</td>
<td>156</td>
<td>57</td>
<td>36.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG group</td>
<td>35</td>
<td>15</td>
<td>42.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>386</td>
<td>108</td>
<td>28.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hc value: The test statistic for the Kruskal-Wallis test; MACE: Major adverse cardiovascular events.

Table 3 Major adverse cardiovascular events rate in patients with different GRACE risk scores receiving different treatments, n (%)  

<table>
<thead>
<tr>
<th>GRACE risk scores (points)</th>
<th>n</th>
<th>Medication group</th>
<th>Stent group</th>
<th>CABG group</th>
<th>Overall MACE rate</th>
<th>Hc value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk group (0-88)</td>
<td>95</td>
<td>65 (6.2)</td>
<td>25 (28.0)</td>
<td>5 (40.0)</td>
<td>13 (13.7)</td>
<td>5.231</td>
<td>0.041</td>
</tr>
<tr>
<td>Intermediate risk group (89-117)</td>
<td>151</td>
<td>71 (31.0)</td>
<td>66 (30.3)</td>
<td>14 (64.2)</td>
<td>48 (31.8)</td>
<td>2.742</td>
<td>0.086</td>
</tr>
<tr>
<td>High risk group (≥ 118)</td>
<td>140</td>
<td>59 (16.9)</td>
<td>65 (46.2)</td>
<td>16 (43.8)</td>
<td>47 (33.6)</td>
<td>5.381</td>
<td>0.040</td>
</tr>
<tr>
<td>Total</td>
<td>386</td>
<td>195 (18.5)</td>
<td>156 (36.5)</td>
<td>35 (42.9)</td>
<td>108 (28.0)</td>
<td>4.412</td>
<td>0.044</td>
</tr>
</tbody>
</table>

CABG: Coronary artery bypass grafting; Hc value: The test statistic for the Kruskal-Wallis test; MACE: Major adverse cardiovascular events.

Table 4 Major adverse cardiovascular events rate in patients with different SYNTAX risk scores receiving different treatments, n (%)  

<table>
<thead>
<tr>
<th>SYNTAX risk scores (points)</th>
<th>n</th>
<th>Medication group</th>
<th>Stent group</th>
<th>CABG group</th>
<th>Overall MACE rate</th>
<th>Hc value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk group (0-22)</td>
<td>330</td>
<td>185 (16.2)</td>
<td>130 (35.4)</td>
<td>15 (60.0)</td>
<td>85 (25.8)</td>
<td>12.213</td>
<td>0.001</td>
</tr>
<tr>
<td>Intermediate risk group (23-32)</td>
<td>42</td>
<td>8 (37.5)</td>
<td>9 (40.9)</td>
<td>12 (41.7)</td>
<td>17 (40.5)</td>
<td>1.984</td>
<td>0.214</td>
</tr>
<tr>
<td>High risk group (≥ 33)</td>
<td>14</td>
<td>2 (50.0)</td>
<td>3 (75.0)</td>
<td>8 (25.0)</td>
<td>6 (42.9)</td>
<td>8.432</td>
<td>0.014</td>
</tr>
<tr>
<td>Total</td>
<td>386</td>
<td>195 (18.5)</td>
<td>156 (36.5)</td>
<td>35 (42.9)</td>
<td>108 (28.0)</td>
<td>4.412</td>
<td>0.044</td>
</tr>
</tbody>
</table>

CABG: Coronary artery bypass grafting; Hc value: the test statistic for the Kruskal-Wallis test; MACE: major adverse cardiovascular events.

DISCUSSION

The incidence of NSTE-ACS is high, which involves about 75% of patients with ACS. Due to the occlusion of multiple coronary arteries and the rapid disease progression, the management of patients with ACS should be performed targeting the stratified risks. The GRACE score is one of the most common risk scoring systems in clinical practice to risk stratify ACS patients based on real clinical symptoms and basic patient data; however, it does not take into account ACS. The SYNTAX score is
a tool to risk stratify ACS patients based on anatomic features of coronary artery lesions. Nevertheless, it does not analyze clinical features and cannot realize the general characteristics of patients[17-22]. Therefore, this study discussed the significance of GRACE combined with SYNTAX scores for the assessment of prognosis of NSTE-ACS.

The findings of this study showed that the incidence of MACE increased with the elevated scores of GRACE and SYNTAX (P < 0.05). The incidence of MACE was 18.5%, 36.5%, and 42.9% in the medication group, stent group, and CABG group, respectively, with the medication group lower than the stent and CABG groups (P < 0.05). Moreover, the incidence of MACE varied in patients receiving different treatments, particularly in the medication group. The incidence of MACE was 6.2%, 28.0%, and 40.0% in patients with a low GRACE risk score, and 16.9%, 46.2%, and 43.8% in patients with a high GRACE risk score in the medication group, stent group, and CABG group, respectively (all P < 0.05). This suggests that it is feasible to use GRACE score for the risk stratification of patients with NSTE-ACS. In terms of SYNTAX score, the incidence of MACE was 16.2%, 35.4%, and 60.0% in patients with a low risk score and 50.0%, 75.0%, and 25.0% in patients with a high risk score in the medication group, stent group, and CABG group, respectively (all P < 0.05). These data indicate that the SYNTAX score can effectively predict the prognosis of NSTE-ACS by stratifying patients into high-, intermediate-, and low-risk groups based on which appropriate care can be given.

Meanwhile, univariate and multivariate Cox analyses showed that GRACE and SYNTAX scores were independent predictors of the occurrence of MACE (all P < 0.05). GRACE and SYNTAX scores have significant predictive value for the assessment of prognosis of NSTE-ACS. In the current study, no significant difference was discovered in long-term prognosis between patients with an intermediate GRACE risk score and patients with an intermediate SYNTAX risk score. It can be attributed to different treatments based on different patient conditions or relevant factors influencing the treatment such as results bias caused by treatment switching. As a limitation to this study, the limited number of cases in the single-center retrospective study may be not powered enough to completely reflect the real-life situation. Multicenter large sample long-term follow-up studies are warranted in the future to further demonstrate these findings.

**CONCLUSION**

In summary, GRACE and SYNTAX scores have significant value for assessing prognosis in NSTE-ACS.

**ARTICLE HIGHLIGHTS**

**Research background**
The GRACE score and SYNTAX score are established clinical risk stratification tools for acute coronary syndromes. However, they were seldomly discussed in patients with non-ST elevation acute coronary syndrome (NSTE-ACS) receiving different types of therapies.

**Research motivation**
Correct diagnosis and early treatment are critical to improve clinical outcomes in patients with NSTE-ACS. Risk stratification may be helpful for the planning of treatment strategy.

**Research objectives**
This study tested the ability of the GRACE and SYNTAX scores to predict outcomes in patients with NSTE-ACS.

**Research methods**
Patients with NSTE-ACS who received agents for secondary prevention of cardiovascular diseases, who received medical therapy plus stents or who underwent coronary artery bypass graft (CABG) surgery were enrolled in the study. GRACE and SYNTAX scores were estimated, and patients in the three groups were further
subdivided into GRACE and SYNTAX score tertile groups. Data on prognosis and outcomes of these patients were collected over a 46 mo follow-up period. The incidence of major adverse cardiovascular events (MACEs) was calculated. The relationship between GRACE and SYNTAX scores and prognosis and outcomes of this population were analyzed and the abilities of GRACE and SYNTAX scores to predict prognosis and outcomes especially MACE were tested.

**Research results**
The incidence of MACE was lower in patients having low and high GRACE and SYNTAX scores who received agents than in patients who underwent stent placement or CABG. Multivariate Cox regression analyses revealed that GRACE and SYNTAX scores were independent factors influencing the occurrence of MACE in patients with NSTE-ACS.

**Research conclusions**
GRACE and SYNTAX scores are useful in predicting MACE in risk stratifying patients with NSTE-ACS who undergo CABG.

**Research perspectives**
The findings need further studies with a larger number of participants to be confirmed.

**REFERENCES**


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**DOI:** https://www.wjgnet.com/10149/November_26_2021/Volume_9/Issue_33


22 **Chen X**, Guo Y, Lai L, Zhang S, Li Z. Intracoronary and peripheral blood levels of TNF-like Cytokine 1A (TL1A) in patients with acute coronary syndrome. *Medicine (Baltimore)* 2020; **99**: e20305 [PMID: 32481400 DOI: 10.1097/MD.00000000000020305]
Effectiveness of enhanced recovery after surgery in the perioperative management of patients with bone surgery in China

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Author contributions: Zhao LY and Zhu WN were responsible for conceptualization, data analysis, methodology, and wrote the original draft; Liu XT, Zhao ZL, Gu R and Ni XM were responsible for data collection, visualization and software; Deng R, Li XY and Gao MJ were responsible for validation, reviewing and editing the manuscript; Zhu WN was responsible for supervision; all authors have read and approved the final version.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Second Affiliated Hospital of Xi’an Jiaotong University.

Informed consent statement: Written informed consent was provided for all participants.

Conflict-of-interest statement: The authors have no conflicts of

Abstract

BACKGROUND

Enhanced recovery after surgery (ERAS) was introduced in China in 2007. Over time, the scope of ERAS has expanded from abdominal surgery to orthopedics, urology and other fields. Continuous development and research has contributed to progress of ERAS in China. In 2019, to promote the application of ERAS in bone tumor surgery, we formed the “Consensus of Experts on Perioperative Management of Accelerated Rehabilitation in Major Surgery of Bone Tumors in China”.

AIM

To evaluate the effect of enhanced recovery after bone tumor surgery in perioperative management in China.

METHODS

One hundred and seven patients who underwent bone tumor surgery at the Second Affiliated Hospital of Xi’an Jiaotong University between May 2019 and April 2021 were randomized into a study group (53 cases) and a control group (54 cases). The study group adopted the ERAS protocol and the control group adopted conventional care. Main outcome measures included postoperative length of stay (LOS), postoperative complications, mortality, and 30-d readmission rates. Secondary outcomes included postoperative visual analog scale (VAS) score of pain, number of blood transfusions, drainage volume in 24 h after operation, patient satisfaction 30 d after discharge, VAS score at 30 d after discharge, and daily standing walking time.

RESULTS
There were no significant differences in the baseline data, clinical features and surgical site between the two groups. The LOS in the study group with the ERAS protocol was 7.72 ± 3.34 d compared with 10.28 ± 4.27 d in the control group who followed conventional care. The incidence of postoperative nausea and vomiting (PONV) in the study group was 19% and 37% in the control group. The VAS scores of pain on postoperative day 1 (POD1) and POD3 in the study group were 4.79 ± 2.34 and 2.79 ± 1.53 compared with 5.28 ± 3.27 and 3.98 ± 2.27 in the control group. The drainage volume in 24 h after the operation was 124.36 ± 23.43 mL in the study group and 167.43 ± 30.87 mL in the control group. The number of blood transfusions in the study group was also lower. The patient satisfaction rate was higher in the study group than in the control group.

CONCLUSION
The ERAS protocol in the perioperative period of bone tumor surgery can decrease LOS, PONV, and postoperative pain, blood transfusion and 24-h drainage, improve patient satisfaction and accelerate recovery.

Key Words: Enhanced recovery after surgery; Bone tumor surgery; Perioperative management; Effect evaluation; Clinical application

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Core Tip: In 2019, the consensus of Chinese experts was proposed for perioperative management of accelerated rehabilitation in major surgery of bone tumors. In order to form a realistic, feasible enhanced recovery after surgery (ERAS) concept, the clinical effect of the ERAS protocol was evaluated retrospectively. The ERAS protocol can shorten hospital stay, reduce the incidence of postoperative nausea and vomiting, reduce postoperative pain, postoperative blood transfusion and postoperative 24-h drainage, and improve patient satisfaction and accelerate recovery. It is worth continuing to improve and popularize ERAS in China.

Citation: Zhao LY, Liu XT, Zhao ZL, Gu R, Ni XM, Deng R, Li XY, Gao MJ, Zhu WN. Effectiveness of enhanced recovery after surgery in the perioperative management of patients with bone surgery in China. World J Clin Cases 2021; 9(33): 10151-10160

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DOI: https://dx.doi.org/10.12998/wjcc.v9.i33.10151

INTRODUCTION
Enhanced recovery after surgery (ERAS) is a series of perioperative optimization measures based on evidence-based medicine that can reduce the physiological and psychological trauma stress, reduce complications, shorten the length of hospital stay (LOS), and promote postoperative rehabilitation[1]. In 2007, ERAS was introduced in China by Li[2] in the context of abdominal surgery, and since then the scope of its application has expanded to orthopedics, urology and other fields, and researchers have continued to develop and explore the applications of ERAS in China. In 2018, “the Chinese Expert Consensus and pathway management guidelines for Accelerated Rehabilitation Surgery” defined ERAS as: “based on evidence-based medicine, with the purpose of reducing the physiological and psychological trauma stress response in surgical patients, optimize the clinical pathway of perioperative management through multidisciplinary cooperation of surgery, anesthesia, nursing and nutrition, so as to reduce the perioperative stress response and postoperative complications, shorten the length of stay, and promote the recovery of patients”[3].

Patients who undergo major bone tumor surgery, perioperative management and rehabilitation are often faced with difficulties and challenges. Major surgery for bone tumor refers to operation on the spine, pelvis and limbs; in such cases, in order to obtain an ideal resection boundary, it is necessary to expose and potentially damage a wide range of anatomical areas. In addition, for patients with malignant bone tumor, previous treatments, metastasis and other factors, can lead to organ damage and
conditions such as anemia, thrombocytopenia, immunosuppression and organ dysfunction. Therefore, reducing or avoiding factors that can negatively impact the management of patients who undergo bone tumor surgery, and promote their rapid postoperative rehabilitation are important clinical priorities[4].

In 2019, in order to promote the application of the ERAS concept in bone tumor surgery, enhance the postoperative rehabilitation and improve the prognosis of patients with major bone tumor surgery, the Bone Oncology Group of the Orthopedic Branch of the Chinese Medical Association promoted discussions on this topic among a group of more than 20 national experts. Based on previous clinical experience and published relevant literature, and following the principle of evidence-based medicine a “Consensus of Experts on Perioperative Management of Accelerated Rehabilitation in Major Surgery of Bone Tumors in China” was formed[4]. The aim of this study was to evaluate the impact of the proposed consensus measures.

MATERIALS AND METHODS

Study population
This study included 107 patients undergoing bone tumor surgery between May 2019 and April 2021 at the Second Affiliated Hospital of Xi’an Jiaotong University. Patients were randomized into a study group (53 cases) and a control group (54 cases). This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi’an Jiaotong University. All patients and their families were informed of the aim of the study and gave signed informed consent.

The inclusion criteria were confirmation of bone tumor occurring in the spine (including sacrum), spine pelvis and major joints of limbs by histopathological examination, and indication for surgical treatment. The exclusion criteria were patients with cognitive impairment and mental illness; or with other malignancies and other serious systemic diseases.

A total of 156 patients were screened for eligibility, of whom 49 were excluded (29 cases did not meet the inclusion criteria, 8 refused to participate, and 12 were lost to follow-up). The remaining 107 patients were randomly divided into a study group and a control group by the order of admission following a computer-generated list of randomization codes. The study group adopted the ERAS pathway and the control group adopted conventional care (Table 1).

ERAS protocol
Our multidisciplinary ERAS working group consisted of personnel with expertise in neurosurgery, anesthesia, nursing, nutrition, physical therapy and rehabilitation. Based on the expert consensus and the current situation of our hospital, the components of ERAS were organized in three chronological sections: preoperative, intraoperative and postoperative. Our ERAS program is a comprehensive pathway of perioperative care including psychological education and intervention, nutritional status assessment and management, use of prophylactic antibiotics, anesthesia management, blood management, pain management, prevention of venous thrombosis, surgical incision and drainage, and postoperative rehabilitation exercise.

Outcome measurements
Main outcome measures included postoperative LOS, postoperative complications, mortality, and 30-d readmission rates. Postoperative complications included local and systemic complications. Local complications were defined as incision swelling, exudation, blister, infection, skin purpura around knee, gasket dislocation, infection around prosthesis. Systemic complications were defined as postoperative nausea and vomiting (PONV), drowsiness, cardiovascular adverse events, respiratory diseases, postoperative urinary retention, mental disorders, among others. Secondary outcomes were postoperative visual analog scale (VAS) score of pain, number of blood transfusions, drainage volume at 24 h after operation, patient satisfaction at 30 d after discharge, VAS score at 30 d after discharge, and daily standing walking time.

Statistical analysis
The SPSS software (version 23.0; IBM Corporation, Armonk, NY, United States) was used to conduct data analysis. The skewness coefficient, kurtosis coefficient, and normal single sample Kolmogorov–Smirnov test were used to assess normality. Data that followed a normal distribution were described as mean ± SD, and an independent
## Table 1 Enhanced recovery after major bone tumor surgery

<table>
<thead>
<tr>
<th>Phase</th>
<th>Item</th>
<th>ERAS pathway</th>
<th>Conventional care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>Patient and family</td>
<td>Detailed communication of the basic knowledge of the tumor, the purpose and method of surgery, rehabilitation process, postoperative further treatment. Requested informed consent for study participation</td>
<td>Routine consultation. Requested informed consent for study participation</td>
</tr>
<tr>
<td></td>
<td>Patient evaluation</td>
<td>Preoperative KPS, pain VAS score, anxiety and depression HADS score, nutritional status NRS 2002 score, VTE Caprini Risk Assessment Scale</td>
<td>Preoperative KPS, pain VAS score, anxiety and depression HADS score, nutritional status NRS 2002 score, VTE Caprini Risk Assessment Scale</td>
</tr>
<tr>
<td></td>
<td>Nutritional intervention</td>
<td>Nutritional consultation for patients with BMI &lt; 18.5 or &gt; 24, serum albumin level &lt; 3.5 g/dL</td>
<td>Nutritional consultation as needed</td>
</tr>
<tr>
<td></td>
<td>Antithrombotic prophylaxis</td>
<td>Active/passive limb movement, plantar vein pump, intermittent air pressure device, color Doppler ultrasound screening of lower extremity vein</td>
<td>Active/passive limb movement, plantar vein pump, intermittent air pressure device</td>
</tr>
<tr>
<td></td>
<td>Preventive analgesia</td>
<td>Use of opioids to reduce central and peripheral sensitivity to pain and relieve preoperative anxiety</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Blood management</td>
<td>HB raised to above 100 g/L</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Diet management</td>
<td>Liquid food 2 h before anesthesia and solid food 6 h before anesthesia for patients without aspiration risk</td>
<td>Fasting time for 6-8 h</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>General anesthesia</td>
<td>Combined IV-inhalation anesthesia, induced with propofol sufentanil and rocuronium, and maintained with propofol, fentanyl, and sevoflurane</td>
<td>Combined IV-inhalation anesthesia, induced with propofol sufentanil and rocuronium, and maintained with propofol, fentanyl, and sevoflurane</td>
</tr>
<tr>
<td></td>
<td>Local incision anesthesia</td>
<td>Local infiltration anesthesia or intraspinal anesthesia according to patient condition</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Control bleeding</td>
<td>Selective interventional embolization and balloon occlusion of abdominal aorta; Intraoperative control of hypotension and antifibrinolytic drugs administration</td>
<td>Selective interventional embolization and balloon occlusion of abdominal aorta</td>
</tr>
<tr>
<td></td>
<td>Pain management</td>
<td>Adductor block under the guidance of ultrasound during anesthesia. Drug injection into the periaortie area. Prescriptions included ropivacaine, morphine, ketorolac tromethamine, betamethasone, and norepinephrine</td>
<td>Opioids</td>
</tr>
<tr>
<td></td>
<td>Infusion restriction</td>
<td>Limited infusion, rational use of colloid and crystal gel combined with intraoperative infusion</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>ICU and extubation</td>
<td>Avoid admission to ICU extubate at end of surgery</td>
<td>Routine admission to ICU delayed extubation in ICU</td>
</tr>
<tr>
<td>Postoperative</td>
<td>Diet</td>
<td>Oral free fluids: 6 h after surgery light diet, 8 h after surgery as tolerated by the patient; semi-liquid/solid diet, 12-24 h after surgery; ordinary diet, 24-48 h after surgery</td>
<td>Oral liquid diet</td>
</tr>
<tr>
<td></td>
<td>Infusion restriction</td>
<td>Daily infusion volume less than 1500 mL.</td>
<td>No restrictions</td>
</tr>
<tr>
<td></td>
<td>Pain management</td>
<td>Combined with selective COX-2 inhibitors, opioids, sedatives, hypnotics, and anxiolytics</td>
<td>Combined with selective COX-2 inhibitors</td>
</tr>
<tr>
<td></td>
<td>Blood management</td>
<td>Elastic bandage applied to the incision of limb surgery, icing, and limb elevation</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Urinary catheter removal</td>
<td>Early removal of urinary catheter within 24 h after surgery whenever possible</td>
<td>Routine removal of urinary catheter on POD 1-2</td>
</tr>
<tr>
<td></td>
<td>PONV</td>
<td>Prevention with dexamethasone or serotonin receptor</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Early mobilization</td>
<td>In-bed mobilization, 6 h after surgery early ambulation, POD1</td>
<td>Routine mobilization and ambulation</td>
</tr>
<tr>
<td>Discharge</td>
<td>Patient assessment</td>
<td>Preoperative KPS, pain VAS score, anxiety and depression HADS score,</td>
<td>Preoperative KPS, pain VAS score, anxiety and depression HADS score Nursing satisfaction</td>
</tr>
<tr>
<td></td>
<td>Other assessments</td>
<td>Complications, LOS</td>
<td>Complications, LOS</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Patient evaluation 30d after discharge</td>
<td>Satisfaction, VAS, daily standing walking time</td>
<td>Satisfaction, VAS, daily standing walking time</td>
</tr>
</tbody>
</table>

BMI: Body mass index; ERAS: Enhanced recovery after surgery; KPS: Karnofsky Performance Status; VAS: Visual analog scale; HADS: Hospital Anxiety
Zhao LY et al. Effectiveness of ERAS in patients in China

RESULTS

Patient characteristics
All patients completed all investigations during admission and follow-up. Baseline characteristics included age, sex, body mass index, preoperative VAS, fasting blood glucose, Karnofsky Performance Status (KPS), and anxiety and depression scores. There were 53 patients in the study group, including 34 men and 19 women. There were 54 patients in the control group, including 38 men and 16 women. The average age of the study group was 48.59 ± 5.21 years (range 22–65 years). The average age of the control group was 46.54 ± 4.86 years (range 21–62 years). There were no significant differences in baseline characteristics between the groups. Clinical data included comorbidities and the surgical site. There were no differences in the prevalence of diabetes, hypertension, chronic heart disease, liver/gallbladder disease and lung disease between the groups. Similarly, the patient distribution was also comparable in terms of site of surgery (spine, pelvis, upper limb joint, and lower limb joint) between the groups (Table 2).

Main outcome measures
A comparison of the main outcome measures after bone tumor surgery between groups was performed. The LOS was 7.72 ± 3.34 d for the study group with ERAS protocol and 10.28 ± 4.27 d for the control group with conventional care. The difference in LOS between the two groups was significant ($P = 0.00$). The incidence of PONV was 30.19% (16/53) in study group and 70.37% (38/54) in the control group ($P < 0.05$). There were no significant differences in postoperative complications and 30-d readmission between groups. No death or venous thromboembolism (VTE) events occurred in either group (Table 3).

Secondary outcome measures
A comparison of the secondary outcome measures after bone tumor surgery between groups was performed. Postoperative VAS pain scores decreased in both groups compared with the baseline data; the pain continued to subside with recovery time. However, the decrease in the pain score of the study group with ERAS Protocol was more pronounced in the study group than in the control group. The VAS scores of pain in postoperative day (POD1) and POD2 in the study group were significantly lower than those in the control group ($P = 0.00$ and 0.01). However, no significant differences between groups were observed 1 mo after discharge. The drainage volume in 24 h after the operation was 124.36 ± 23.43 mL in the study group and 167.43 ± 30.87 mL in the control group. The rate of blood transfusion was 13.21% (7/53) in the study group and 35.19% (19/54) in the control group. The difference in drainage volume ($P = 0.00$) and blood transfusion ($P = 0.00$) was significant. Patient satisfaction was evaluated according to three categories: very satisfied, satisfied and dissatisfied. For the purpose of statistical analysis, the very satisfied and satisfied categories were pooled. The satisfaction rate in study group was 84.91% (45/53), which was higher than that in the control group (32%) (Table 4).

DISCUSSION

ERAS was first proposed by Kehlet et al[5] in 1997. ERAS is a management mode that aims to increase patient comfort and reduce perioperative complications from the perspective of reducing stress response of surgical patients[6]. Prior research suggests that ERAS can not only accelerate patient recovery and reduce the incidence of

and Depression Scale; NRS 2002: Nutritional Risk Screening 2002; VTE: Venous thromboembolism; PONV: Postoperative nausea and vomiting; ICU: Intensive care unit; POD: Postoperative day; LOS: Length of stay.
Table 2 Patient baseline demographics and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
<th>t/χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>34/19</td>
<td>38/16</td>
<td>0.47</td>
<td>0.49</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48.59 ± 5.21 (22-65)</td>
<td>46.54 ± 4.86 (21-62)</td>
<td>2.24</td>
<td>0.13</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.73 ± 3.92</td>
<td>19.21 ± 4.04</td>
<td>0.14</td>
<td>0.89</td>
</tr>
<tr>
<td>Preoperative VAS</td>
<td>6.57 ± 1.08</td>
<td>6.61 ± 1.24</td>
<td>0.23</td>
<td>0.56</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>6.42 ± 1.11</td>
<td>6.61 ± 1.67</td>
<td>2.89</td>
<td>0.07</td>
</tr>
<tr>
<td>Complication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (16.98)</td>
<td>4 (7.41)</td>
<td>1.49</td>
<td>0.22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (66.04)</td>
<td>27 (50.0)</td>
<td>2.82</td>
<td>0.09</td>
</tr>
<tr>
<td>Chronic heart disease</td>
<td>6 (11.32)</td>
<td>6 (11.11)</td>
<td>0.12</td>
<td>0.97</td>
</tr>
<tr>
<td>Liver/gallbladder</td>
<td>4 (7.55)</td>
<td>3 (5.56)</td>
<td>0.01</td>
<td>0.98</td>
</tr>
<tr>
<td>Lung</td>
<td>7 (13.21)</td>
<td>9 (16.67)</td>
<td>0.02</td>
<td>0.86</td>
</tr>
<tr>
<td>KPS</td>
<td>90 (60-100)</td>
<td>90 (70-100)</td>
<td>1.71</td>
<td>0.18</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 (1-20)</td>
<td>7 (2-17)</td>
<td>0.42</td>
<td>0.34</td>
</tr>
<tr>
<td>Depression</td>
<td>4 (1-18)</td>
<td>6 (2.18)</td>
<td>0.27</td>
<td>0.45</td>
</tr>
<tr>
<td>Surgical site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>15</td>
<td>16</td>
<td>0.61</td>
<td>0.89</td>
</tr>
<tr>
<td>Pelvis</td>
<td>7</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limb joint</td>
<td>7</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limb joint</td>
<td>24</td>
<td>27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 mean ± SD (range).
2 mean ± SD.

Table 3 Comparison of the main outcome measures between groups after bone tumor surgery

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
<th>t/χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS (d)</td>
<td>7.72 ± 3.34</td>
<td>10.28 ± 4.27</td>
<td>23.47</td>
<td>0.00</td>
</tr>
<tr>
<td>Complications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PONV</td>
<td>16 (30.19)</td>
<td>38 (70.37)</td>
<td>17.28</td>
<td>0.00</td>
</tr>
<tr>
<td>Incision infection</td>
<td>8 (15.09)</td>
<td>14 (25.93)</td>
<td>1.92</td>
<td>0.17</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (9.43)</td>
<td>7 (12.96)</td>
<td>0.34</td>
<td>0.56</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>5 (9.43)</td>
<td>3 (5.96)</td>
<td>0.58</td>
<td>0.45</td>
</tr>
<tr>
<td>VTE</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-d readmission, n (%)</td>
<td>7 (13.21)</td>
<td>11 (20.37)</td>
<td>0.98</td>
<td>0.32</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 mean ± SD. LOS: Length of stay; PONV: Postoperative nausea and vomiting; VTE: Venous thromboembolism.

complications, but also reduce medical costs, shorten LOS, and increase patient satisfaction[7-9]. In recent years, ERAS has been widely used in many surgical fields including orthopedics in China[10-12].

Most patients with bone tumor surgery have anxiety and fear before operation, as confirmed in this study. Another study found that explicit preoperative psychological education and intervention can substantially relieve anxiety and emotional stress before bone surgery[13]. Preoperative education is helpful to improve patients’
Table 4 Comparison of the secondary outcome measures between two groups after bone tumor surgery

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
<th>t or χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS of POD 1</td>
<td>4.79 ± 2.34</td>
<td>5.28 ± 3.27</td>
<td>13.47</td>
<td>0.00</td>
</tr>
<tr>
<td>VAS of POD 3</td>
<td>2.79 ± 1.53</td>
<td>3.98 ± 2.27</td>
<td>8.23</td>
<td>0.01</td>
</tr>
<tr>
<td>VAS 1 mo after discharge</td>
<td>0.88 ± 0.12</td>
<td>1.23 ± 0.67</td>
<td>2.24</td>
<td>0.13</td>
</tr>
<tr>
<td>Drainage volume (mL)</td>
<td>124.36 ± 23.45</td>
<td>167.43 ± 30.87</td>
<td>12.23</td>
<td>0.00</td>
</tr>
<tr>
<td>Blood transfusion, n (%)</td>
<td>7 (13.21)</td>
<td>19 (35.19)</td>
<td>7.02</td>
<td>0.00</td>
</tr>
<tr>
<td>Standing walking time (h)</td>
<td>3.25 ± 3.23</td>
<td>2.92 ± 4.17</td>
<td>3.13</td>
<td>0.07</td>
</tr>
<tr>
<td>Satisfaction, n</td>
<td></td>
<td></td>
<td>8.72</td>
<td>0.00</td>
</tr>
<tr>
<td>Satisfied</td>
<td>45</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>8</td>
<td>22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 mean ± SD. Visual analog scale (VAS) and of postoperative day 1 (POD 1): VAS score on the first day after operation; VAS and of POD 3: VAS score on the third day after operation. VAS: Visual analog scale; POD: Postoperative day.

...confidence and satisfaction, and facilitate early rehabilitation and discharge[14].

In the study group (ERAS group), doctors tried to understand their patients’ concerns and problems and were sensitive to the emotional reaction of patients. They also provided to patients and their families detailed information about the tumor, the purpose and method of the operation, the rehabilitation process, and further treatment plan and prognosis. Patients who were cured shared their own experience, which could help build overall patient confidence in rehabilitation. At the same time, the family members of patients were more enlightened and concerned about patients. Through preoperative psychological education and intervention, we can form a trust relationship among patients, family members and medical staff, so that patients can maintain an optimistic attitude and the confidence to overcome the disease.

Malnutrition and low serum protein levels are independent risk factors for postoperative complications. Therefore, nutritional risk screening and assessment should be carried out before major surgery for bone tumors[15,16]. About 27% of orthopedic patients have different degrees of hypoproteinemia, which is positively correlated with age[17]. Even in some bone tumor patients with good preoperative nutritional status, due to the large amount of intraoperative blood loss or decreased postoperative food intake and other factors, their nutritional indicators may also decline significantly. For patients with definite malnutrition, oral immunonutrition supplement can be preferred and used continuously for 5–7 d preoperatively. Preoperative parenteral nutrition therapy is only suitable for patients with severe malnutrition risk and enteral nutrition cannot meet their needs. Standard whole protein formula is recommended for postoperative nutrition[18]. Surgical site infection, in particular deep tissue infection, is a serious complication that can lead to failure of bone tumor surgery[19]. Therefore, prophylactic use of antibiotics should be carried out before the operation. The consensus is that preoperative fasting time of general anesthesia should be 6–8 h, which may lead to discomfort and increased insulin resistance and protein breakdown. Therefore, patients without aspiration risk are given liquid food 2 h before and solid food 6 h before anesthesia[20]. Preoperative anemia is also an independent risk factor for postoperative complications and death. Therefore, anemia screening should be performed, and patients should have hemoglobin > 100 g/L[21]. Compared with other operations, bone tumor surgery is often more traumatic, and can result in more pain and more severe stress responses. Therefore, personalized analgesia, preventive analgesia and multimodal analgesia should be considered. Pain relief in our study group with ERAS protocol was more pronounced that that in the control group. The combination of different postoperative analgesic methods not only improves the effect of perioperative pain relief, but also allows single drug dose reduction and helps minimize toxic and adverse effects. Sleep and anxiety can be further improved and pain relief can be alleviated by including hypnotic and sedative approaches.

Currently, understanding of early mobilization is limited because patients with postoperative complications and pain are unable to complete early postoperative activities, and it is there controversial whether early mobilization is an exposure factor or a result. In the ERAS group, the drainage tube was pulled out 24 h after the...
operation, which facilitated early mobilization and early ambulation, and helped accelerate patient recovery. Adequate pain control is also important for early mobilization and early ambulation.

In this study, the mean LOS in the study group was 7.72 d compared to 10.28 d in the control group. Related studies in China have reported that the average LOS under the ERAS concept was 10 d, with a median of 8 d. In contrast, the average LOS in the control group was 18 d, with a median of 13 d. In other countries, the average LOS of patients with ERAS was shorter than in China, and was 5-6 d. However, about 50%-80% of the discharged patients in developed countries are taken out of hospital care institutions, which might help explain these differences between countries. Therefore, the readmission rate of discharged patients after surgery and the factors influencing readmission LOS warrant further investigation. In this study, the incidence of PONV, postoperative 24-h blood drainage and postoperative blood transfusion in the ERAS group were better than those in the conventional treatment group. No VTE or death occurred during the perioperative period in either of the groups. However, there were no significant differences in postoperative complications such as incision infection, urinary tract infection and pulmonary infection caused by long-term bed rest; understanding the reasons for this lack of improvement in the study group require further investigation.

Our study also had some limitations. The follow-up time was short and the patient sample size was small. There was some heterogeneity regarding the sites of surgery (four sites). All these factors might influence the results, and therefore a better control for confounding is needed in future studies. In addition, because ERAS provides more detailed and personalized services to patients, it requires higher quality of medical staff and the need for more allocated doctor’s time. In China, there are still many difficulties in the application and promotion of ERAS given insufficient number and uneven quality of medical staff. Further research is needed to design a more concise, easier to understand, and more efficient ERAS protocol to be implemented in China.

CONCLUSION

The application of ERAS in the perioperative period of bone tumor surgery can shorten the duration of hospital stay, and reduce the incidence of PONV, postoperative pain, and the need for postoperative blood transfusion and postoperative 24-h drainage. ERAS has the potential to improve patient satisfaction and accelerate recovery. Further improvements and promotion of ERAS in the context of bone surgery are warranted.

ARTICLE HIGHLIGHTS

Research background
Enhanced recovery after surgery (ERAS) has gradually been applied and promoted in various clinical disciplines in China.

Research motivation
This research attempted to propose appropriate ERAS protocol for patients with bone surgery in the perioperative management in China.

Research objectives
This study aimed to evaluate the clinical application of the Consensus of Experts on Perioperative Management of accelerated rehabilitation in major surgery of Bone Tumors in China.

Research methods
A total of 107 patients undergoing bone tumor surgery were randomized into a study group (53 cases) and control group (54 cases). Retrospective analysis was used to measure the nursing effect of two groups of patients with different nursing measures.

Research results
ERAS protocol can shorten the postoperative hospital stay of patients with bone tumors, reduce the incidence of postoperative nausea and vomiting, reduce
postoperative pain, reduce postoperative blood transfusion and postoperative 24-h drainage, improve patient satisfaction and accelerate rehabilitation.

**Research conclusions**

ERAS protocol is worth popularizing in the perioperative period of Chinese patients with bone tumors.

**Research perspectives**

Assessing the effectiveness of measures with practical results.

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Clinical Trials Study

Association between plasma dipeptidyl peptidase-4 levels and cognitive function in perinatal pregnant women with gestational diabetes mellitus

Si-Ri-Gu-Leng Sana, En-You Li, Xi-Jin Deng, Lei Guo

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Author contributions: Li EY designed the study; Sana SRGL designed the study, collected data, and wrote and revised the manuscript; Deng XJ interpreted and analyzed the data; Guo L collected the data.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University, No. IRB-SC-04/01.0.

Clinical trial registration statement: This study is registered at Chinese Clinical Trial Registry, No. ChiCTR2000038703.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: The authors declared no potential conflicts of interest with respect to

Abstract

BACKGROUND
Dipeptidyl peptidase-4 (DPP4) is associated with cognitive dysfunction in patients with type 2 diabetes.

AIM
To assess a possible relationship between serum DPP4 and cognitive function in perinatal pregnant women with gestational diabetes mellitus (GDM).

METHODS
The study subjects were divided into three groups: GDM group (n = 81), healthy pregnant (HP) group (n = 85), and control group (n = 51). The Montreal Cognitive Assessment (MoCA) was used to assess the cognitive status of each group. Venous blood samples were collected to measure blood lipids, glycated hemoglobin, and glucose levels. For each participant, a 3-mL blood sample was collected and centrifuged, and the serum was collected. Blood samples were stored at -80 °C, and DPP4, interleukin-6 (IL-6), and 8-iso-prostaglandin F2α (8-iso-PGF2α), and brain-derived neurotrophic factor (BDNF) were detected using ELISA.

RESULTS
The MoCA scores in the GDM and HP groups were significantly different from those in the control group in terms of visuospatial/executive function and attention (P < 0.05); however, the scores were not significantly different between the GDM and HP groups (P > 0.05). In terms of language, the GDM group had significantly different scores from those in the other two groups (P < 0.05).
the research, authorship, and/or publication of this article.

**Data sharing statement:** The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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

**Country/Territory of origin:** China

**Specialty type:** Medicine, research and experimental

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review report’s scientific quality classification**
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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**P-Reviewer:** Dąbrowski M

terms of memory, a significant difference was found between the HP and control groups (P < 0.05), as well as between the GDM and HP groups. The levels of DPP4, IL-6, and 8-iso-PGF2α in the GDM group were significantly higher than those in the HP and control groups (P < 0.05); however, the differences between these levels in the HP and control groups were not significant (P > 0.05). The level of BDNF in the GDM group was significantly lower than that in the HP and control groups (P < 0.05), although the difference in this level between the HP and control groups was not significant (P > 0.05).

**CONCLUSION**
Cognitive dysfunction in perinatal pregnant women with GDM mainly manifested as memory loss, which might be associated with elevated DPP4 levels.

**Key Words:** Gestational diabetes mellitus; Dipeptidyl peptidase-4; Cognitive function; Oxidative stress; Perinatal pregnant women; Montreal cognitive assessment

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**Core Tip:** It is generally believed that diabetes can cause cognitive impairment, and even is an important cause of Alzheimer’s disease. This study investigated whether gestational diabetes mellitus (GDM) induced cognitive decline in perinatal pregnant women and assessed a possible relationship between serum dipeptidyl peptidase-4 (DPP4) levels and maternal cognitive function in perinatal pregnant women with GDM, and detected DPP4 levels in cord blood. DPP4 may cause cognitive impairment by aggravating inflammatory response and oxidative stress response.

**Citation:** Sana SRGL, Li EY, Deng XJ, Guo L. Association between plasma dipeptidyl peptidase-4 levels and cognitive function in perinatal pregnant women with gestational diabetes mellitus. *World J Clin Cases* 2021; 9(33): 10161-10171
**URL:** [https://www.wjgnet.com/2307-8960/full/v9/i33/10161.htm](https://www.wjgnet.com/2307-8960/full/v9/i33/10161.htm)
**DOI:** [https://dx.doi.org/10.12998/wjcc.v9.i33.10161](https://dx.doi.org/10.12998/wjcc.v9.i33.10161)

**INTRODUCTION**
With the advent of the two-child policy in China, the number of elderly parturient women is increasing, which has led to a rise in many pregnancy-related complications, the most common of which is gestational diabetes mellitus (GDM). The global incidence of DM during pregnancy is 15%, of which, GDM comprises 87.5% of cases [1]. GDM causes serious adverse effects to the mother and fetus, and increases the risk of eclampsia, maternal metabolic disorders, miscarriage, premature birth, obstructed labor, macrosomia, fetal distress, neonatal pulmonary immaturity, and neonatal hypoglycemia[2]. Although the pathogenesis of GDM is poorly understood, it might be associated with insulin resistance, and may share similarities with the pathogenesis of type 2 DM (T2DM). Most of the women with GDM regain normal glucose metabolism after delivery but face a significantly higher risk of developing DM than healthy pregnancy women in the future[3].

Several recent studies have found that T2DM can lead to cognitive dysfunction[3], which mostly manifests as impairments in various abilities such as memory and orientation. Zheng et al[4] confirmed the correlation between cognitive dysfunction and serum dipeptidyl peptidase-4 (DPP4) activity in patients with T2DM; they also found that the underlying mechanism was related to DPP4-mediated activation of inflammatory responses and oxidative stress. Thus, they suggested that altered DPP4 activity could be a risk factor for cognitive dysfunction in T2DM. Other studies have also reported a decline in verbal memory, associative learning, reaction time, and verbal recall in healthy pregnant (HP) women[5-7]. However, only a few studies have examined the presence of altered cognitive function in patients with GDM. Therefore, this study aimed to determine whether having GDM for nearly 6 mo during the perinatal period, combined with the stress of anxiety during pregnancy, could cause mild cognitive impairment (MCI), and whether there are subsequent changes in serum
DPP4 levels.

### MATERIALS AND METHODS

#### Subjects and protocols

Patients aged 18–35 years, with American Society of Anesthesiologists physical status I/II, were included in this study. A total of 100 consecutive perinatal pregnant women with GDM who were diagnosed, followed up, and treated at the First Affiliated Hospital of Harbin Medical University were included in the study (GDM group). One hundred age-matched perinatal pregnant women without DM comprised the HP group. The healthy control group included 51 nonpregnant female volunteers of similar age with normal blood glucose levels. All patients and volunteers read and signed informed consent forms before enrolment in the study. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University, and was registered with the Chinese Clinical Trial Register (registration number: ChiCTR2000038703).

GDM was diagnosed with at least one abnormal result during the oral glucose tolerance test: plasma glucose during fasting, ≥ 92 mg/dL (5.1 mmol/L); at 1 h, ≥ 180 mg/dL (10.0 mmol/L); or at 2 h, ≥ 153 mg/dL (8.5 mmol/L). Women with fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), glycated hemoglobin (HbA1c) ≥ 6.5%, or random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) were diagnosed with overt diabetes and excluded. Subjects on medications that affect cognitive function, including corticosteroids, antidepressants, and antiepileptics, were also excluded. In addition, all patients with other chronic diseases were excluded[8]. The Hamilton Depression Rating Scale was used to assess the psychological status of pregnant women; those with a score > 7, who might have depression, were excluded[9].

On the survey date, all enrolled patients underwent routine medical history inquiries, physical examinations, and laboratory measurements. Clinical research coordinators used a standard questionnaire to collect information on demographic characteristics and medical history. All pregnant women were instructed to maintain their usual physical activity and diet for at least 3 d before the survey. After an overnight fast of ≥ 10 h, venous blood samples were collected to measure blood lipid, HbA1c and glucose levels. For each participant, a 3-mL blood sample was collected and centrifuged, and the serum was collected. Blood samples were stored at -80 °C, and DPP4, interleukin-6 (IL-6), 8-iso-prostaglandinF2α (8-iso-PGF2α), and brain-derived neurotrophic factor (BDNF) were detected using ELISA (Mibio, Shanghai, China). All measurements were performed within 6 mo of sample collection.

Umbilical cord blood was collected at the time of delivery from participants in the GDM and HP groups. Serum DPP4 level was measured using ELISA in these groups as well.

#### Assessment of cognitive function

To assess cognitive function, the Montreal Cognitive Assessment (MoCA), which is a brief cognitive screen used in a variety of clinical settings to screen for MCI, was administered[10]. The cognitive assessment was conducted in a quiet room, without distractions, by a physical therapist trained in the administration of the MoCA. The maximum score for the MoCA is 30, and the assessment evaluates visuospatial/executive, naming, attention, language, abstraction, orientation, and delayed recall abilities, among others. A score of ≤ 25 indicates MCI[11,12].

#### Statistical analysis

The data were analyzed using SPSS 19.0. All data were tested for normality and homogeneity of variance. Normally distributed data were expressed as mean ± SD. Normally distributed continuous variables were compared using Student’s t test, while those with non-normal distributions were compared using the Mann–Whitney U test; multiple comparisons between groups were performed using the least significant difference method. Categorical data were presented as numbers and percentages, and comparisons between groups were performed using the two-sided χ² test. Correlations of DPP4 and BDNF levels with those of IL-6 and 8-iso-PGF2α, respectively, were performed using Pearson’s correlation coefficient, and P < 0.05 was considered statistically significant.
RESULTS

Demographic information
A total of 166 pregnant women and 51 nonpregnant healthy volunteers were enrolled in this study; they included 83 pregnant women with GDM in the GDM group, 85 HP women in the HP group, and 51 nonpregnant healthy volunteers in the control group (Figure 1). The weight, blood glucose level, and HbA1c level of the participants in the GDM group were significantly higher than those in the other two groups ($P < 0.05$) (Table 1).

MoCA scores
The MoCA scores in the GDM and HP groups were significantly different from those in the control group in terms of visuospatial/executive function and attention ($P < 0.05$); however, the scores were not different between the GDM and HP groups ($P > 0.05$). In terms of language, the GDM group had significantly different scores from those in the other two groups ($P < 0.05$). In terms of memory, a significant difference was found between the HP and control groups ($P < 0.05$), as well as between the GDM and HP groups ($P < 0.05$) (Table 2).

Expression of serum indicators
The levels of DPP4, IL-6, and 8-iso-PGF2α in the GDM group were significantly higher than those in the HP and control groups ($P < 0.05$); however, the differences between these levels in the HP and control groups were not significant ($P > 0.05$). The level of BDNF in the GDM group was significantly lower than that in the HP and control groups ($P < 0.05$), although the difference in this level between the HP and control groups was not significant ($P > 0.05$) (Figure 2 and Table 3). In the GDM group, the elevated DPP4 level significantly correlated with the elevated levels of IL-6 and 8-iso-PGF2α ($P < 0.05$). Moreover, the elevated IL-6 and 8-iso-PGF2α levels significantly correlated with decreased BDNF levels ($P < 0.05$) (Table 4). Cord blood DPP4 level in the GDM group was significantly higher than that in the HP group ($P < 0.05$) (Figure 2 and Table 3).

DISCUSSION

Although the viewpoint that pregnant women experience deficits in memory is widespread, evidence supporting this supposition is limited in the literature, especially in humans[13]. Based on the results of this study, the following conclusions can be drawn. (1) Perinatal pregnant women with GDM experience cognitive decline, which mainly involves memory loss; (2) Elevated serum DPP4 level is involved in the cognitive decline of perinatal pregnant women with GDM, and they are significantly correlated. Possible mechanisms underlying these findings may include the activation of inflammatory mediators and oxidative stress pathways due to elevated DPP4 level; and (3) DPP4 levels are significantly higher in the cord blood of women with GDM than those without GDM.

Our demographic results showed that pregnant women with GDM had significantly different body weight as well as blood glucose and HbA1c levels than those in the HP group. Although the blood glucose levels in the GDM group were maintained within the normal range, most patients had blood glucose or HbA1c levels near the upper limit, thus indicating the persistence of insulin resistance and metabolic disorders. Some studies suggest that women with GDM have a 20%–70% chance of developing T2DM within 10 years of delivery[14]. The pathogenesis of GDM is complex, involving beta-cell dysfunction, abnormal neuroendocrine function, and abnormal lipid metabolism[15]. Current treatments for GDM are limited to dietary interventions and insulin use, which often has unsatisfactory therapeutic efficacy due to the presence of insulin resistance. Therefore, an in-depth analysis on the etiology, mechanisms, and treatment strategies of GDM is of crucial significance for reducing complications during pregnancy and neonatal morbidity.

In this study, the MoCA scale, which is the most sensitive instrument for detecting cognitive decline, was used to assess cognitive function in perinatal pregnant women with GDM. Our results showed that the GDM and HP groups were significantly different from the control group in terms of executive function and attention, but there was no difference between the GDM and HP groups for these parameters. In addition, there was a significant difference in language scores between the GDM group and the other two groups. It is worth noting that in terms of memory, there was a significant
Table 1 Demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>GDM</th>
<th>HP</th>
<th>CG</th>
<th>F</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>81</td>
<td>85</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>29.40 ± 4.06</td>
<td>29.86 ± 4.39</td>
<td>29.63 ± 4.33</td>
<td>0.24</td>
<td>0.79</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.86 ± 4.79</td>
<td>164.11 ± 5.78</td>
<td>164.14 ± 5.05</td>
<td>0.06</td>
<td>0.94</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.96 ± 11.58</td>
<td>74.35 ± 9.57</td>
<td>58.60 ± 7.42</td>
<td>68.32</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Glu</td>
<td>4.90 ± 1.32</td>
<td>3.99 ± 0.71</td>
<td>4.83 ± 0.54</td>
<td>22.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HBA1c (%)</td>
<td>5.81 ± 0.61</td>
<td>4.73 ± 0.93</td>
<td>5.32</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Education, n (%)

Primary school | 8 (9.9) | 2 (2.4) | 1 (2.0) | 6.95 | 0.14 |
High school    | 22 (27.2) | 20 (23.5) | 14 (27.5) |       |       |
University     | 51 (63.0) | 63 (74.1) | 36 (70.6) |       |       |

Data are expressed as means ± SD or number. GDM: Gestational diabetes mellitus; HP: Healthy pregnant group; CG: Control group; HbA1c: Glycated hemoglobin; Glu: Glucose.

Table 2 MoCA test scores

<table>
<thead>
<tr>
<th></th>
<th>GDM</th>
<th>HP</th>
<th>CG</th>
<th>P value (GDM vs HP)</th>
<th>P value (GDM vs CG)</th>
<th>P value (HP vs CG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>81</td>
<td>85</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visuospatial/executive</td>
<td>4.52 ± 0.84</td>
<td>4.65 ± 0.63</td>
<td>4.94 ± 0.31</td>
<td>0.21</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Naming</td>
<td>3.00 ± 0.00</td>
<td>3.00 ± 0.00</td>
<td>3.00 ± 0.00</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Attention</td>
<td>5.53 ± 0.84</td>
<td>5.58 ± 0.70</td>
<td>5.92 ± 0.27</td>
<td>0.64</td>
<td>0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Language</td>
<td>2.65 ± 0.53</td>
<td>2.83 ± 0.40</td>
<td>2.96 ± 0.20</td>
<td>0.01</td>
<td>&lt; 0.001</td>
<td>0.08</td>
</tr>
<tr>
<td>Abstraction</td>
<td>1.98 ± 0.16</td>
<td>1.98 ± 0.14</td>
<td>2.00 ± 0.00</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Orientation</td>
<td>6.00 ± 0.00</td>
<td>5.99 ± 0.10</td>
<td>6.00 ± 0.00</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>2.80 ± 1.14</td>
<td>3.61 ± 1.20</td>
<td>4.16 ± 0.92</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Total</td>
<td>26.99 ± 1.78</td>
<td>28.01 ± 1.80</td>
<td>29.00 ± 1.16</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MoCA ≤ 25</td>
<td>20 (24.7)</td>
<td>2 (2.4)</td>
<td>0</td>
<td>&lt; 0.001</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or number. MoCA: Montreal cognitive assessment; GDM: Gestational diabetes mellitus; HP: Healthy pregnant group; CG: Control group.

difference between the HP and control groups, as well as between the GDM and HP groups. This indicates that perinatal pregnant women with GDM experience a significant decline in memory. Since the memory task is worth 5 points in the MoCA, and accounts for the largest proportion of scores among all abilities, it may have contributed substantially to the differences in the total score between the groups. However, all groups were within the normal range. Thus, the results of the MoCA scale support our previous speculation that although GDM patients do not reach the threshold for MCI, they still experience some degree of cognitive decline.

The effect of childbirth on women’s cognitive ability is an important issue because it might affect the job opportunities of working women of childbearing age. As such, we discuss the influence of pregnancy on women’s cognitive function with caution. The average score of HP women was lower than that of healthy nonpregnant volunteer women of similar age with respect to the MoCA score. However, the degree of cognitive decline is smaller than that in pregnant women with GDM. In the late stages of pregnancy, most women are no longer in a working environment, and the brain moves into a state of excessive relaxation in terms of cognition, which might be one of the reasons for the mild cognitive decline in pregnant women[16,17]. The mild stress, anxiety, and depression surrounding childbirth during pregnancy could also affect the
Table 3 Concentration of diabetes related factors of each group

<table>
<thead>
<tr>
<th></th>
<th>DPP4 (UCB)</th>
<th>BDNF</th>
<th>IL-6</th>
<th>8-iso-PGF2α</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDM (n = 81)</td>
<td>8.94 ± 8.50</td>
<td>1.56 ± 0.18</td>
<td>29.72 ± 7.14</td>
<td>9.02 ± 1.50</td>
</tr>
<tr>
<td>HP (n = 85)</td>
<td>2.87 ± 2.31</td>
<td>0.18 ± 0.16</td>
<td>51.72 ± 15.82</td>
<td>8.10 ± 1.08</td>
</tr>
<tr>
<td>CG (n = 51)</td>
<td>2.85 ± 1.76</td>
<td>/</td>
<td>43.53 ± 8.93</td>
<td>8.11 ± 1.02</td>
</tr>
</tbody>
</table>

P value (GDM vs HP) < 0.001 < 0.001 < 0.001 < 0.001 < 0.001

Table 4 Correlations of DPP4 and BDNF with IL-6 and 8-iso-PGF2α

<table>
<thead>
<tr>
<th></th>
<th>Cor</th>
<th>P value</th>
<th>Cor</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>0.617</td>
<td>0.006</td>
<td>-0.749</td>
<td>0.001</td>
</tr>
<tr>
<td>8-iso-PGF2α</td>
<td>0.547</td>
<td>0.019</td>
<td>-0.349</td>
<td>0.029</td>
</tr>
</tbody>
</table>

DPP4: Dipeptidyl peptidase-4; IL-6: Interleukin-6; 8-iso-PGF2α: 8-iso-prostaglandinF2α; BDNF: Brain-derived neurotrophic factor.

Figure 1 Patient recruitment flowchart. GDM: Gestational diabetes mellitus; HP: Healthy pregnant group; CG: Control group.

cognitive function of pregnant women to a certain extent[18,19]. However, most of these negative emotions during pregnancy would resolve following childbirth. Conversely, the levels of DPP4 and BDNF were closer to those of healthy women; therefore, we believe that the decline of cognitive function in pregnant women is minimal.
Our focus in this study was on memory loss in perinatal pregnant women with GDM, which was pronounced when compared with that in the HP group. This may be a transient phenomenon, and its long-term effects are still unclear; however, its mechanisms might be similar to that of cognitive impairment in patients with T2DM. Several recent studies have shown that DPP4 is strongly associated with cognitive impairment in T2DM patients[4], which prompted us to examine DPP4 levels. DPP4 (also known as CD26) is an exopeptidase that cleaves peptides after the second position from the N terminus (NH2-Xaa-Pro)[20]. DPP4 is a widely expressed multifunctional enzyme that exists in two forms: one is a membrane-anchored cell surface protein, and the other is a soluble form present in the plasma[21,22]. DPP4 levels are higher in subjects who are obese and have T2DM, predisposing them to hypoglycemia, inflammation and oxidative stress[23,24]. DPP4 degrades glucagon-like peptide-1 (GLP-1), as well as several other peptides, including glucose-dependent insulinotropic polypeptide, brain natriuretic peptide, substance P, neuropeptide Y, and stromal-derived factor-1α[25]. More interestingly, there is a study showing that increased DPP4 activity is independently associated with MCI in elderly patients with T2DM[4]. Reports that DPP4 is associated with cognitive dysfunction are limited[26]. These reports have mainly been about the cognitive dysfunction in T2DM. DPP4 play crucial roles in GLP-1 degradation and in the development of inflammation and oxidative stress[27]. Inflammation and oxidative stress have been widely demonstrated to be strongly associated with cognitive decline[28]. DPP4 inhibitors ameliorate cognitive impairment by suppressing inflammatory reactions, oxidative stress and GLP-1 degradation[29]. DPP4 inhibitors might have therapeutic potential for reducing amyloid-β-protein-induced impairment of insulin signaling and neurotoxicity in the pathogenesis of Alzheimer’s disease[30]. In this study, the results of the DPP4 assay showed that women in the GDM group had significantly higher expression levels than those in the HP group. We hypothesized that the high level of DPP4 expression may have contributed to the cognitive decline in patients with GDM. To investigate the reason for this, we further tested the patients’ level of inflammatory response and oxidative stress.

Systemic inflammation has been suggested to play an important pathogenic role in the late severe stages of cognitive decline, and inflammatory markers, such as IL-6, were only found to be elevated in patients with dementia but not in those with cognitive decline[31,32]. We propose that this discrepancy could be due in part to differences in the methods of detecting inflammatory cytokines and the diagnosis of cognitive dysfunction. The majority of the studies support the possibility that systemic inflammation could be a pathophysiological cascade response to cognitive decline, and do not explicitly exclude low-grade inflammatory diseases, such as T2DM, cardiovascular disease, and GDM. The present study showed that the serum IL-6 level in perinatal pregnant women with GDM is significantly elevated and correlates with the elevated DPP4 level. Therefore, we speculate that elevated serum DPP4 in perinatal
pregnant women with GDM might exacerbate the progression of cognitive dys-
function to some extent via its proinflammatory effects.

Besides systemic inflammation, oxidative stress has also been shown to cause
cognitive decline. 8-iso-PGF2α is a biologically active prostaglandin-like substance and
a specific product resulting from the oxygen free radical peroxidation of cellular
membranes. This indicator can accurately reflect lipid peroxidation in patients with
hypoxia–ischemia–reperfusion[33]. The production of 8-iso-PGF2α is not dependent on
cyclooxygenase (COX), but on the damage caused by oxygen free radicals to polyunsaturated fatty acids (arachidonic acid) in lipid cell membranes. Thus, its expression
levels in vivo are not affected by the use of nonsteroidal anti-inflammatory drugs, such
as aspirin, which can alter COX activity. Therefore, 8-iso-PGF2α is an ideal biochemical indicator for the clinical determination of the degree of free radical oxidation in
patients and the efficacy of antioxidant therapy. Furthermore, studies have shown that
increased peripheral blood 8-iso-PGF2α levels in pregnant women positively correlate
with disease severity[34]. One study confirmed that DPP4 increases the production of
reactive oxygen species in endothelial cells in a dose-dependent manner[35]. Our data
also suggest a positive correlation between 8-iso-PGF2α and DPP4 activity.

We also examined the serum levels of BDNF, which is a plasma marker associated
with cognitive function. BDNF downregulation could lead to synaptic loss and
neurodegeneration[36]. Our results indicate that patients in the GDM group had
significantly lower expression levels. This suggests that patients in the GDM group not
only experienced cognitive decline, but also showed changes in plasma marker levels,
which is the greatest cause of our concern.

In this study, we found that DPP4, IL-6, and 8-iso-PGF2α levels were significantly
higher and BDNF level was lower in pregnant women with GDM, and that these
biomarkers were mutually correlated to a certain extent. Zheng et al[4] found that
DPP4, IL-6 and 8-iso-PGF2α levels were elevated in patients with T2DM and
associated with their cognitive dysfunction. Furthermore, the increased DPP4 levels
 correlated with increased IL-6 and 8-iso-PGF2α levels. In this study, we found that
elevated serum DPP4 levels in perinatal pregnant women with GDM positively
correlated with elevated serum IL-6 and 8-iso-PGF2α levels, while the latter was also
correlated with decreased BDNF levels. Therefore, we speculate that elevated DPP4
levels might exacerbate the inflammatory response and oxidative stress in pregnant
women with GDM. These inflammatory and oxidative stress factors can cross the
blood–brain barrier and act on the nervous system to reduce BDNF levels, which will
affect hippocampal function, thereby exacerbating memory loss. DPP4 might not only
be involved in the process of cognitive dysfunction in pregnant women with GDM,
but also in insulin resistance, lipid oxidative stress, and other pathophysiological
processes. It may also serve as a potential target for GDM treatment, which is the next
step in our research.

The limitations of this study were as follows: (1) the sample size was small; and (2)
we observed the cognitive status of pregnant women with GDM and discussed the
pathophysiological mechanisms associated with DPP4 from the perspective of inflam-
matory factors and oxidative stress. However, complex mechanisms may be involved
in memory loss in pregnant women with GDM, not limited to the effects of DPP4
alone. Therefore, further elucidation of the underlying mechanisms is needed.

This study also found significantly elevated levels of DPP4 in the cord blood,
suggesting that DPP4 could affect fetal development through the placental barrier.
However, we did not examine the effect of this change on the fetus.

We believe that in addition to strict dietary control and glycemic control, it is also
important to stabilize the moods of perinatal pregnant women with GDM to reduce
inflammatory and stress responses. In particular, we should pay attention to methods
of controlling intraoperative patient stress during anesthesia for painless natural
delivery or caesarean delivery. This is not only crucial for the mother but also for the
fetus.

CONCLUSION

Cognitive dysfunction in perinatal pregnant women with GDM mainly manifested as
memory loss, which might be associated with elevated DPP4 levels.
ARTICLE HIGHLIGHTS

Research background
Studies have confirmed that type 2 diabetes mellitus (DM) can cause cognitive impairment. The mechanism is not clear. Dipeptidyl peptidase-4 (DPP4) may be involved in this process.

Research motivation
The main problem in this study is whether cognitive impairment exists in pregnant women with gestational DM (GDM) and whether it is related to DPP4. This has a great impact on the physical and mental health of pregnant women with perinatal GDM and the health of the fetus.

Research objectives
Objective to study the cognitive function of pregnant women with GDM, and to find out whether the pathway is related to DPP4.

Research methods
They were divided into three groups: GDM group, healthy pregnant group and control group. Women in the three groups were scored with Montreal Cognitive Assessment. Venous blood was collected from women in each group, serum was separated, and serum indexes such as DPP4, interleukin-6, and 8-iso-prostaglandin-F2 α, and brain-derived neurotrophic factor (BDNF) were detected by ELISA.

Research results
Compared with the other two groups, the GDM group had cognitive impairment, especially memory impairment. DPP4 may induce the change of BDNF by promoting oxidative stress and inflammatory response.

Research conclusions
GDM can lead to cognitive dysfunction in pregnant women, mainly manifested as memory loss. DPP4 may be involved in this process.

Research perspectives
Perinatal cognitive decline is worth our attention, especially in GDM pregnant women. How to prevent and treat is the key. Whether DPP4 can be used as a therapeutic target needs further study.

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Paricalcitol in hemodialysis patients with secondary hyperparathyroidism and its potential benefits

Xiu Chen, Feng Zhao, Wei-Juan Pan, Jia-Mei Di, Wei-Nan Xie, Ling Yuan, Zhi Liu

Abstract

BACKGROUND
Secondary hyperparathyroidism (SHPT) is a common complication in patients with end-stage renal disease and it is also common in hemodialysis patients. SHPT can increase bone fragility and calcification of blood vessels and soft tissues, which greatly increases the risk of death.

AIM
To discuss the outcome, safety and other potential benefits of paricalcitol injection in hemodialysis patients with SHPT.

METHODS
We recruited 40 patients who received hemodialysis at our hospital for chronic renal failure with SHPT between March and December 2019. They received paricalcitol injection for 24 wk (starting dose, 0.06–0.08 μg/kg), three times per week. They were followed up at the baseline (week 0), week 4, week 12 and week 24. The primary outcome indicator was the percentage of patients with a > 30% decrease in intact parathyroid hormone (iPTH) levels at week 24 compared with the baseline. The secondary outcome indicators included percentage decrease in iPTH levels at week 24, standard-reaching rate of iPTH (percentage of patients with iPTH down to 130–585 pg/mL), changes in serum levels of calcium (Ca), phosphate (P), Ca × P product, alkaline phosphatase (ALP), creatinine (Cre), hemoglobin (Hb), and C-reactive protein (CRP), and incidence of adverse events (AEs).

RESULTS
After 24 wk of treatment, iPTH levels decreased significantly (598.88 ± 381.29 pg/mL vs 888.84 ± 376.88 pg/mL, P < 0.05). More than 30% decrease of iPTH was found in 21 of 36 (58.33%) patients. The average decrease in iPTH levels was 32.16
INTRODUCTION

Secondary hyperparathyroidism (SHPT) is a common complication in patients with end-stage renal disease. Hyperphosphatemia, hypocalcemia and 1,25(OH)2D deficiency are considered important in the pathogenesis of SHPT[1]. SHPT is a component of chronic kidney disease-mineral and bone disorder, which is featured by increased fibroblast growth factor 23 and serum parathyroid hormone (PTH) concentrations, decreased 1,25(OH)2 vitamin D concentrations and abnormal serum phosphate (P) and calcium (Ca) concentrations[2-4]. SHPT can increase bone fragility and calcification of blood vessels and soft tissues. Patients with SHPT are at a higher risk for bone fractures and cardiovascular diseases, which, in turn, have a significant adverse impact on quality of life[5]. Clinically, nonselective vitamin D receptor activators (VDRAs) are the primary medication for SHPT, such as calcitriol and alfalcacitol. It has been shown that the long-term use of VDRAs may enhance the intestinal absorption of Ca and phosphorus and tubular reabsorption, leading to an increase in serum levels of Ca and phosphorus and risk of vascular calcification[6]. Since paricalcitol, a selective VDRA, is available on the market, several studies have confirmed that paricalcitol can selectively act on the parathyroid glands, inhibiting parathormone secretion. Paricalcitol mildly affects intestinal Ca and phosphorus absorption. Paricalcitol is also effective for SHPT patients resistant to nonselective VDRAs[7-9]. This study investigated the outcomes, safety and potential benefits of paricalcitol injection in hemodialysis patients with SHPT.

CONCLUSION

Paricalcitol was a safe and effective treatment for hemodialysis patients with SHPT. It decreased serum levels of iPTH, ALP and P and maintained stability of serum Ca levels.

Key Words: Paricalcitol; Hemodialysis; Secondary hyperparathyroidism; Drug efficacy; Drug safety

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URL: https://www.wjgnet.com/2307-8960/full/v9/i33/10172.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i33.10172

Core Tip: In this study, 40 patients with chronic renal failure were treated with paricalcitol for 24 wk. It was found that paricalcitol can significantly reduce intact parathyroid hormone, alkaline phosphatase and serum phosphate levels, and maintain a relatively stable serum calcium level. Therefore, paricalcitol is effective and safe in the treatment of hemodialysis patients with secondary hyperparathyroidism.
MATERIALS AND METHODS

Patients
We recruited 40 patients with chronic renal failure complicated by SHPT and receiving hemodialysis at our hospital between March and December 2019. There were 23 men and 17 women, with an average age of 49.10 ± 12.86 years. Inclusion criteria: (1) Age > 18 years; (2) Regular hemodialysis for ≥ 3 mo, three times per week, and hemodialysis continued during medication; (3) iPTH levels > 300 pg/mL; (4) Life expectancy > 6 mo; and (5) Good adherence to treatment. Exclusion criteria: (1) History of paricalcitol treatment before enrollment; (2) History of treatment with other active forms of vitamin D and its analogs (including calcitriol, alfacalcidol, doxercalciferol, fluoro-calcidol and maxacalcitol) and calcimimetics (cinacalcet); (3) Hypercalcemia or Ca × P product > 65 mg²/dL²; (4) Allergic to the investigational drug; (5) Serious heart disease, liver injury, active inflammatory disease, or malignancy; (6) Ready for kidney transplantation or parathyroidectomy; (7) Pregnant or lactating women; (8) Unwilling to take effective contraceptive measures; and (9) Participating in other studies in the same period. The present study was approved by the Ethics Review Committee of the hospital. All patients were enrolled on a voluntary basis and gave signed informed consent.

Methods
The investigational drug was paricalcitol injection (Zemplar®; Jiangsu Hengrui Medicine Co. Ltd., strength 1 mL: 5 μg) and stored at 30 °C. The starting dose of the paricalcitol injection was 0.06–0.08 μg/kg. Within 30 min before the end of the hemodialysis, paricalcitol injection was administered via the hemodialysis venous catheter (venous port) three times per week. The dose was adjusted according to the serum levels of iPTH, Ca and P, which were detected once every 2-4 wk. The specific dose adjustment criteria are shown in Table 1. If hypercalcemia occurred or the corrected Ca × P product was continuously above 65 mg²/dL², the dose should be reduced or discontinued until the above parameters returned to normal. After that, paricalcitol administration was resumed starting at a lower dose. The treatment lasted for 24 wk. Follow-up was conducted at the baseline and at weeks 4, 12 and 24. The patients were followed up on all designated days, with a window period of ± 4 d.

Observation indicators
Primary outcome indicator: Percentage of patients with > 30% decrease in iPTH levels at week 24 compared with the baseline. Secondary outcome indicators: Decrease in iPTH levels at week 24; standard-reaching rate of iPTH (percentage of patients with iPTH down to 130–585 pg/mL)[10]; changes in serum levels of Ca, P, Ca × P, alkaline phosphatase (ALP), creatinine (Cre), hemoglobin (Hb), and C-reactive protein (CRP); adverse events (AEs). The occurrence of any AEs during treatment was closely observed.

Statistical analysis
SPSS 19.0 software was used for data analysis. Measurement data (obeying normal distribution) were expressed as mean ± SD. Comparisons between the measurements at the baseline and at each time point of follow-up were conducted using the paired t test. Counts were described by cases (percentages) and subjected to Pearson’s χ² test. P < 0.05 indicated a significant difference.

RESULTS

Demographics and baseline features of the enrolled patients
A total of 40 patients were recruited, including 23 men and 17 women. Thirty-six patients finished all treatments planned, and four were lost to follow-up (Table 2).

Changes in iPTH levels
The baseline iPTH level was 888.84 ± 376.88 pg/mL. After 24 wk of treatment, it decreased to 598.88 ± 381.29 pg/mL, and the average decrease was 32%, indicating a significant difference (t = 4.589, P < 0.05) (Figure 1A). After 24 wk of treatment, 21/36 patients (58.33%) had a > 30% decrease in iPTH levels. The standard-reaching rate of iPTH was 24/36 (66.67%).
Table 1 Dose adjustment criteria for paricalcitol injection

<table>
<thead>
<tr>
<th>PTH level compared with baseline</th>
<th>Dose adjustment of paricalcitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reaching the standard, unchanged or increased; or decreased by &lt; 30%</td>
<td>Increase dose by 2-4 μg</td>
</tr>
<tr>
<td>When 150-300 pg/mL or PTH down by ≥ 30%</td>
<td>Maintain original dose</td>
</tr>
<tr>
<td>When PTH &lt; 150 pg/mL or serum Ca &gt; 11.0 mg/mL or Ca × P product &gt; 70 mg²/dL²</td>
<td>Decrease dose by 2-4 μg</td>
</tr>
</tbody>
</table>

Ca: Calcium; iPTH: Intact parathyroid hormone; P: Phosphate.

Table 2 Demographics and baseline features of 40 patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yr</td>
<td>49.10 ± 12.86</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (57.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Duration in mo of dialysis</td>
<td>55.20 ± 29.32</td>
</tr>
<tr>
<td>Weekly dose of paricalcitol in g/wk</td>
<td>12.38 ± 2.77</td>
</tr>
<tr>
<td>iPTH in pg/mL</td>
<td>888.84 ± 376.88</td>
</tr>
<tr>
<td>ALP in IU/L</td>
<td>133.45 ± 56.86</td>
</tr>
<tr>
<td>Blood P in mmol/L</td>
<td>2.16 ± 0.66</td>
</tr>
<tr>
<td>Blood Ca in mmol/L</td>
<td>2.38 ± 0.16</td>
</tr>
<tr>
<td>Ca × P product in mg²/dL²</td>
<td>63.97 ± 20.30</td>
</tr>
<tr>
<td>Hb in g/L</td>
<td>114.82 ± 20.45</td>
</tr>
<tr>
<td>Cre in mol/L</td>
<td>807.43 ± 254.64</td>
</tr>
<tr>
<td>CRP in mg/L</td>
<td>8.60 ± 16.76</td>
</tr>
</tbody>
</table>

Ca: Calcium; Cre: Creatinine; CRP: C-reactive protein; Hb: Hemoglobin; iPTH: Intact parathyroid hormone; P: Phosphate.

Changes in ALP levels
After 24 wk of treatment, ALP levels decreased significantly compared with the baseline (113.72 ± 41.73 IU/L vs 133.45 ± 56.86 IU/L) (t = 2.401, P < 0.05) (Figure 1B).

Changes in serum Ca and P levels and Ca × P product
During treatment, serum Ca levels remained stable. At week 12, the serum Ca level increased to 2.45 ± 0.19 mmol/L, but was still within the normal range (2.1–2.5 mmol/L). At week 24, the serum Ca level (2.39 ± 0.20 mmol/L) was not significantly different from that at the baseline (2.38 ± 0.16 mmol/L) (t = 0.242, P > 0.05). At week 24, the serum P level (1.91 ± 0.40 mmol/L) was not significantly different from that at the baseline (1.91 ± 0.40 mmol/L) (t = 0.717, P > 0.05). At week 24, Ca × P product (56.38 ± 13.22 mg²/dL²) was not significantly different from that at the baseline (63.97 ± 20.30 mg²/dL²) (t = 2.717, P < 0.05) (Figure 1C and D).

Changes in Hb, Cre and CRP levels
At each time point of follow-up, there were no significant differences in Hb and CRP levels compared with the baseline (P > 0.05). At weeks 4 and 24, the Cre level was not significantly different from that at the baseline (P > 0.05). However, there was a significant difference in Cre levels at week 12 compared with the baseline (P < 0.05) (Table 3).

AEs
During paricalcitol treatment, the Hb level was decreased in two cases (5.56%), and a transient elevation of serum P was found in one case (2.78%). After dose adjustment,
Table 3 Changes in hemoglobin, creatinine and C-reactive protein levels over time

<table>
<thead>
<tr>
<th>Time</th>
<th>Hb in g/L</th>
<th>t</th>
<th>P value</th>
<th>Cre in mol/L</th>
<th>t</th>
<th>P value</th>
<th>CRP in mg/L</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>114.82 ± 20.45</td>
<td></td>
<td></td>
<td>807.43 ± 254.64</td>
<td></td>
<td></td>
<td>8.60 ± 16.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>109.69 ± 19.78</td>
<td>1.530</td>
<td>0.131</td>
<td>749.67 ± 398.06</td>
<td>1.062</td>
<td>0.292</td>
<td>7.13 ± 10.71</td>
<td>0.642</td>
<td>0.523</td>
</tr>
<tr>
<td>Week 12</td>
<td>111.47 ± 21.11</td>
<td>0.967</td>
<td>0.337</td>
<td>586.40 ± 358.51</td>
<td>4.326</td>
<td>0.000</td>
<td>7.72 ± 4.98</td>
<td>0.486</td>
<td>0.629</td>
</tr>
<tr>
<td>Week 24</td>
<td>116.21 ± 23.50</td>
<td>0.380</td>
<td>0.705</td>
<td>803.27 ± 192.31</td>
<td>0.112</td>
<td>0.911</td>
<td>8.23 ± 14.82</td>
<td>0.206</td>
<td>0.838</td>
</tr>
</tbody>
</table>

Hb: Hemoglobin; Cre: Creatinine; CRP: C-reactive protein.

Figure 1 Changes in the biochemical index level over time. aP < 0.05, bP < 0.01 vs baseline. A: Intact parathyroid hormone level; B: Alkaline phosphatase level; C: Serum calcium and phosphate levels; D: Serum calcium × phosphate product. iPTH: Intact parathyroid hormone; ALP: Alkaline phosphatase; Ca: Calcium; P: Phosphate.

all of these cases returned to normal.

**DISCUSSION**

The hemodialysis patients enrolled in this study also had SHPT and were treated with paricalcitol at a median starting dose of 0.06–0.08 µg/kg. iPTH levels decreased from 888.84 ± 376.88 to 598.88 ± 381.29 pg/mL after treatment. Twenty-one of 36 (58.33%) patients had a > 30% decrease in iPTH. The standard-reaching rate of iPTH (percentage of patients with iPTH levels down to 130–585 pg/mL) was 66.67% (24/36 patients). Koc et al.[11] reported that after 6 mo of treatment, iPTH levels decreased from 518.9 to 264.0 pg/mL. There were 63.0% of patients with a > 30% decrease in iPTH levels. Olaizola et al.[12] reported that after 6 mo of paricalcitol treatment in hemodialysis patients with SHPT, 17 of 19 (89.47%) patients had a > 30% decrease in iPTH levels. Twelve of 19 (63.16%) patients had iPTH levels down to 150–300 pg/mL. The effect of paricalcitol on iPTH levels was most significant in the first 4 wk. After that, iPTH levels changed less noticeably. This confirmed the efficacy of paricalcitol in inhibiting iPTH, which was coupled to progressive weakening of its inhibitory effect on iPTH over time. Therefore, excessive inhibition of iPTH caused by paricalcitol was
prevented, which means that paricalcitol is safer than calcitriol.

Active vitamin D can stimulate intestinal Ca and P absorption by activating the intestinal VDRs, thereby contributing to hypercalcemia. Nonselective VDRAs, such as alfacalcidol and calcitriol, have no significantly different affinity for VDRs in intestinal mucosal cells and parathyroid cells. Paricalcitol is a highly selective VDRA with a higher affinity for VDRs in parathyroid cells than for those in intestinal mucosal cells. As intestinal Ca transport is weakened, the incidence of hypercalcemia decreases. Serum Ca and P levels in patients were detected in the present study. In the first 12 wk of paricalcitol treatment, there was a transient mild increase in average serum Ca levels. This has been reported in other studies[13] and may be considered a response in the adaptive period. Such a finding might have also been attributed to the diet of individual patients at the initial stage. Serum Ca levels stabilized after introduction of a Ca-restricted diet and the dose of paricalcitol was reduced. The Ca × P product decreased throughout the treatment period. After 24 wk of treatment, there were significant differences in serum P levels and Ca × P product compared with the baseline. These results indicated that paricalcitol reduced the risk of hyperphosphatemia. Li et al[14] reported no significant differences in the serum Ca and P levels and Ca × P product in hemodialysis patients with SHPT before and after paricalcitol treatment. Their findings disagree with ours, probably due to the differences in treatment duration.

The number and activity of osteoclasts usually increase in SHPT patients due to an excessively high iPTH level. Besides, bone transport and destruction are promoted, resulting in ALP elevation. In the present study, the ALP level decreased significantly after 24 wk of paricalcitol treatment compared with the baseline among the hemodialysis patients with SHPT, indicating that paricalcitol potentially corrects the SHPT-induced changes in bone histomorphology, which might be related to its inhibitory effect on bone metabolism. Some researchers believe that elevation of ALP is associated with a higher incidence of cardiovascular diseases in patients with chronic kidney disease. It is also one of the major reasons for the high mortality of hemodialysis patients[15]. A decrease in ALP levels indicates that hemodialysis patients with SHPT may benefit from paricalcitol treatment.

The microinflammatory state in hemodialysis patients may be closely related to such complications as anemia and cardiovascular disease in hemodialysis patients. Some studies have shown that paricalcitol is not only effective for SHPT complicating hemodialysis but also benefits patients by regulating bone metabolism, participating in anti-inflammatory and antioxidative stress activities, and improving anemia[16]. Cre is the most common indicator of kidney function, and Hb is an important indicator of anemia. CRP not only indicates the inflammatory state but also participates in cardiovascular injury. It has been found that during paricalcitol treatment, Hb and CRP levels at different time points are not significantly different from those at the baseline. In our study, at week 12, the Cre level was markedly reduced compared with the baseline. Later, the Cre level began to increase. These changes suggested that paricalcitol had no evident effect on kidney function indicators while reducing iPTH levels. The fact that the Cre level first decreased and then increased might be explained by the abnormal kidney function in hemodialysis patients. Paricalcitol may reduce the release of inflammatory factors such as CRP[17]. It is reported that paricalcitol has no significant impact on the inflammatory factors in hemodialysis patients with SHPT[18], which agrees with our findings.

CONCLUSION

In conclusion, paricalcitol significantly decreased serum levels of iPTH, ALP and P in hemodialysis patients with SHPT. In contrast, serum Ca, Hb, Cre and CRP levels remained stable. However, our study had a small sample size without a control group. In future, multicenter studies with a larger sample size will be performed to provide evidence for the clinical use of paricalcitol.

ARTICLE HIGHLIGHTS

Research background

Secondary hyperparathyroidism (SHPT) is a common complication in patients with end-stage renal disease. SHPT is a component of chronic kidney disease-mineral and
bone disorder, which is featured by increased fibroblast growth factor 23 and serum parathyroid hormone concentrations, decreased 1,25(OH)2 vitamin D concentrations and abnormal serum phosphate and calcium concentrations.

**Research motivation**
The long-term use of vitamin D receptor activators (VDRAs) may enhance the intestinal absorption of calcium and phosphorus and tubular reabsorption, leading to an increase in serum levels of calcium and phosphorus and risk of vascular calcification. But Paricalcitol mildly affects intestinal calcium and phosphorus absorption. Paricalcitol may be better than VDRAs in this aspect.

**Research objectives**
This study aimed to discuss the outcome, safety and other potential benefits of paricalcitol injection in hemodialysis patients with SHPT.

**Research methods**
Total 40 patients who received hemodialysis for chronic renal failure with SHPT received paricalcitol injection for 24 wk, three times per week. The primary outcome indicator was the percentage of patients with a > 30% decrease in intact parathyroid hormone (iPTH) levels at week 24 compared with the baseline.

**Research results**
After 24 wk of treatment, iPTH levels decreased significantly. More than 30% decrease of iPTH was found in 21 of 36 (58.33%) patients. The average decrease in iPTH levels was 32.16 ± 4.33%; the standard-reaching rate of iPTH levels was 66.67% (24/36); and alkaline phosphatase levels decreased significantly compared with the baseline. There were no significant differences in the serum levels of calcium, hemoglobin, creatinine and C-reactive protein compared with the baseline.

**Research conclusions**
This study suggested that the paricalcitol was a safe and effective treatment for hemodialysis patients with SHPT.

**Research perspectives**
Multicenter studies with a larger sample size will be performed to provide evidence for the clinical use of paricalcitol.

**REFERENCES**


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18 Yun Y, Zhang C, Liu NQ, Zhou GY, Li DT. [The effects of paricalcitol on inflammatory state and oxidative stress in maintenance hemodialysis patients]. *Zhongguo Xueye Jinghua* 2018; **17**: 677-681
Observational Study

Did the severe acute respiratory syndrome-coronavirus 2 pandemic cause an endemic *Clostridium difficile* infection?

Camelia Cojocariu, Irina Girleanu, Anca Trifan, Andrei Olteanu, Cristina Maria Muzica, Laura Huiban, Stefan Chiriac, Ana Maria Singeap, Tudor Cuciureanu, Catalin Sfarti, Carol Stanciu

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**Author contributions:** All authors participated in discussion, writing and/or editing of the manuscript, have read and approved the final version submitted and accept responsibility for its content; Trifan A, Cojocariu C and Stanciu C participated in the design of the review, data collection, analysis and interpretation, manuscript preparation and revision, and approved the final version of the final draft submitted; Huiban L, Olteanu A, Sfarti C, Muzica C, Chiriac S, Cuciureanu T, Girleanu I and Singeap AM performed the acquisition of data and contributed to the drafting of the manuscript; Sfarti C, Muzica C, Huiban L and Girleanu I contributed to the analysis and interpretation of data.

**Institutional review board statement:** The Institutional

**Background**

*Clostridium difficile* infection (CDI) has increased in prevalence during the last years. The coronavirus disease 2019 (COVID-19) pandemic has negatively influenced patient outcomes. The majority of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2)-infected patients received antibiotics during hospitalization.

**Aim**

To analyze the factors that influenced CDI development after SARS-CoV-2 infection.

**Methods**

Between March 2020 to December 2020, we performed a prospective observational study including 447 patients diagnosed with CDI who were admitted to our tertiary referral university hospital. The diagnosis of CDI was based on the presence of diarrhea (≥ 3 watery stools within 24 h) associated with *Clostridium difficile* toxins A or B. We excluded patients with other etiology of acute diarrhea.

**Results**

Among the total 447 (12.5%) patients with CDI, most were male (54.3%) and mean age was 59.7 ± 10.8 years. Seventy-six (17.0%) had history of COVID-19 (COVID-19) pandemic has negatively influenced patient outcomes. The majority of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2)-infected patients received antibiotics during hospitalization.

**Abstract**

*BACKGROUND*

*Clostridium difficile* infection (CDI) has increased in prevalence during the last years. The coronavirus disease 2019 (COVID-19) pandemic has negatively influenced patient outcomes. The majority of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2)-infected patients received antibiotics during hospitalization.

*AIM*

To analyze the factors that influenced CDI development after SARS-CoV-2 infection.

*METHODS*

Between March 2020 to December 2020, we performed a prospective observational study including 447 patients diagnosed with CDI who were admitted to our tertiary referral university hospital. The diagnosis of CDI was based on the presence of diarrhea (≥ 3 watery stools within 24 h) associated with *Clostridium difficile* toxins A or B. We excluded patients with other etiology of acute diarrhea.

*RESULTS*

Among the total 447 (12.5%) patients with CDI, most were male (54.3%) and mean age was 59.7 ± 10.8 years. Seventy-six (17.0%) had history of COVID-19, most being elderly (COVID-19: 62.6 ± 14.6 years vs non-COVID-19: 56.8 ± 17.6 years, \( P = 0.007 \)), with history of alcohol consumption (43.4% vs 29.4%, \( P = 0.017 \)), previous hospitalizations (81.6% vs 54.9%, \( P < 0.001 \)) and antibiotic treatments (60.5% vs
The coronavirus disease 2019 (COVID-19) pandemic was associated with an increased prevalence of Clostridium difficile (C. difficile) infections. Previous hospitalization and antibiotic treatment are known risk factors for C. difficile infection. Patients with a past history of COVID-19 infection, however, required higher doses of vancomycin and were more prone to developing recurrent disease. Rational antibiotic use should be implemented in all patients with COVID-19 infection. Diarrhea is a symptom of COVID-19 infection, which could delay the diagnosis of C. difficile infection. All the patients should be tested for C. difficile toxins A and B if watery diarrhea develops.

CONCLUSION
CDI risk is unrelated to history of SARS-CoV-2 infection. However, previous COVID-19 may necessitate higher doses of vancomycin for CDI.

Key Words: COVID-19 infection; Clostridium difficile infection; Risk factors; Antibiotic use; Pandemic; Recurrence

INTRODUCTION
Since 1978, when Clostridium difficile (C. difficile) was found to be the cause of pseudo-membranous colitis[1,2], numerous epidemiological data have shown that C. difficile infection (CDI) is the leading cause of nosocomial infectious diarrhea worldwide[3,4]. Indeed, it is one of the most common healthcare-associated infections[5]. Over the last two decades, there has been a dramatic worldwide increase in both incidence and severity of CDI[6]. In the United States, CDI causes about half a million infections and almost 30000 deaths annually[7]; in Europe, about 152905 people are infected with C. difficile, with an annual mortality above 8000 people[8,9]. The increased incidence of CDI, the risk of recurrence and difficult treatment in relapses are associated with high economic costs, which burdens the health system worldwide[1,2]. The prevention of CDI remains a significant concern for health systems, which are actively seeking to prevent outbreaks and maximize patient safety.

The coronavirus disease 2019 (COVID-19) pandemic in 2020 profoundly altered medical practice and introduced multiple challenges for gastroenterologists in approaching patients with digestive diseases, due to the many digestive and hepatic manifestations of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection. Frequently, residual and/or post-infection issues can alter the course of patients with digestive disorders (especially patients with inflammatory bowel disease, advanced liver disease, etc.). 2020 has certainly been a challenging year for gastroenterologists; in particular, this pandemic year has profoundly altered medical practice, and has brought multiple challenges in approaching patients with digestive diseases, given that many digestive and hepatic manifestations of SARS-CoV-2 infection, most often residual/post-infection, may alter the course of patients with...
digestive disorders (especially for patients with inflammatory bowel disease, advanced liver disease, etc.).

Diarrhea is one of the most common gastrointestinal symptoms in patients with COVID-19, showing a prevalence ranging from 11% to 17%[8,9]. SARS-CoV-2 can actively infect and replicate in the gastrointestinal tract through the angiotensin-converting enzyme 2 receptors disrupting the normal intestinal flora, leading to gastrointestinal symptoms, including diarrhea[9-15]. Before the COVID-19 pandemic the most common cause of diarrhea (excluding inflammation and organic intestinal lesions) was irritable bowel syndrome and functional disorders.

Patients with SARS-CoV-2 infection have numerous risk factors for CDI, including receipt of broad-spectrum antibiotic treatment, hospitalization, elderly age, and existence of multiple comorbidities or immunocompromised status. During the COVID-19 pandemic, many patients received antibiotic treatment, sometimes with no clear indication or as primary prophylaxis for pneumonia[12]. One study showed that 91% of COVID-19 patients received antibiotic treatment[14], but generally over 70% of COVID-19 patients were treated with broad-spectrum antibiotics (mostly respiratory quinolones) in order to treat or to prevent bacterial co-infections and super-infections [13,16,17]. We hypothesized that an increase in CDI incidence and recurrence occurred during the COVID-19 pandemic.

An Italian retrospective study during the COVID-19 pandemic found a significant decrease in the incidence of healthcare-associated CDI in 2020 compared to the previous 3 years (explained by increased pandemic precautions). However, other data showed that COVID-19 departments actually had a higher incidence of CDI compared to non-COVID-19 wards, but upon statistical analysis, the difference did not reach the threshold of significance[4,18].

Considering these contradictory data, the aim of this study was to assess the impact of the COVID-19 pandemic on the characteristics of CDI patients and to analyze the factors that influenced the incidence of CDI during the COVID-19 pandemic.

MATERIALS AND METHODS

Study population

We performed a prospective observational study including patients with CDI between March 2020 to December 2020. We analyzed data from this period because on March 1, 2020, the Clinical Hospital for Infectious Disease Iasi was declared a COVID-19 Unit, and as a result the Institute of Gastroenterology and Hepatology was designated the clinic to hospitalized patients with CDI. The diagnosis of CDI was based on the presence of diarrhea (≥ 3 watery stools within 24 h) associated with detection of C. difficile toxin A or B (by enzyme immunoassay) in stool samples[19]. Hospital-acquired CDI was defined as a stool sample positive for C. difficile toxin(s) at least 72 h after hospital admission. Each patient’s stool was tested only once. We collected demographic data (sex, age, residence), clinical and laboratory parameters, use of antibiotics, information regarding previous hospitalizations, comorbidities, associated medication, previous COVID-19 infection, treatment of CDI, and discharge. CDI data (first episode/relapse and relapse number), length of hospital stay and mortality during admission were also analyzed. The treatment started with vancomycin 125 mg every 6 h, and therapeutic response was defined as the absence of diarrhea after at least 72 h of treatment. We have excluded patients with other etiologies of acute diarrhea.

The study was approved by the Local Medical Ethics Committee (No. 12 /2020/ March 15th, 2020). All patients provided written informed consent before study inclusion or further analysis.

Statistical analysis

Categorical variables were expressed as frequency and percentage. Continuous variables were expressed as mean ± standard variation for normally distributed continuous data. All data were normally distributed. Groups were compared using the χ² test for categorical variables and using the independent t test or Mann-Whitney U test for continuous variables (depending on data distribution). Univariate analysis was performed for each recorded data type. Variables with P < 0.1 in univariate analysis were included in the multivariate analysis (logistic regression). The odds ratio (OR) with 95% confidence interval (CI) was calculated for qualitative variables included in the logistic regression. A P < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 20.0 software (IBM Corp., Armonk, NY, United
RESULTS

A total of 3562 patients were admitted to our tertiary hospital during the study period, of whom 447 (12.5%) were diagnosed with CDI. Most of the patients were male (243 patients, 54.3%). The mean age was 59.7 ± 10.8 years, and over half of the patients had previous hospitalizations (266 patients, 59.5%). Baseline characteristics of the patients included in the study are presented in Table 1. Of all the patients included in the study, 76 (17.0%) had a history of COVID-19. All of the COVID-19 patients were diagnosed with healthcare-associated CDI. Nineteen patients (25.0%) had recurrent CDI. All patients with CDI were treated with vancomycin (125 mg) every 6 h orally. In patients with a history of COVID-19, 26 (34.2%) received an increased dose of vancomycin (250 mg every 6 h for 10 d) and 28 (36.8%) received a high dose of vancomycin (500 mg every 6 h) because they did not respond to the initial dose. In addition, 14 patients (18.4%) received vancomycin enemas. Two patients in the COVID-19 group received fidaxomycin, as they were non-responders to even the maximal doses of vancomycin. Seventeen patients from the COVID-19 group with recurrent CDI received the tapering vancomycin regimen. Compared with the COVID-19 group, the majority of patients with no history of COVID-19 and CDI (302 patients, 81.4%) responded to the conventional doses of vancomycin (125 mg every 6 h for 10 d), and none of these patients needed fidaxomycin.

There was no significant difference in gender and hospitalization days as well as for the inflammatory syndrome between patients with a past history of COVID-19 who developed CDI and those without a history of COVID-19 (Table 1). However, the patients with a history of COVID-19 and CDI had a higher mean age (62.6 ± 14.6 vs 56.8 ± 17.6, P = 0.007), previous antibiotic treatment (60.5% vs 35.5%, P < 0.001), previous hospitalizations (81.6% vs 54.9%, P < 0.001), were chronic alcohol consumers (43.4% vs 29.4%, P = 0.017) and were more prone to recurrent disease (25.0% vs 13.1%, P = 0.011). Thirty-one patients (6.9%) died during hospitalization. The mortality rate was similar in both groups (6.6% vs 7.0%, P = 0.893).

The results of the univariate and multivariate regression analyses are shown in Table 2. The multivariate analysis demonstrated that age more than 60-years-old (OR = 2.59, 95%CI: 1.452-4.624, P = 0.001), urban area residence (OR = 2.33, 95%CI: 1.286-4.221, P = 0.005), previous antibiotic treatments (OR = 1.90, 95%CI: 1.083-3.365, P = 0.025), previous hospitalizations (OR = 2.5, 95%CI: 1.263-4.986, P = 0.009) and chronic alcohol consumption (OR = 2.55, 95%CI: 1.459-4.459, P = 0.001) were risk factors for CDI development in patients with a history of COVID-19.

DISCUSSION

An increase in the number of CDI cases was expected during the COVID-19 pandemic due to the numerous risk factors of patients with COVID-19 (elderly, multiple comorbidities requiring immunosuppressive treatment, prolonged hospitalization that is frequently in intensive care units, and antibiotic treatment)[5,7,20-22]. Our results demonstrated that 12.5% of patients admitted to our tertiary hospital were diagnosed with CDI. More than half of our patients with CDI had previous hospitalizations, and 17.0% of them were previously hospitalized for COVID-19. We found that all of the COVID-19 patients were diagnosed with healthcare-associated CDI. Our results are completely different from those of an Italian retrospective study during the COVID-19 pandemic that found a significant decrease in the incidence of healthcare-associated CDI in 2020 compared to the previous 3 years[4]. The authors explained that the decrease of CDI was due to increased pandemic precautions.

The growing number of CDI cases is only one of many causes for concern. In recent years, one of the clinical challenges in patients with CDI is recurrent infection, which is often difficult to treat. Recurrent CDI is defined as an episode of CDI occurring within 8 wk of a previous episode[1,22], and it may be due to relapse of the previous CDI by the same strain or reinfection by a different strain[23]. About 15%-30% of CDI patients with an initial response to antimicrobial treatment have a risk of recurrence of the infection, and it is important to note that the risk of further recurrence significantly increases[1]. In our cohort, 19 patients (25.0%) had recurrent CDI.
There was no significant difference in gender and hospitalization days as well as for the existence of inflammatory syndrome between patients with a history of COVID-19 that developed CDI and those without a history of COVID-19. However, the patients with a history of COVID-19 and CDI were elderly, were from an urban area, had previous antibiotic use, and were chronic alcohol consumers.

Although the majority of the literature on the epidemiologic features of CDI is based on the association of antibiotic therapy and hospitalization settings\[^{17,24-26}\], some other potential risk factors for CDI, such as advanced age, immunosuppression, comorbidities, chemotherapy, renal insufficiency, hypoalbuminemia, organ transplantation and use of proton pump inhibitors, have been identified to explain the increased incidence of CDI\[^{7,21,27}\].
COVID-19 may present as acute diarrhea and abdominal pain. Even in these conditions, with symptoms suggestive for COVID-19, testing for C. difficile must be done every time because patients with SARS-CoV-2 infection are at high risk for CDI.

Although CDI can affect individuals of all ages, the elderly are recognized as high-risk for this infection[17,27]. Older patients represent a vulnerable population for CDI because they often have multiple comorbidities, have frequent and prolonged hospitalizations, receive broad-spectrum antibiotics, and have altered host defense against infections[27]. At the same time, COVID-19 seems to primarily affect elderly patients, patients who usually have severe forms of the disease, and patients who were frequently treated with antibiotics.

Sandhu et al[28] collected data of several studies regarding concomitant antibiotic use in patients with COVID-19 in the United States. Most of these patients received empiric antibacterial therapy with either moxifloxacin, cefoperazone or azithromycin [29]. These antibiotics are known to be strongly associated with CDI, and the authors reported that CDI was due to the overuse of antibiotics in COVID-19 patients[28-31].

We found that chronic alcohol consumption was a risk factor for CDI after COVID-19 infection. Chronic alcohol consumption influences gut microbiota by decreasing the bacterial diversity and increasing intestinal permeability and systemic inflammation [32]. We found no other studies on the increased risk of CDI in chronic alcohol users, but we have two explanations for our result. The first is based upon the fact that almost 40% of our hospitalized patients had liver cirrhosis; the main etiology of which was alcoholism. The second is based upon the numerous data showing that during the pandemic alcohol consumption increased worldwide, sometimes to a worrisome degree[33].

Our study has some strengths and several limitations. This is the first prospective study that characterized CDI after SARS-CoV-2 infection. The identification of risk factors for CDI after COVID-19 highlights the importance of recognizing vulnerable groups, such as the elderly population and patients who consume alcohol. The limitations of our study are represented by the small sample of cases and the fact that our data came from a single-center care unit without information on the C. difficile strains. We do not yet have a definite explanation for the fact that patients with CDI after COVID-19 require higher doses of vancomycin.

CONCLUSION
We observed that patients with a history of COVID-19 and CDI were from an urban area, had a higher mean age, had previous antibiotic treatments and hospitalizations, were chronic alcohol consumers, and were more prone to recurrent disease. Also, escalating the doses of vancomycin to obtain the therapeutic effect was another feature of the patients studied. In these patients, the antibiotic treatment for COVID-19 should be personalized in order to diminish the risk of CDI. Further large studies are needed in order to establish if it is cost-effective to start CDI treatment with higher doses of vancomycin in patients with a past history of COVID-19.

ARTICLE HIGHLIGHTS

Research background
The coronavirus disease 2019 (COVID-19) pandemic profoundly altered medical practice and has brought forth multiple challenges for gastroenterologists in handling of patients with digestive diseases, due to the many digestive and hepatic manifestations of COVID-19. Frequently, residual/post-infection issues can alter the course of patients with digestive disorders (especially patients with inflammatory bowel disease, advanced liver disease, etc.). Clostridium difficile infection (CDI) was also a challenge for gastroenterology during the COVID-19 pandemic.

Research motivation
Many patients diagnosed with COVID-19 have numerous risk factors for CDI, including broad-spectrum antibiotic treatment, hospitalization, elderly age, multiple comorbidities, and immunocompromised status.
Research objectives
The aim of this study was to analyze the factors that influenced CDI development after COVID-19.

Research methods
Between March 2020 to December 2020, we performed a prospective observational study including 447 patients diagnosed with CDI who had been admitted to our tertiary referral university hospital. The diagnosis of CDI was based on the presence of diarrhea (≥ 3 watery stools within 24 h) associated with C. difficile toxin A or B.

Research results
Most of the patients in our study were male (54.3%), and showed a mean age of 59.7 ± 10.8 years. Of all the patients included in the study, 76 (17.0%) had a history of COVID-19. The patients with a history of COVID-19 were more likely to be elderly, have a history of alcohol consumption and have previous hospitalizations and antibiotic treatments than the patients without a history of COVID-19. The patients with a history of COVID-19 also needed higher doses of vancomycin and were prone to recurrent disease. Age over 60 years, residence in an urban area, previous antibiotic treatment, and previous and current alcohol consumption were identified as risk factors for CDI development in patients with COVID-19.

Research conclusions
Hospitalizations, antibiotic use and alcohol consumption represent risk factors for CDI development in patients over 60-years-old from an urban area with a history of COVID-19. These patients were at higher risk of recurrence and needed higher doses of vancomycin for CDI treatment.

Research perspectives
Our study highlights the importance of judicious use of antibiotics and recognizing the need for vancomycin for CDI treatment. COVID-19. These patients were at higher risk of recurrence and needed higher doses of vancomycin for CDI treatment.

REFERENCES


Effect of nursing intervention based on Maslow's hierarchy of needs in patients with coronary heart disease interventional surgery

Ji-Xue Xu, Lin-Xue Wu, Wei Jiang, Gui-Hong Fan

Abstract

BACKGROUND
It is very important to provide effective nursing programs to regulate the physical and mental state of patients and to improve treatment compliance after interventional surgery for coronary heart disease (CHD).

AIM
To explore the effect of a nursing intervention based on Maslow’s hierarchy of needs theory on patients with CHD undergoing percutaneous coronary intervention.

METHODS
Ninety-four patients with CHD undergoing interventional surgery in our hospital from January 2020 to February 2021 were randomly divided into a research group (n = 47) and a control group (n = 47). The control group received routine nursing, and the research group received a nursing intervention based on Maslow’s hierarchy of needs theory. The scores of self-efficacy, negative emotion [depression (SDS), anxiety (SAS)], intervention compliance (standardized medication, moderate exercise, healthy diet, and regular review), and nursing satisfaction were calculated before and after intervention for the two groups.

RESULTS
Before intervention, there was no significant difference in the scores of disease general management self-efficacy, disease management self-efficacy, and total self-efficacy between the two groups (P = 0.795, 0.479, and 0.659, respectively). After intervention, these three scores in the research group were higher than those in the control group (P < 0.001). Before intervention, there was no significant difference in the scores of SAS and SDS between the two groups (P = 0.149 and 0.347, respectively). After intervention, the scores of SAS and SDS in the research group were lower than those in the control group (P < 0.001). The standardized drug use rate (97.87%), moderate exercise rate (97.87%), healthy diet rate (95.74%),
and regular reexamination rate (97.87%) in the research group were higher than those in the control group (85.11%, 82.98%, 80.85%, and 87.23%, respectively) (P = 0.027, 0.014, 0.025, and 0.049, respectively). Nursing job satisfaction in the research group (93.62%) was higher than that in the control group (78.72%) (P = 0.036).

**CONCLUSION**

A nursing program based on Maslow’s hierarchy of needs theory can effectively alleviate negative emotion, enhance self-efficacy and intervention compliance, and ensure that the patients are highly satisfied with the nursing work.

**Key Words:** Maslow’s hierarchy of needs; Nursing; Coronary heart disease; Interventional surgery; Compliance

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**INTRODUCTION**

Coronary heart disease (CHD) is clinically a multiple cardiovascular disease. It is mainly a type of heart disease that is caused by myocardial ischemia and hypoxia due to coronary vascular stenosis or obstruction. If the patient does not receive timely and effective intervention, heart failure can develop as the disease progresses. It is also accompanied by different degrees of edema, fatigue, and dyspnea, among others. Furthermore, acute pulmonary edema, cardiogenic shock, and other manifestations may occur in cases of acute exacerbations, which is a great threat to the life and health of patients. As an important measure for the clinical treatment of CHD, interventional surgery can restore myocardial blood supply and reduce the risk of death. However, it affects treatment compliance and is not conducive to the outcomes of diseases due to postoperative drug treatment. The resulting treatment costs and patients’ concerns about the therapeutic effect and recurrence of the disease lead to a huge physical and mental burden on patients[1-3]. Consequently, it is very important to provide effective nursing programs to regulate the physical and mental state of patients and improve treatment compliance after interventional surgery for CHD. Hence, promotion of good disease outcomes is vital[4,5].

Routine nursing care for patients is mostly done passively. Paying attention only to the completion of one’s work and not paying enough attention to the pathological needs and emotional needs of patients can result in limitations of the clinical application of nursing care[6,7]. Maslow’s hierarchy of needs theory divides human needs into five levels, including physiology, safety, attribution and love, respect, and self-realization. It advocates nursing care according to the stage of the patient to meet the individual pathological psychological needs to the maximum extent.

Hence, this study selected 94 patients undergoing interventional surgery for CHD in our hospital to explore the application value of nursing intervention based on Maslow’s hierarchy of needs theory.
MATERIALS AND METHODS

General data
This study was approved by the Ethics Committee of our hospital. A total of 94 patients with CHD undergoing interventional surgery in our hospital from January 2020 to February 2021 were randomly divided into a research group \( (n = 47) \) and a control group \( (n = 47) \).

Selection criteria
Inclusion criteria: The inclusion criteria were as follows: (1) Patients who met the diagnostic criteria of CHD\(^8\); (2) Patients aged < 80 years; (3) All patients treated with interventional therapy; and (4) Patients and their families who were aware of this study and signed the consent form.

Exclusion criteria: Patients who met the following criteria were excluded: Patients with (1) Benign and malignant tumors; (2) Mental diseases; (3) Subarachnoid hemorrhage; (4) Stroke; (5) Organic diseases involving the kidney and liver; (6) Speech and communication disorders and hearing impairment; or (7) A history of alcohol and drug dependence; and (8) Those receiving antianxiety/antidepressants.

Methods
Control group: Routine nursing was performed. This included health education and formulation of individualized health education programs with reference to patients' cognition of rehabilitation after coronary intervention, including the importance of rehabilitation exercise, medication knowledge and matters needing attention, and ways to deal correctly with cardiac emergencies, among others. Health education can be carried out in various forms, such as health lectures and patient exchanges. Rehabilitation training and passive exercise were conducted after leaving the danger period, and rehabilitation exercise plan, exercise intensity, and exercise form were determined according to the individual condition of patients and comprised mainly aerobic exercises, such as tai chi, walking, and simple gymnastics. The psychological state of patients was mastered through active communication and targeted intervention. Meal plans were made according to the patients’ personal preferences and the need for disease rehabilitation, mainly including light and digestible foods.

Research group: Nursing intervention was based on Maslow’s hierarchy of needs theory. Physiological needs include the following: (1) Keeping the respiratory tract unobstructed, cleaning up oral and respiratory secretions and foreign bodies in time, guiding patients on how to cough and breathe deeply, regularly assisting patients to change their posture, turning over and tapping on their backs to promote sputum excretion, providing sputum suction and oxygen therapy, controlling blood oxygen saturation at 90%, and providing ventilator intervention during signs of respiratory weakness; (2) Closely monitoring vital signs, such as blood oxygen saturation, blood pressure, heart rate, self-consciousness, and other vital signs to help patients position themselves correctly and comfortably; (3) Guiding patients to promote sleep by means of soaking their feet and providing music, prolonging sleep time, improving sleep quality, and ensuring adequate sleep; and (4) Advising patients to eat more foods that are rich in fiber and vitamins while controlling total caloric intake and minimizing salt intake to 6 g.

Safety requirements include the following: (1) Prevention of urinary and respiratory infections, regular disinfection of wards, ventilation, ultraviolet disinfection once a day, postural drainage and sputum drainage to avoid the occurrence of persistent pneumonia, daily replacement of humidifying bottles and oxygen tubes, strict disinfection of sputum suction/ventilator, strict compliance with aseptic operation when carrying out relevant nursing measures, and nursing care of urinary catheter and oral cavity twice a day; (2) Preventing pressure sores, assisting patients to turn over every 2 h, massaging pressure areas, ensuring that sheets are dry and tidy, keeping the skin dry and clean, paying attention to gentle movements when moving patients, prohibiting procrastination, and using bed sore mats for those with vague consciousness and serious illness; and (3) Installing guardrails and bedside lamps for the hospital bed to avoid adverse events, such as falls, and ensuring that the floor of toilets and the ward is dry and clean, placing anti-skid signs and floor mats, and installing handrails in the corridor.

Love and belonging needs include the following: Evaluating patients’ psychological state, giving targeted psychological counseling, encouraging patients to express their subjective feelings, assisting patients in dealing with problems encountered during...
rehabilitation, teaching patients how to regulate their emotions, making patients aware of the importance of maintaining a positive mentality to alleviate their disease, and making them actively regulate negative emotions. When communicating with patients, one should pay attention to patience and enthusiasm, give patients full respect, gain their trust and goodwill, maintain a good nurse-patient relationship, and communicate with patients’ families and friends in a timely manner. In addition, it is necessary to explain the important impact of external support on patients’ recovery and psychological state, encourage them to spend more time with patients, ensure that love, care, and family warmth and support are provided, and eliminate loneliness.

Respecting needs include the following: Decreased self-care ability of patients undergoing interventional therapy for CHD and affected by the disease itself and the treatment. Patients are extremely prone to self-remorse or guilt; therefore, nurses should be patient enough to meet the reasonable needs of patients to the maximum extent or to provide reasons for not being able to meet such needs in order to avoid harming the self-esteem of patients. During the intervention, one should pay attention to strengthening the positive behavior of patients in the form of affirmation and praise to make them correct their bad behavior independently.

Self-fulfilling needs include the following: Waiting for the patient’s condition to become stable, guiding them to carry out functional rehabilitation training, and enhancing their ability of life in daily life. In addition, it is necessary to organize communication meetings in order to share rehabilitation experiences.

Observation index
The scores of self-efficacy of the two groups before and after intervention were calculated. According to the Chronic Disease Self-Efficacy Scale, the scores were based on six items, including disease common management self-efficacy and disease management self-efficacy, from “complete lack of confidence” to “absolute confidence” (1-10). The higher the score, the better.

The scores of negative emotions [depression (SDS), anxiety (SAS)] of the two groups before and after intervention were evaluated according to the SDS and SAS scale. This is classified according to the following: Mild depression: SDS score 53-62, moderate depression: 63–72, severe depression: ≥ 73; mild anxiety: SAS: 50–59, moderate anxiety: 60–69, and severe anxiety: ≥ 69[10]. Statistics on the compliance of intervention between the two groups included standardized medication, moderate exercise, healthy diet, and regular reexamination. The nursing job satisfaction questionnaire was designed by the patients, and nursing job satisfaction of the two groups was assessed. The total score of intervention attitude and quality was graded using a 100 points scale, where 90-100 points was classified as very satisfactory, 70–89 points as satisfactory, and < 70 points as dissatisfactory. Nursing job satisfaction was calculated as follows:

Nursing job satisfaction = (very satisfied + satisfied) / total number of cases × 100%.

Statistical analyses
The data obtained were analyzed using SPSS version 22.0 (Armonk, NY, United States). Measurement data were expressed with mean ± SD, and analyzed using t test. Counting data were expressed with n (%), and were analyzed using χ² test. P < 0.05 indicated statistically significant differences.

RESULTS

Demographic data
The clinical data of the two groups were balanced and comparable (P > 0.05), as shown in Table 1.

Chronic Disease Self-Efficacy Scale demographic data
Before intervention, there was no significant difference in the scores of disease general management self-efficacy, disease management self-efficacy, and total self-efficacy between the research group and the control group (P = 0.795, 0.479, 0.659, respectively). After intervention, the three scores in the research group were higher than those in the control group (P < 0.001) (Table 2).

SAS and SDS scores
Before intervention, there was no significant difference in the SAS and SDS scores
### Table 1 Comparison of two groups of general data, n (%)

<table>
<thead>
<tr>
<th>Items</th>
<th>Research group, n = 47</th>
<th>Control group, n = 47</th>
<th>t/χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (62.49 ± 9.63)</td>
<td>49.76</td>
<td>48.79</td>
<td>0.909</td>
<td>0.366</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.386</td>
<td>0.535</td>
</tr>
<tr>
<td>Male (51.09)</td>
<td>24</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (48.94)</td>
<td>23</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Course of disease in yr (3.75 ± 2.25)</td>
<td>1.0-6.5</td>
<td>0.5-7.5 (4.00 ± 2.55)</td>
<td>0.504</td>
<td>0.616</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school and junior high school (44.68)</td>
<td>21</td>
<td>25</td>
<td>0.805</td>
<td>0.423</td>
</tr>
<tr>
<td>High school (40.43)</td>
<td>19</td>
<td>16</td>
<td>0.492</td>
<td>0.624</td>
</tr>
<tr>
<td>College or above (14.89)</td>
<td>7</td>
<td>6</td>
<td>0.120</td>
<td>0.905</td>
</tr>
<tr>
<td>Concomitant disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (12.77)</td>
<td>6</td>
<td>4</td>
<td>0.231</td>
<td>0.818</td>
</tr>
<tr>
<td>High blood pressure (23.40)</td>
<td>11</td>
<td>14</td>
<td>0.421</td>
<td>0.675</td>
</tr>
<tr>
<td>Others (10.64)</td>
<td>5</td>
<td>7</td>
<td>0.236</td>
<td>0.814</td>
</tr>
<tr>
<td>Occupation type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmers (38.30)</td>
<td>18</td>
<td>21</td>
<td>0.528</td>
<td>0.599</td>
</tr>
<tr>
<td>Workers (8.51)</td>
<td>4</td>
<td>2</td>
<td>0.220</td>
<td>0.826</td>
</tr>
<tr>
<td>Cadres (6.38)</td>
<td>3</td>
<td>6</td>
<td>0.342</td>
<td>0.733</td>
</tr>
<tr>
<td>Others (46.81)</td>
<td>22</td>
<td>18</td>
<td>0.716</td>
<td>0.476</td>
</tr>
</tbody>
</table>

### Table 2 Comparison of chronic disease self-efficacy scale scores between the two groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Self-efficacy of disease commonality management</th>
<th>Disease management self-efficacy</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td>47</td>
<td>8.89 ± 2.83</td>
<td>20.23 ± 4.12</td>
<td>29.12 ± 4.69</td>
</tr>
<tr>
<td>Control</td>
<td>47</td>
<td>9.05 ± 3.11</td>
<td>19.65 ± 3.79</td>
<td>28.70 ± 4.51</td>
</tr>
<tr>
<td>t</td>
<td>0.261</td>
<td>0.710</td>
<td></td>
<td>0.443</td>
</tr>
<tr>
<td>P value</td>
<td>0.795</td>
<td>0.479</td>
<td></td>
<td>0.659</td>
</tr>
<tr>
<td>After intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td>47</td>
<td>16.05 ± 3.23</td>
<td>29.09 ± 3.88</td>
<td>45.14 ± 5.35</td>
</tr>
<tr>
<td>Control</td>
<td>47</td>
<td>13.13 ± 2.94</td>
<td>24.30 ± 4.23</td>
<td>37.43 ± 4.81</td>
</tr>
<tr>
<td>t</td>
<td>4.583</td>
<td>5.743</td>
<td></td>
<td>7.385</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

between the two groups (P = 0.149 and P = 0.347, respectively). After intervention, both scores in the research group were lower than those in the control group (P < 0.001) (Table 3).

**Intervention compliance**

The standardized drug use rate (97.87%), moderate exercise rate (97.87%), healthy diet rate (95.74%), and regular reexamination rate (97.87%) in the research group were higher than those in the control group (85.11%, 82.98%, 80.85%, and 87.23%, respectively) (P = 0.027, 0.014, 0.025, and 0.049, respectively) (Table 4).

**Nursing job satisfaction**

Nursing job satisfaction in the research group (93.62%) was higher than that in the control group (78.72%) (P = 0.036) (Table 5).
Xu JX et al. A nursing intervention study based on Maslow’s hierarchy of needs

**Table 3 Comparison of anxiety and depression scores between two groups (mean ± SD)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>SAS</th>
<th>SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td>47</td>
<td>58.31 ± 5.08</td>
<td>60.56 ± 6.62</td>
</tr>
<tr>
<td>Control</td>
<td>47</td>
<td>59.92 ± 5.64</td>
<td>61.89 ± 7.01</td>
</tr>
<tr>
<td>t</td>
<td>1.454</td>
<td>0.946</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.149</td>
<td>0.347</td>
<td></td>
</tr>
<tr>
<td>After intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research</td>
<td>47</td>
<td>43.64 ± 4.89</td>
<td>45.60 ± 5.44</td>
</tr>
<tr>
<td>Control</td>
<td>47</td>
<td>48.59 ± 5.33</td>
<td>51.31 ± 6.07</td>
</tr>
<tr>
<td>t</td>
<td>4.706</td>
<td>4.803</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

SAS: Anxiety; SDS: Depression.

**Table 4 Comparison of intervention compliance between the two groups, n (%)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Standardize the use of drugs</th>
<th>Moderate exercise</th>
<th>Healthy diet</th>
<th>Regular review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research</td>
<td>47</td>
<td>46 (97.87)</td>
<td>46 (97.87)</td>
<td>45 (95.74)</td>
<td>46 (97.87)</td>
</tr>
<tr>
<td>Control</td>
<td>47</td>
<td>40 (85.11)</td>
<td>39 (82.98)</td>
<td>38 (80.85)</td>
<td>41 (87.23)</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>4.919</td>
<td>6.021</td>
<td>5.045</td>
<td>3.859</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.027</td>
<td>0.014</td>
<td>0.025</td>
<td>0.049</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5 Comparison of nursing job satisfaction between the two groups, n (%)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Very satisfied</th>
<th>Satisfied</th>
<th>Dissatisfied</th>
<th>Total satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research</td>
<td>47</td>
<td>29 (61.70)</td>
<td>15 (31.91)</td>
<td>3 (6.38)</td>
<td>44 (93.62)</td>
</tr>
<tr>
<td>Control</td>
<td>47</td>
<td>19 (40.43)</td>
<td>18 (38.30)</td>
<td>10 (21.28)</td>
<td>37 (78.72)</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>4.374</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.036</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

It is difficult for patients to recover immediately after interventional surgery. Additionally, patients are affected by the disease itself as well as by the interventional surgery and postoperative rehabilitation treatment. There are different degrees of depression and anxiety, which have adverse effects on intervention compliance and disease rehabilitation\[11-13\]. Consequently, it is very important for patients with CHD to have the support of effective nursing interventions after interventional operations.

Routine nursing lacks systematisms and timeliness, and problems, such as unhealthy diet and irregular medication use, still occur during the intervention period. Hence, it is difficult to meet the rehabilitation needs of patients with CHD after intervention\[14\]. Maslow’s hierarchy of needs theory holds that there are five different levels of needs, and there are significant differences in the urgency of various needs across different periods. Patients usually show the strongest urgency for physiology, safety, attribution, and love during hospitalization, followed by the need for respect and self-realization. Additionally, the needs of the next level will appear only after the needs of the former level are effectively met. With changes in medical concepts, meeting the multiple levels of needs of patients to the greatest extent has become the goal of clinical nursing work\[15-17\]. Therefore, nursing should start at the most basic level, by prioritizing meeting the physiological needs of patients and systematically...
meeting the needs of other levels of patients to provide patients with targeted and effective nursing services in clinical practice. Lester et al.[18] showed that a nursing intervention based on Maslow’s hierarchy of needs, during the rehabilitation of patients with acute myocardial infarction after PCI, effectively improved their medication compliance and regulated their psychological state. The results of a study by Zalenski et al.[19] showed that such a nursing intervention alleviated the negative emotion of inpatients in cardiology departments, restored their ability to engage in daily life, improved their quality of life, shortened hospitalization time, and urged patients to recover and leave the hospital as soon as possible. The results of this study showed that the scores on all dimensions of self-efficacy in the research group with the nursing plan based on Maslow’s hierarchy of needs theory were higher than those in the control group. However, the SDS and SAS scores in the research group were lower than those in the control group. Findings also showed that the standardized medication rate (97.87%), moderate exercise rate (97.87%), healthy diet rate (95.74%), and regular review rate (97.87%) in the research group were higher than those in the control group ($P < 0.05$). In addition, nursing intervention could effectively alleviate the negative mood of patients undergoing coronary intervention surgery, improve self-efficacy, and improve patients’ compliance to interventions. This may be because conventional nursing pays attention to providing only basic nursing services for patients. The nursing process tends to be mechanized, and its content and form are single; hence, it is difficult to meet effectively the physical and mental needs of patients. Nursing plans based on Maslow’s hierarchy of needs theory provide personalized nursing services based on the specific nursing needs of patients, which involve many aspects, such as psychological, physiological, spiritual, social, and cultural needs, along with logical nursing measures. With clear intervention objectives, various nursing measures are associated with good certainty, predictability, and pertinence, which can effectively meet the pathophysiological needs of the patients. Furthermore, attention should be paid to the gradual transition from physiological needs to high-level needs in order to improve the psychological state and enhance the compliance of patients to interventions while urging them to cooperate actively with the treatment and nursing work in the nursing plan based on this theory[20]. In addition, the physiological needs of patients in the research group are effectively met through dietary guidance; ensuring cleanliness and hygiene in the ward and regularly assisting in turning over patients, along with strengthening safety protections that effectively meet the safety needs of patients; psychological interventions and strengthening external support can meet patients’ love and belonging needs and respect needs; patient exchanges can meet the needs of self-realization, enhance self-value, and regulate physical and mental states from multiple levels during the nursing period.

In addition, satisfaction with the nursing job in the research group was higher than that in the control group ($P < 0.05$). This suggests that the nursing scheme based on Maslow’s hierarchy of needs theory can also deepen the recognition of nursing work among patients undergoing interventional surgery for CHD. The main reason is that it can alleviate negative emotions and improve the self-efficacy of patients, providing higher satisfaction.

**CONCLUSION**

Generally, the intervention for patients with CHD based on Maslow’s hierarchy of needs theory can effectively alleviate patients’ negative emotions, enhance self-efficacy, and enhance intervention compliance. In addition, patients report high satisfaction with the nursing work. However, most of the indicators selected in this study were subjectively evaluated by patients and objective indicators were lacking. Therefore, the effectiveness of the research still needs to be further explored and confirmed by clinical selection of other objective indicators.

**ARTICLE HIGHLIGHTS**

**Research background**

If patients with coronary heart disease (CHD) do not receive timely and effective intervention, heart failure can develop as the disease progresses.
Research motivation
Routine nursing care for patients is mostly done passively, with not enough attention paid to the pathological needs and emotional needs of patients.

Research objectives
We want to explore the application value of nursing intervention based on Maslow’s hierarchy of needs theory.

Research methods
We selected 94 patients with CHD undergoing interventional surgery in our hospital and divided into research group and control group.

Research results
Nursing job satisfaction in the research group (93.62%) was higher than that in the control group (78.72%).

Research conclusions
The intervention for patients with CHD based on Maslow’s hierarchy of needs theory has high satisfaction with the nursing work.

Research perspectives
The effectiveness of the research still needs to be further explored and confirmed by clinical selection of other objective indicators.

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Impacts of statin and metformin on neuropathy in patients with type 2 diabetes mellitus: Korean Health Insurance data

Hong Ki Min, Se Hee Kim, Jong Han Choi, Kyomin Choi, Hae-Rim Kim, Sang-Heon Lee

Abstract

BACKGROUND
Neuropathy is a common chronic complication in type 2 diabetes mellitus (T2DM). Statin and metformin are commonly used medications in T2DM patients, and some studies showed statin- or metformin-induced neuropathy.

AIM
To evaluate the incidence of neuropathy among patients with T2DM associated with statin and metformin therapies.

METHODS
Korean Health Insurance Review and Assessment national patient sample data from 2016 and 2017 were used. Patients with T2DM and no complications were divided into statin/metformin/statin + metformin users and non-users. Neuropathy incidence was defined by International Statistical Classification of Diseases and Related Health Problems, 10th revision codes and concomitant prescriptions for anticonvulsants or antidepressants. Logistic regression analyses were conducted to examine the associations between statin/metformin/statin + metformin therapies and the incidence of neuropathy. Propensity score (PS) matching was performed on the basis of age, sex and comorbidities.

RESULTS
Overall, 34964 and 35887 patients with T2DM and no complications were included in the Korean Health Insurance Review and Assessment national patient sample datasets from 2016 and 2017, respectively. Statin therapy was associated
with increased risks of neuropathy in 2016 and 2017 [PS-matched odds ratio (OR) = 1.22, 95% confidence interval (CI): 1.08-1.38; PS-matched OR = 1.17, 95%CI: 1.03-1.33, respectively]. Metformin therapy was associated with reduced risks of neuropathy in 2016 and 2017 (PS-matched OR = 0.30, 95%CI: 0.21-0.42; PS-matched OR = 0.44, 95%CI: 0.32-0.60, respectively). Combined statin + metformin therapy was not significantly associated with neuropathy in 2016 or 2017 (PS-matched OR = 0.85, 95%CI: 0.61-1.19; PS-matched OR = 0.95, 95%CI: 0.66-1.38, respectively).

CONCLUSION
Statin therapy was associated with enhanced risk of new-onset neuropathy in patients with T2DM, but metformin therapy showed the opposite association.

Key Words: Diabetes mellitus; Neuropathies; Hydroxymethylglutaryl-CoA reductase inhibitors; Metformin

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Core Tip: Diabetic neuropathy is one of the most common chronic complications in patients with type 2 diabetes mellitus. Statin is a commonly used lipid lowering agent in patients with type 2 diabetes mellitus, and metformin is background medication for type 2 diabetes mellitus. In some observational studies, statin and metformin were associated with an increased risk of neuropathy. In the present study using Korean Health Insurance Review and Assessment national patient sample data, the use of statin was associated with increased risk of diabetic neuropathy occurrence, whereas metformin use showed a negative association with diabetic neuropathy.

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INTRODUCTION
The prevalence of type 2 diabetes mellitus (T2DM) and dyslipidemia are increasing with increased population aging worldwide[1,2]. These two diseases are related to cardiovascular disease (CVD), such that they result in higher incidences of CVD-related morbidities and mortalities. Therefore, the proper management of T2DM and dyslipidemia is important for preventing CVD[3,4]. Furthermore, the treatment targets for dyslipidemia differ among comorbidities, and patients with very high risks of CVD are recommended to have low-density lipoprotein-cholesterol levels below 70 mg/dL[3]. Several major risk factors for CVD are known, including dysglycemia (e.g., T2DM)[3]. In practice, statins (i.e., hydroxymethylglutaryl-CoA reductase inhibitors) are used as first-line therapy for dyslipidemia[3]. Despite their broad usage, some studies have shown that statins may induce neuropathy[5,6].

Metformin, a biguanide, is a first-line oral medication for patients with T2DM that can reduce hepatic glucose production and intestinal glucose absorption, but it also enhances insulin sensitivity[4]. In addition to its primary therapeutic effects, metformin has demonstrated anti-inflammatory effects through the modulation of the AMPK/mTOR pathway[7]. Furthermore, metformin does not induce hypoglycemia, which is a critical side effect of other anti-diabetic drugs. Although metformin is commonly used as a background medication in patients with T2DM[4,8], a potential risk for metformin-induced neuropathy has recently been proposed. Patients with T2DM and neuropathy reportedly have lower vitamin B12 levels, and a higher metformin dose is associated with lower vitamin B12 levels[9]. However, the association between metformin and diabetic neuropathy remains controversial[10].

Dyslipidemia in patients with T2DM is more severe in terms of inducing atherosclerosis, high triglyceride levels, reduced high-density lipoprotein-cholesterol levels...
and elevated low-density lipoprotein-cholesterol levels\cite{11}. Furthermore, there are shared risk factors (e.g., old age and obesity) between T2DM and dyslipidemia\cite{12,13}. Therefore, the use of anti-diabetic medications and statins in both groups of patients are common situations in clinical practice. In addition, neuropathy is a chronic microvascular complication in patients with T2DM that depends on the duration and severity of T2DM. Therefore, primary prevention \textit{via} proper glycemic control is important\cite{12}. In addition, the avoidance of additional risk of neuropathy is an important consideration. However, little is known regarding the impact of commonly used medications, \textit{i.e.} statins and metformin, on neuropathy development in patients with T2DM.

The Korean health insurance system covers the entire population of residents in Korea. All health care facilities provide medical services to patients, then submit insurance benefit claims to the national health insurance service. These insurance claims are collected in the Health Insurance Review and Assessment (HIRA) database, which is used annually to produce representative sample data comprising approximately 3\% of all insurance claims, the HIRA national patient sample (NPS). HIRA-NPS data are useful for analyzing various medical insurance-related data including treatments, procedures, prescriptions, patient demographics and health care provider information. Furthermore, these data can be used to analyze the incidences of specific disorders based on operational definitions.

In the present study, we evaluated the influence of statin, metformin and statin + metformin therapies on the incidence of neuropathy in patients with T2DM using Korean HIRA-NPS data from 2016 and 2017.

\section*{MATERIALS AND METHODS}

\subsection*{Data sources}

Korean HIRA-NPS data are produced annually, and this study included HIRA-NPS data from 2016 and 2017. Korea has a unique government-funded insurance system, in which claims data are generated when healthcare facilities file insurance benefit claims with HIRA. These claims data include diverse information such as patient demographics; detailed information concerning treatments, costs, prescriptions and healthcare provider information. The Korean HIRA annually provides sample data, the NPS, by randomly extracting nationwide health insurance claims data using a sampling strategy stratified according to sex and age. Each HIRA-NPS dataset includes data collected for the entire index year. Approximately 3\% of all covered patients, approximately 1.45 million individuals, are selected for inclusion in the sample, and their personal information is anonymized. Therefore, HIRA-NPS claims data represent real-world clinical circumstances that occur throughout Korea.

This study was conducted in accordance with the tenets of the Declaration of Helsinki (1964). Written informed consent for enrollment was waived because the data were provided by HIRA. This study was approved by the Institutional Review Board of Konkuk University Medical Center (Approval number: 2020-12-057).

\subsection*{Data extraction}

Considering the characteristics of HIRA-NPS data, operational definitions of T2DM and new-onset neuropathy were used in this study. Patients were selected based on the International Statistical Classification of Diseases and Related Health Problems, 10\textsuperscript{th} revision (ICD-10). At baseline, ICD-10 codes for T2DM without chronic complications were selected for the following ICD-10 codes: E110, E111, E119, E120, E121, E129, E130, E131, E139, E140, E141 and E149. In addition, participants were included if they had anatomic therapeutic chemical codes for prescriptions of the anti-diabetic medications A10A and A10B for more than 30 d within the first 3 mo. Patients were excluded if they were prescribed antidepressants (N06A) or anticonvulsants (N03AX12 and N03AX16) within the first 3 mo because these could be used for diabetic neuropathy\cite{14}. Considering the etiology of T2DM, patients older than 30 years of age were included in the study. To exclude other causes of neuropathy, patients with connective tissue diseases (ICD-10 codes: M05, M06, M30, M31, M32, M33, M34, M35 and M45), renal failure (ICD-10 codes: I120, I131, I132, N17, N18 and N19) and malignancy (ICD-10 codes: C00–C97) were excluded at baseline. The first 3 mo were selected as the duration of exposure to statin/metformin/statin + metformin, and exposure to each medication was defined as a prescription for more than 30 d of treatment. Patients who had never been prescribed these medications were defined as the non-exposure group. The statin + metformin non-exposure group was defined as patients who had never been prescribed these medications.
patients who had not been exposed to statins or metformin. Anatomical therapeutic chemical codes were used to identify prescriptions for statins (C10AA01–C10AA08) and metformin (A10BA02). Patients with combination medications, such as statins with other dyslipidemia or antihypertensive medications or metformin with other anti-diabetic medications, were excluded from the assessment of medication exposure to specifically evaluate the influence of statins or metformin on neuropathy incidence. The incidence of new-onset neuropathy was investigated within the final 9 mo of the index year. The combined disease codes for diabetic neuropathy (ICD-10 codes: E114, E124, E134, E144, G590 and G632) and prescriptions of either tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors or anticonvulsants recommended by the American Diabetes Association[14] [anatomic therapeutic chemical codes: N03AX12 (gabapentin), N03AX16 (pregabalin), N06AA01 (desipramine), N06AA02–N06AA05 (imipramine), N06AA09 (amitriptyline), N06AA10 (nortriptyline), N06AX16 (venlafaxine) and N06AX21 (duloxetine)] for more than 30 d were used to identify patients with new-onset neuropathy. The ICD-10 codes for diabetic neuropathy were selected because the use of anticonvulsants or serotonin–norepinephrine reuptake inhibitors is covered by national health insurance for patients with diabetic neuropathy but not for patients with nonspecific neuropathy. Therefore, in Korea, neuropathy medications (i.e. anticonvulsants or antidepressants) are usually prescribed after the submission of the ICD-10 codes for diabetic neuropathy in patients with T2DM. In this study, we identified drug-induced neuropathy by only including patients with ICD-10 codes for diabetic neuropathy and combined prescriptions of antidepressants or anticonvulsants after at least 90 d of exposure to statin/metformin/statin + metformin therapies. The schematic diagram of the research protocol is presented in Figure 1. The patients were divided into the following 10-year age-group intervals: 30–39, 40–49, 50–59, 60–69 and > 70 years.

Statistical analysis
Baseline demographic characteristics are summarized as numbers and percentages and compared using the χ² test or Fisher’s exact test. Propensity score (PS)-matching was performed by 1:1 matching according to age, sex and comorbidities included in the Charlson Comorbidity Index[15]. Logistic regression analyses were performed to calculate crude and PS-matched odds ratios (ORs) for new-onset neuropathy. Values of P < 0.05 were considered to indicate statistical significance. All tests were performed using R software (R for Windows 3.3.2; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Comparison of baseline characteristics and incidence of neuropathy between statin/metformin/statin + metformin users and non-users

The HIRA-NPS datasets for 2016 and 2017 included 1468033 and 1473083 patients, respectively. In each year, 34964 and 35887 patients had T2DM without diabetic complications, respectively (Figure 2). Statin therapy analyses showed that 17413 patients received statin therapy, and 17267 patients did not receive statin therapy in 2016. In 2017, 18707 patients received statin therapy, and 16882 patients did not. The overall age distributions between the two groups were comparable in both 2016 and 2017 (Supplementary Tables 1 and 2). The incidence of neuropathy was greater in statin users than in statin non-users in 2016 [582/17413 (3.34%) vs 477/17267 (2.76%), P = 0.0017]. In 2017, statin users had a greater incidence of neuropathy compared with statin non-users, but this difference was not statistically significant [562/17413 (3.34%) vs 477/17267 (2.76%), P = 0.0507]. However, comparisons after PS matching showed similar results in both 2016 and 2017, such that the incidence of neuropathy was greater in statin users than in statin non-users [2016: 579/17267 (3.35%) vs 477/17267 (2.76%), P = 0.0014; 2017: 523/16882 (3.10%) vs 449/16882 (2.66%), P = 0.0160; Table 1].

Metformin therapy analyses showed that 30683 patients received metformin therapy, and 3922 patients did not receive metformin therapy in 2016. In 2017, 31624 patients received metformin therapy, and 4004 patients did not. The overall age distribution did not differ significantly between the two groups in 2016 or 2017 (Supplementary Tables 3 and 4). The incidence of neuropathy was lower in metformin users than in metformin non-users in 2016 [914 (2.98%) vs 158 (4.03%), P = 0.0004]. In 2017, metformin users had a reduced incidence of neuropathy compared with metformin non-users, but this difference was not statistically significant [959 (3.03%) vs 143 (3.57%), P = 0.0635]. Comparisons after PS matching showed lower incidences of
Table 1 Incidence of neuropathy in statin user and non-user group

<table>
<thead>
<tr>
<th></th>
<th>Statin user, n (%)</th>
<th>Statin non-user, n (%)</th>
<th>P value</th>
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<th>Statin user, n (%)</th>
<th>Statin non-user, n (%)</th>
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<td><strong>2016</strong></td>
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<tr>
<td>Neuropathy incidence</td>
<td>582/17413 (3.34)</td>
<td>477/17267 (2.76)</td>
<td>0.0017</td>
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<td>579/17267 (3.35)</td>
<td>477/17267 (2.76)</td>
<td>0.0014</td>
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<td><strong>2017</strong></td>
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<tr>
<td>Neuropathy incidence</td>
<td>562/18707 (3.00)</td>
<td>449/16882 (2.66)</td>
<td>0.0507</td>
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<td>523/16882 (3.10)</td>
<td>449/16882 (2.66)</td>
<td>0.0160</td>
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Propensity score-matching was performed by including baseline age, gender and comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, AIDS).

Figure 1 Schematic of the study plan including the medication exposure period and event (newly developed neuropathy) detection period. Neuropathy was checked as new onset neuropathy that was detected at least 90 d after first exposure to issued medication to reduce detection bias and determine whether new onset neuropathy was affected by these medications. T2DM: Type 2 diabetes mellitus; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10\textsuperscript{th} revision; SNRI: Serotonin-norepinephrine reuptake inhibitor.

Risks of neuropathy in statin/metformin/statin + metformin users

Logistic regression analysis demonstrated that statin therapy was significantly and positively associated with neuropathy incidence in both 2016 and 2017 [PS-matched OR = 1.22, 95% confidence interval (CI): 1.08-1.38; PS-matched OR = 1.17, 95%CI: 1.03-1.33, respectively]. Furthermore, metformin therapy was consistently negatively associated with neuropathy incidence in both 2016 and 2017 (PS-matched OR = 0.30, 95%CI: 0.21-0.42; PS-matched OR = 0.44, 95%CI: 0.32-0.60, respectively). Combined statin + metformin therapy was not associated with a significant risk of neuropathy in 2016 or 2017. The results of logistic regression analyses are summarized in Table 4.

neuropathy in metformin users in both 2016 and 2017 (Table 2).

Combined statin + metformin therapy analyses showed that 14524 patients received both therapies in 2016, but 2175 patients received neither therapy. In 2017, 16096 received both therapies, but 2040 patients received neither therapy. The age distributions were comparable between statin + metformin users and non-users in both 2016 and 2017 (Supplementary Tables 5 and 6). In 2016, statin + metformin users had a lower incidence of neuropathy compared with statin + metformin non-users [438 (3.02%) vs 83 (3.82%), P = 0.0452]. This difference was also present in 2017 but was not statistically significant [472 (2.93%) vs 65 (3.19%), P = 0.5239]. Comparisons after PS matching showed that the incidences of neuropathy were comparable between the two groups in both 2016 and 2017 (Table 3).
Table 2 Incidence of neuropathy in metformin user and non-user group

<table>
<thead>
<tr>
<th></th>
<th>Metformin user, n (%)</th>
<th>Metformin non-user, n (%)</th>
<th>P value</th>
<th>Metformin user, n (%)</th>
<th>Metformin non-user, n (%)</th>
<th>P value</th>
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<tr>
<td>2016 Neuropathy incidence</td>
<td>914/30683 (2.98)</td>
<td>158/3922 (4.03)</td>
<td>0.0004</td>
<td>49/3922 (1.25)</td>
<td>158/3922 (4.03)</td>
<td>&lt; 0.0001</td>
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<td>2017 Neuropathy incidence</td>
<td>959/31624 (3.03)</td>
<td>143/4004 (3.57)</td>
<td>0.0635</td>
<td>64/4004 (1.60)</td>
<td>143/4004 (3.57)</td>
<td>&lt; 0.0001</td>
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</table>

1Propensity score-matching was performed by including baseline age, gender, and comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, AIDS).

Table 3 Incidence of neuropathy in statin + metformin user and non-user group

<table>
<thead>
<tr>
<th></th>
<th>Statin + metformin user, n (%)</th>
<th>Non-user, n (%)</th>
<th>P value</th>
<th>Statin + metformin user, n (%)</th>
<th>Non-user, n (%)</th>
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<tr>
<td>2016 Neuropathy incidence</td>
<td>438/14524 (3.02)</td>
<td>83/2175 (3.82)</td>
<td>0.0452</td>
<td>71/2175 (3.26)</td>
<td>83/2175 (3.82)</td>
<td>0.3248</td>
</tr>
<tr>
<td>2017 Neuropathy incidence</td>
<td>472/16096 (2.93)</td>
<td>65/2040 (3.19)</td>
<td>0.5239</td>
<td>62/2040 (3.04)</td>
<td>65/2040 (3.19)</td>
<td>0.7868</td>
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</table>

1Propensity score-matching was performed by including baseline age, gender, and comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, AIDS).

**DISCUSSION**

In the present study, we demonstrated an elevated risk of neuropathy among statin users and a reduced risk of neuropathy among metformin users in patients with T2DM. Notably, combined statin + metformin therapy was not associated with new-onset neuropathy in patients with T2DM. These findings were based on real-world insurance claims data from the Korean population. Statins can cause neuropathy, and impaired mitochondrial transport and a reduction in vitamin E levels have been proposed as underlying mechanisms [16]. An analysis of 757 patients with diabetes revealed a significantly greater relative risk of peripheral neuropathy in patients with diabetes who were receiving statin therapy [6]. Our results included a larger sample size than in previous studies and confirmed the elevated risk of neuropathy in patients with T2DM during statin therapy.

The influence of metformin therapy on neuropathy incidence is not yet established. Strict control of hyperglycemia is the most important treatment principle for preventing diabetic microvascular complications including neuropathy [17], and metformin exerts anti-diabetic effects via several mechanisms. Therefore, metformin can function to prevent the onset of diabetic neuropathy. In an animal study, metformin treatment protected against neural damage by increasing the levels of neural growth factor, vascular endothelial growth factor and anti-inflammatory factors [18]. Another animal study demonstrated that metformin preserved peripheral nerve fiber density and that the beneficial effects of metformin were comparable with those of alpha lipoic acid, an antioxidant used in the clinical treatment of diabetic neuropathy [19].

By contrast, metformin causes vitamin B12 deficiency and may subsequently induce diabetic neuropathy [20]. In a cross-sectional study, low to borderline vitamin B12 levels were more common in patients with diabetic neuropathy than in patients without (64% vs 17%) [9]. However, another study demonstrated a non-significant
Table 4 Logistic regression analyses for neuropathy occurrence in 2016 and 2017 Health Insurance Review and Assessment national patient sample data

|                  | OR    | 95%CI        | Propensity score-matched'
|------------------|-------|--------------|-----------------------------
|                  |       |              |                             |
| 2016             |       |              |                             |
| Statin use       | 1.22  | 1.07-1.38    | 1.22                        |
| Metformin use    | 0.73  | 0.61-0.87    | 0.30                        |
| Statin + metformin use | 0.78  | 0.62-1.01    | 0.85                        |
| 2017             |       |              |                             |
| Statin use       | 1.13  | 1.00-1.29    | 1.17                        |
| Metformin use    | 0.84  | 0.71-1.02    | 0.44                        |
| Statin + metformin use | 0.92  | 0.70-1.21    | 0.95                        |

1Propensity score-matching was performed by including baseline age, gender, and comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, AIDS). OR: Odds ratio; CI: Confidence interval.

association between metformin therapy and vitamin B12 levels and showed that vitamin B12 levels were not associated with the severity or prevalence of neuropathy in patients with T2DM[10]. The vitamin B12 reductions were dose-dependent in patients with T2DM who were receiving metformin therapy, and patients with metformin daily doses greater than 1500 mg had a significant risk of vitamin B12 deficiency[21]. In the present study, we found a reduced risk of neuropathy in patients with T2DM who were receiving metformin therapy. Further studies to stratify patients according to metformin daily doses and prospectively collect vitamin B12 and blood glucose levels could reveal whether metformin dose influences the incidence of neuropathy and which aspect (vitamin B12 or blood glucose) more strongly influences neuropathy development during metformin therapy.

We demonstrated that combined metformin + statin therapy did not enhance or reduce the risk of neuropathy in patients with T2DM, although statin therapy enhanced the risk of neuropathy and metformin therapy reduced the risk of neuropathy in these patients. The present results do not clearly indicate whether
concomitant metformin administration can reduce the risk of statin-induced neuropathy in patients with T2DM because the findings were based on epidemiological data. However, metformin is regarded as background anti-diabetic medication and is used in most patients with T2DM, except those with contraindications or severe metformin-related side effects[4,8]. Our results suggest a beneficial effect of metformin in terms of reducing the risk of neuropathy, especially in patients with T2DM who are receiving statin therapy.

There were some limitations in the present study. First, the data were retrospectively collected and did not include important baseline characteristics (e.g., duration of T2DM and doses of each medication). Although PS matching was used to reduce the effects of confounders, unidentified confounders or selection biases might have been present. Therefore, the enhanced neuropathy risk associated with statin therapy does not directly indicate a role for statins in the onset of neuropathy. Similarly, the reduced neuropathy risk associated with metformin therapy does not directly indicate a protective role of metformin against the onset of neuropathy. Second, claims data have intrinsic limitations in terms of possible misdiagnosis and misprescription, and it is difficult to distinguish between T2DM-induced and medication-induced neuropathies. However, HIRA-NPS data are extracted from the overall Korean population and are therefore suitable for the assessment of specific disease risks. Third, HIRA-NPS data only provide 1-year follow-up data for each index year, which is a relatively short time period. Fourth, although the NPS sample was collected using a stratification strategy and could be analyzed easily, it only included approximately 3% of the overall health insurance claims data. Therefore, the analysis of data collected over longer time periods from larger samples should be performed in future studies. Furthermore, in vivo and in vitro basic research is needed to determine the mechanisms by which statins and metformin contribute to the onset or prevention of neuropathy.

CONCLUSION

We demonstrated the influence of statin and metformin therapies on the incidence of neuropathy in patients with T2DM. Statin therapy enhanced the risk of neuropathy in patients with T2DM, whereas metformin therapy reduced this risk. Combined statin + metformin therapy did not have a significant impact on the incidence of neuropathy. Therefore, when prescribing statin therapy for patients with T2DM, physicians should assess the potential for neuropathy development and consider the addition of metformin to reduce this risk.

ARTICLE HIGHLIGHTS

Research background
Statin and metformin are widely used medications in patients with type 2 diabetes mellitus (T2DM). These medications have been claimed as causative agents for neuropathy.

Research motivation
To identify the incidence and risk of statin, metformin and statin + metformin therapy on new onset neuropathy.

Research objectives
The incidence of neuropathy was evaluated and compared between T2DM patients who used or did not use statin/metformin/statin + metformin by using Korean Health Insurance Review and Assessment - national patient sample data.

Research methods
The prospective cohort study used nation-wide health insurance data.

Research results
Statin therapy showed a positive association (odds ratio = 1.22, 95% confidence interval: 1.08-1.38), whereas metformin therapy showed a negative association with new onset neuropathy (odds ratio = 0.30, 95% confidence interval: 0.21-0.42) in
patients with T2DM. Combination therapy of statin and metformin did not have an effect on new onset neuropathy of T2DM patients.

**Research conclusions**

The widely used medications in T2DM, statin and metformin, could have an effect on new onset neuropathy development in T2DM patients. Physicians should pay attention to new onset neuropathy when using statin in T2DM patients.

**Research perspectives**

Nevertheless, further studies are required to reveal underlying mechanisms of statin and metformin on new onset neuropathy of T2DM.

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Is endoscopic retrograde appendicitis therapy a better modality for acute uncomplicated appendicitis? A systematic review and meta-analysis

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Abstract

BACKGROUND
Previous studies had shown endoscopic retrograde appendicitis therapy (ERAT) is an effective treatment for acute appendicitis. However, different studies reported conflicting outcomes regarding the effectiveness of ERAT in comparison with laparoscopic appendectomy (LA).

AIM
To compare the effectiveness of ERAT with LA.

METHODS
Randomized controlled trials (RCTs) and retrospective studies of ERAT for acute uncomplicated appendicitis were searched in PubMed, Cochrane Library, Web of Science, Embase database, China National Knowledge Infrastructure (CNKI), the WanFang Database, and Chinese Scientific Journals Database (VIP) from the establishment date to March 1 2021. Heterogeneity was assessed using the I-squared statistic. Pooled odds ratios (OR), weighted mean difference (WMD), and standard mean difference (SMD), with 95% confidence intervals (CI) were calculated through either fixed-effects or random-effects model. Sensitivity analysis was also performed. Publication bias was tested by Egger’s test, and Begg’s test. The quality of included RCT were evaluated by the Jadad scale, while Newcastle-Ottawa scale is adopted for assessing the methodological quality of case-control studies. All statistical analysis was performed using Stata 15.1 statistical software. All statistical analysis was performed using Stata 15.1 statistical software. This study is registered with PROSPERO, CRD42021243955.

RESULTS
After screening, 10 RCTs and 2 case-control studies were included in the current systematic review. Firstly, the length of hospitalizations [WMD = -1.15, 95%CI: -1.99, -0.31; P = 0.007] was shorter than LA group. Secondly, the level of postoperative CRP [WMD = -10.06, 95%CI: (-17.39, -2.73); P = 0.007], TNF-α [WMD = -7.70, 95%CI: (-8.47, -6.93); P < 0.001], and IL-6 Levels [WMD = -9.78, 95%CI: (-10.69, -8.88); P < 0.001; P < 0.001] in ERAT group was significantly lower than LA group. Thirdly, ERAT group had a lower incidence of intestinal obstruction than LA group. [OR = 0.19, 95%CI: (0.05, 0.79); P = 0.020]. Moreover, the quality of 10 RCTs were low with 0-3 Jadad scores, while the methodological quality of two case-control studies were fair with a score of 2 (each).

CONCLUSION
Compared with LA, ERAT reduces operation time, the level of postoperative inflammation, and results in fewer complications and shorter recovery time, with preserving the appendix and its immune and biological functions.

Key Words: Endoscopic retrograde appendicitis therapy; Acute appendicitis; Meta-analysis; Laparoscopic appendectomy; Randomized controlled study

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Core Tip: Acute appendicitis is one of the common surgical emergencies all over the world, with a mean cost of about $9000 per procedure. It is recognized that the conventional treatment of acute appendicitis was laparoscopic appendectomy (LA), while an increasing number of surgical complications, include bleeding, adhesive intestinal obstruction, infection of the incision, and intestinal fistula, have been reported. Therefore, we conducted a meta-analysis to compare the effectiveness of endoscopic retrograde appendicitis therapy (ERAT) with standard treatment. After screening, 12 studies were included in the current systematic review and we found that, compared with LA, ERAT reduces operation time, the level of postoperative inflammation, and results in fewer complications and shorter recovery time, with preserving the appendix and its immune and biological functions.
INTRODUCTION

Acute appendicitis is one of the common surgical emergencies all over the world, with a mean cost of about $9000 per procedure[1,2].Appendicitis is one of the most frequent specific underlying causes in patients presenting to emergency departments with abdominal pain[3,4].The majority (approximately 70%-80%) of acute appendicitis cases are of uncomplicated nature[5,6].It is reported that the incidence of appendicitis is rising, which is about 1 per 1,000 in the America[7,8].At present, the etiology of acute appendicitis is still unknown. Common etiological factors, including luminal obstruction from appendiceal fecalith, stool, lymphoid hyperplasia, and neoplasm result in about half of the cases, with stool and appendiceal fecalith as more common causes[9].

LA is currently widely applied for the treatment of acute appendicitis. Although patients could benefit from LA with a decreased wound infection rate, shorter hospital stay, and better diagnostic power[10], some complications cannot be ignored. Liang TJ et al[11] investigated 864 patients who developed acute appendicitis recurrence in a median follow-up of 6.5 years. The authors found that 258 patients were performed LA, which accounted for about 30%. What’s more, an increasing number of surgical complications after LA, including bleeding, adhesive intestinal obstruction, infection of the incision, appendiceal remnants, and intestinal fistula[12].

In 2012, Liu et al[13] proposed a new endoscopic minimally invasive treatment for appendicitis, namely Endoscopic retrograde appendicitis therapy (ERAT). After preoperative bowel preparation, the appendix was intubated through the colonoscopy with a transparent cap at the head end, and the diagnosis of appendicitis was confirmed by angiography under X-ray monitoring. It can also relieve the obstruction of the appendix lumen, drain the pus, and flush the lumen to control the inflammation. It also allows the placement of drainage tube into the lumen to ensure the smooth drainage through the appendiceal orifice, reduce the risk of recurrence of appendicitis caused by obstruction.

Previous studies had shown ERAT as an effective treatment for acute appendicitis complicated with local perforation and/or periappendiceal abscess[14]. However, different studies reported conflicting outcomes regarding the effectiveness of ERAT in comparison with LA. Therefore, we conducted a meta-analysis to compare the effectiveness of ERAT with LA for adults.

MATERIALS AND METHODS

Preferred reporting items for systematic reviews and meta-analyses

The Preferred Reporting Items declared by the Systematic Review and Meta-Analysis (PRISMA)[15] was utilized in the performance of this study. The databases including PubMed, Cochrane Library, Web of Science, Embase database, China National Knowledge Infrastructure (CNKI), the WanFang Database, and Chinese Scientific Journals Database (VIP), were searched by using the searching terms including acute appendicitis (acute uncomplicated appendicitis) and endoscopic retrograde appendicitis therapy [endoscopic retrograde appendiceal radiography (ERAR), endoscopic appendiceal irrigation (EAI), and endoscopic appendiceal stent placement (ERSP)]. By taking the retrieval in PubMed as an example, the concrete retrieval strategies are as follows: (acute appendicitis [Mesh Terms] OR acute appendicitis [Title/Abstract] OR acute uncomplicated appendicitis[Mesh Terms] OR acute uncomplicated appendicitis [Title/Abstract]) AND (endoscopic retrograde appendicitis therapy [Mesh Terms] OR endoscopic retrograde appendicitis therapy [Title/Abstract] OR endoscopic retrograde appendiceal radiography [Mesh Terms] OR endoscopic appendiceal irrigation [Title/Abstract] OR endoscopic appendiceal stent placement [Title/Abstract]).
The retrieval time of each database is from the establishment of the database to March 1, 2021. The reference of related literatures and reviews were also retrieved manually to ensure that there was no omission, and the prospective study of ERAT on acute appendicitis published in the literatures are statistically analyzed. The protocol of this systematic review and meta-analysis has already prospectively registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (reference no. CRD42021243955).

Study selection
Studies that met the following criteria were considered to be eligible for inclusion: (1) Study design: Randomized controlled trials, retrospective studies, and prospective studies; (2) Patients: The subjects were clinically diagnosed as acute uncomplicated appendicitis patients; (3) Outcomes: Literatures should provide accurate comprehensive statistical indicators: Sample Size, length of hospitalizations, operation time, recovery time, length of hospitalization, risk of complications; (4) Intervention and control: Intervention was endoscopic retrograde appendicitis therapy, while control group receiving LA; and (5) Articles published in English or Chinese. Exclusion criteria: (1) Duplicate publications; (2) Studies without sufficient data; and (3) Care reports, meta-analysis and reviews, study without English abstract and studies only with abstract were also excluded.

Literature quality evaluation and data extraction
Literature screened by two reviewers independently according to the inclusion and exclusion criteria mentioned above. Any disagreements were resolved through discussion with a third reviewer to reach a consensus. The following data were extracted: first author’s name, the time of publication, the type of appendicitis, the participants of the experimental and control group, interventions, and outcomes (the bed rest time, time interval of body temperature returning to normal range, and time interval of white blood cell count returning to normal range, et al). Included RCT studies were evaluated by the Jadad scale regarding quality and methodology, where a higher score (total score of seven) suggests more rigorosity of a trial’s methodological design[16]. For both case-control and cohort studies, Newcastle-Ottawa scale [17] is adopted for assessing the methodological quality, which provides a comprehensive score system with eight items.

Statistical analysis
Heterogeneity test was performed with Stata 15.0 statistical software (Stata Corp., College Station, TX). The bed rest time, body temperature return to normal time and white blood cells return to normal time were combined by standard mean difference (SMD) with 95%CI, while duration of operation, length of hospitalizations, and levels of inflammatory factors were combined by weighted mean difference (WMD) with 95%CI. Q-test and I2-test were used to analyze the heterogeneity of the studies included in this meta-analysis. If $P > 0.100$ and $I^2 < 50\%$, it was considered that there was small heterogeneity among the studies, and fixed effect model was chosen; otherwise, random effect model was used to merge SMD with 95%CI[18]. The pooled relative risk (RR) with 95%CI: Was performed to analyze the risk of complications. Data of the outcomes were recorded for this meta-analysis when three or more trials reported the same outcome. Sensitivity analyses were performed to investigate the robustness of this meta-analysis. Meanwhile, the risk of publication bias was evaluated by Egger’s test, Begg’s test, and funnel plots[19]. If the heterogeneity shown $P < 0.100$ and $I^2 > 50\%$, considered that there was large heterogeneity among the studies. Egger’s test was assessed by using Stata 15.0.
**Table 1** Detailed characteristics of included studies in this meta analysis

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Studies types</th>
<th>Patients age</th>
<th>Treatment</th>
<th>Sample size</th>
<th>Disease</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang et al [20], 2020</td>
<td>RCT</td>
<td>1 to 13 years old</td>
<td>Modified ERAT</td>
<td>36/47</td>
<td>Acute uncomplicated appendicitis in children</td>
<td>Length of hospital stay</td>
</tr>
<tr>
<td>Deng et al [21], 2018</td>
<td>RCT</td>
<td>18-62 years old</td>
<td>ERAT</td>
<td>20/20</td>
<td>Acute appendicitis</td>
<td>Duration of operation, Bed rest time; time interval of body temperature returning to normal range; time interval of white blood cells count returning to normal time range, complication</td>
</tr>
<tr>
<td>Huang et al [22], 2020</td>
<td>RCT</td>
<td>18-65 years old</td>
<td>ERAT</td>
<td>78/119</td>
<td>Acute appendicitis</td>
<td>Duration of operation, bed rest time, complication</td>
</tr>
<tr>
<td>Lin et al [23], 2016</td>
<td>RCT</td>
<td>18-70 years old</td>
<td>ERAT</td>
<td>44/45/36</td>
<td>Simple appendicitis</td>
<td>Length of hospital stay, bed rest time, time interval of body temperature returning to normal range, inflammatory factors, complication</td>
</tr>
<tr>
<td>Ma et al [24], 2020</td>
<td>RCT</td>
<td>19-74 years old</td>
<td>ERAT</td>
<td>20/20</td>
<td>Non-complex appendicitis</td>
<td>Duration of operation, length of hospital stay, time interval of body temperature returning to normal range, inflammatory factors, complication</td>
</tr>
<tr>
<td>Wang et al [25], 2017</td>
<td>RCT</td>
<td>3 to 13 years old</td>
<td>ERAT</td>
<td>42/42</td>
<td>Acute uncomplicated appendicitis in children</td>
<td>Duration of operation, length of hospital stay, bed rest time, time interval of body temperature returning to normal range, complication</td>
</tr>
<tr>
<td>Pan et al [26], 2018</td>
<td>RCT</td>
<td>19-62 years old</td>
<td>ERAT</td>
<td>35/36</td>
<td>Acute appendicitis</td>
<td>Duration of operation, length of hospital stay, bed rest time, inflammatory factors</td>
</tr>
<tr>
<td>Shen et al [27], 2020</td>
<td>Case-control</td>
<td>NA</td>
<td>ERAT combined with antibiotics treatment</td>
<td>42/57</td>
<td>Acute appendicitis</td>
<td>Length of hospital stay</td>
</tr>
<tr>
<td>Ye et al [28], 2016</td>
<td>RCT</td>
<td>18-70 years old</td>
<td>ERAT</td>
<td>57/57</td>
<td>Non-perforated acute appendicitis</td>
<td>Length of hospital stay, bed rest time, inflammatory factors, complication</td>
</tr>
<tr>
<td>Zhu et al [29], 2018</td>
<td>RCT</td>
<td>NA</td>
<td>ERAT</td>
<td>17/24</td>
<td>Atypical acute appendicitis</td>
<td>Complication</td>
</tr>
<tr>
<td>Yang et al [30], 2016</td>
<td>RCT</td>
<td>20-60 years old</td>
<td>ERAT</td>
<td>35/35</td>
<td>Acute uncomplicated appendicitis</td>
<td>Duration of operation, bed rest time, length of hospital stay, time interval of body temperature returning to normal range</td>
</tr>
<tr>
<td>Li et al [31], 2016</td>
<td>Case-control</td>
<td>14-73 years old</td>
<td>ERAT</td>
<td>21/20</td>
<td>Uncomplicated acute appendicitis</td>
<td>Duration of operation, length of hospital stay, bed rest time, time interval of body temperature returning to normal range, time interval of white blood cells count returning to normal time range, complication</td>
</tr>
</tbody>
</table>

ERAT: Endoscopic retrograde appendicitis therapy.

**Note:** Studies [27,31] were fair, with a score of 2 (each). The Jadad score of included studies were shown in Table 2 and Newcastle-Ottawa scale score was shown in Supplementary Table 1.
### Table 2 Detailed quality assessment of included studies using modified Jadad score

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Randomization</th>
<th>Concealment of allocation</th>
<th>Double blinding</th>
<th>Description of withdrawals and dropouts</th>
<th>Total score</th>
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<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Huang et al[3], 2020</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lin et al[4], 2016</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ma et al[5], 2020</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Wang et al[6], 2017</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pan et al[7], 2018</td>
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<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Wu et al[8], 2019</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ye et al[9], 2016</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Zhang et al[10], 2017</td>
<td>1</td>
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<tr>
<td>Zhu et al[11], 2018</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Yang et al[12], 2016</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

**Figure 1** Flow diagram representing the selection of studies.

**Bed rest time**

Eight records reported the bed rest time in ERAT group and LA group. The bed rest time in ERAT group was shorter than LA group [WMD = -3.68, 95%CI: (-4.78, -2.58); \( P < 0.001 \)], with high heterogeneity [\( Q = 736.21, P \) heterogeneity < 0.001, \( I^2 = 99.0\% \)]. Shown in Figure 2.

**Time interval of body temperature returning to normal range**

The time interval of body temperature returning to normal range in ERAT group was shorter than LA group based on 6 included studies. [SMD = -0.43, 95%CI: (-1.58, 0.73); \( P = 0.481 \)] with high heterogeneity [\( Q = 113.64, P \) heterogeneity < 0.001, \( I^2 = 95.6\% \)]. Shown in Figure 3.
Figure 2 Forest plot of bed rest time.

Figure 3 Forest plot of time interval of body temperature returning to normal range.

Time interval of white blood cell count returning to normal range

Based on 2 included studies, the time interval of leukocyte count returning to normal range in patients receiving ERAT group was shorter than that in LA group [SMD = -1.11, 95%CI: (-1.58, -0.63); P < 0.001] with low heterogeneity [Q = 0.24, P heterogeneity = 0.630, I² = 0.00%]. See Figure 4.

Duration of operation

Seven studies reported the duration of ERAT in comparison to LA. There was no difference regarding duration of operation between ERAT group and LA group [WMD = -13.90, 95%CI: (-29.56, 1.76); P = 0.08] with high heterogeneity [Q = 227.42, P heterogeneity < 0.001, I² = 97.4%]. Shown in Figure 5.

Length of hospitalizations

Based on 8 included studies, the length of hospitalizations in ERAT group was shorter than LA group. [WMD = -1.15, 95%CI: (-1.99, -0.31); P = 0.007] with high heterogeneity [Q = 227.42, P heterogeneity < 0.001, I² = 97.6%]. Shown in Figure 6.

Levels of inflammatory factors

C-reactive protein (CRP): Based on 3 included studies [24, 26, 28], there was no difference of pre-operative CRP levels between ERAT group and LA group [WMD = -0.28, 95%CI: (-1.14, 0.58); P = 0.53] with high heterogeneity [Q = 7.21, P heterogeneity = 0.03, F = 72.0%]. However, the level of post-operative CRP in ERAT group was significantly lower than that in LA group. [WMD = -10.06, 95%CI: (-17.39, -2.73); P = 0.007] with high heterogeneity [Q = 109.28, P heterogeneity < 0.001, P = 98.0%]. Shown in Table 3.

Tumor necrosis factor-α (TNF-α): Based on 2 included studies [24, 26], there was no difference of pre-operative levels of TNF-α between ERAT group and LA group [WMD = -0.21, 95%CI: (-1.32, 0.90); P = 0.71] with low heterogeneity [Q = 0.17, P heterogeneity = 0.68, P = 0.00%]. However, the level of TNF-α in ERAT group was significantly lower than LA group after operating, [WMD = -7.70, 95%CI: (-8.47, -6.93); P < 0.001] with high heterogeneity [Q = 138.67, P heterogeneity < 0.001, F = 99.0%]. Shown in Table 3.
Interleukin 6 (IL-6): Based on 3 included studies[24,26,28], no difference of pre-operative levels of IL-6 was found between ERAT group and LA group [WMD = -0.11, 95% CI: (-1.04, 0.82); P = 0.81] with low heterogeneity [Q = 2.13, I^2 = 0%]. However, the level of IL-6 in ERAT group was significantly lower than LA group, post-operatively. [WMD = -9.78, 95% CI: (-10.69, -8.88); P < 0.001] with high heterogeneity [Q = 163.52, I^2 = 99.0%]. Shown in Table 3.

Complications

Intestinal obstruction: Four studies[22,24,28,31] reported the intestinal obstruction after operation. The pooled result shown that ERAT group had a lower incidence of intestinal obstruction than LA group. [OR = 0.19, 95% CI: (0.05, 0.79); P = 0.020] with low heterogeneity [Q = 2.13, I^2 = 0%]. Shown in Table 3.

Abdominal infection: Two studies[24,31] reported the abdominal infection after operation.
operation. The pooled result found that ERAT group had a lower incidence of abdominal infection than LA group [OR = 0.10, 95%CI: (0.01, 0.83); \( P = 0.350 \)] with low heterogeneity [\( Q = 0.60, P \) heterogeneity = 0.44, \( I^2 = 0.00\% \)]. Shown in Table 3.

**Urinary tract infection (UTI):** The pooled result of 3 studies\[25,28,31\] reporting postoperative UTI did not find statistically significant difference between ERAT group and LA group [OR = 0.27, 95%CI: (0.04, 1.65); \( P = 0.160 \)] with low heterogeneity [\( Q = 0.07, P \) heterogeneity = 0.97, \( I^2 = 0.00\% \)]. Shown in Table 3.

**Sensitivity analysis**

Furtherly, sensitivity analysis was performed to investigate the robustness of this meta-analysis. The results of sensitivity analysis shown that one study had a significant influence on the result of duration of operation\[26\], one study had a significant influence on the result of time interval of body temperature returning to the normal range\[23\], one study had a significant influence on the result of CRP (post-operative)\[26\], no study had a significant influence on the result of TNF (pre-operative) and one study had a significant influence on the result of IL-6 (pre-operative)\[28\].

**Bias analysis**

No obvious publication bias was depicted by the funnel plot (Supplementary Figure 1) and result from Egger’s test (\( t = -0.06, P = 0.954 \)) and Begg’s test (\( Z = 0.30, P = 0.764 \)) indicated no evidence of publication bias with regard to the duration of the operation. All outcomes of bias analysis were shown in Table 4.

**DISCUSSION**

Acute appendicitis, as one of the common surgical diseases, is the most common causes of surgical acute abdomen\[32\]. The latest study reported that the morbidity of acute appendicitis is as high as 6% in the population\[33\]. It has been found that the appendix can secrete a variety of useful substances and hormones (such as digestive enzymes, hormones that promote intestinal peristalsis, hormones related to growth), and play immune function to resist various diseases\[34\]. In addition, as the appendix contains a variety of intestinal microorganisms, it plays a key role in maintaining the balance of intestinal flora\[35\]. At present, the treatment for acute non-complex appendicitis includes surgery and conservative antibiotic treatment\[36\]. In order to preserve the potentially important function of the appendix, a retrograde endoscopic appendicitis treatment for acute simple appendicitis was first proposed in 2012. ERAT has the advantages of convenient operation, small trauma, and rapid relief of pain after the pressure of the appendix cavity is lifted\[37\]. In order to explore the safety of ERAT and provide more evidence for clinical treatment, this meta-analysis was conducted to investigate postoperative complications, length of hospitalizations, operation time, postoperative bed rest time, and indicators of recovery. The results showed that ERAT had shorter time intervals of white blood cell count returning to normal range, length of hospitalizations, and bed rest time. Meanwhile, the incidence of complications is lower, and the postoperative recovery time is faster compared with LA.
Table 4 Publication bias of outcomes by Egger's test and Begg's test

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Egger's test</th>
<th>Begg's test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time interval of body temperature returning to normal range</td>
<td>1.17</td>
<td>0.306</td>
</tr>
<tr>
<td>Time interval of White white blood cells count returning to normal range</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Duration of operation</td>
<td>-0.9</td>
<td>0.409</td>
</tr>
<tr>
<td>Length of hospitalizations (vs LA)</td>
<td>-0.48</td>
<td>0.868</td>
</tr>
<tr>
<td>Length of hospitalizations (vs Anti)</td>
<td>-1.72</td>
<td>0.336</td>
</tr>
<tr>
<td>CRP (pre-operative)</td>
<td>2.23</td>
<td>0.268</td>
</tr>
<tr>
<td>CRP (post-operative)</td>
<td>-0.19</td>
<td>0.878</td>
</tr>
<tr>
<td>TNF-α (pre-operative)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TNF-α (post-operative)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IL-6 (pre-operative)</td>
<td>-1.27</td>
<td>0.425</td>
</tr>
<tr>
<td>IL-6 (post-operative)</td>
<td>-7.43</td>
<td>0.085</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>2.03</td>
<td>0.179</td>
</tr>
<tr>
<td>Abdominal infection</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11.87</td>
<td>0.053</td>
</tr>
<tr>
<td>Bed rest time</td>
<td>-3.1</td>
<td>0.021</td>
</tr>
</tbody>
</table>

LA: Laparoscopic appendectomy.

In 2008, Mason et al.[38] proposed that about 70% of patients with acute appendicitis do not need appendectomy and can be treated conservatively. Recently, Prechal et al.[39] pointed out in a meta-analysis that appendectomy is more effective than antibiotic treatment in the treatment of acute uncomplicated appendicitis, and that the incidence of complications of the two treatment schemes is almost the same. Although ERAT emerges recently as a relatively new modality of treatment, it shows unique advantages. The latest research reported by Liu et al.[18], the abdominal pain of 32 acute uncomplicated appendicitis patients resolved immediately after ERAT operation, and the clinical success rate was 97%. Colonoscopic irrigation, as a type of ERAT, was performed on 10 patients with acute appendicitis by Feng Jia et al.[40]. Follow-up results found that there was no tenderness in the abdomen on physical examination, and no fever and other symptoms after operation. Notably, during the follow-up period of 1-8 mo, no complications occurred, and 9 cases had no recurrence of appendicitis. Chen et al.[41] performed ERAT on 101 patients with acute appendicitis, the results showed that the success rate of appendiceal intubation was 96% (97/101), the success rate of treatment was 97.9% (94/96). Meanwhile, the operation time, the temperature recovery time, the white blood cell recovery time, and the abdominal pain relief time was shorter than the control group. What is more, no postoperative complications were detected. In addition, regarding the complication after ERAT, Li Yingchao et al.[31] compared ERAT with LA and the results showed that perforation occurred in 1 case (5%) in ERAT group, and complications occurred in 3 cases (15%) in LA group. After more than half a year of follow-up, 2 cases in ERAT group were highly suspected of “chronic appendicitis” (recurrence rate 2/20, 10%), while no recurrence of appendicitis in LA group was reported, however, during a follow-up period of at least six months after surgery, 10 cases in LA group had postoperative diarrhea and constipation. Conversely, the results from Deng Garlin et al.[21] showed that the incidence of postoperative complications of the ERAT group was lower than that of the LA group, but the difference was not statistically significant (P > 0.05). Ma Zhuangfu et al.[24] found that 1 sary intestinal obstruction occurred in ERAT group, while 6 sary intestinal obstructions occurred in LA group. Notably, our study shown that ERAT group had a lower incidence of intestinal obstruction than LA group based on 7 included studies. Lin et al.[23] found that no patients with UTI and abdominal infection after ERAT, while 2 patients with UTI and 1 patient with abdominal infection were discovered in LA group, while this comprehensive meta-
analysis demonstrated that there was no difference between ERAT group and control group regarding abdominal infection and UTI.

The serum inflammatory factors of the patients between ERAT and control group were analyzed by Pan Hongwei [26], and the results showed the serum levels of hypersensitive CRP, IL-6, and TNF-α between ERAT group and LA group were significantly decreased after operation compared with those before operation, and the ERAT group was lower than the control group; The serum levels of hypersensitive CRP, IL-6, and TNF-α in the two groups were significantly decreased after operation compared with those before operation, and the ERAT group was lower than the control group ($P < 0.05$). CRP is an acute response protein secreted by the liver, and is also an essential inflammatory medium [42] to measure the intensity of response to trauma. IL-1β, TNF-α, and IL-6 are common pro-inflammatory factors, and their secretion is increased in both acute and chronic inflammation, jointly promoting multiple pathological injury processes such as tissue destruction and edema formation [43,44]. IL-6 is also a typical pro-inflammatory factor, produced by activated T cells and fibroblasts, and can cooperatively activate inflammation-related signals with TNF-α to induce cascade reaction [45] and induce the production of other pro-inflammatory factors [46]. It is a common anti-inflammatory factor and has the effect of reducing inflammatory cell overactivation [47]. Therefore, we conducted the pooled analysis of these markers which shown that there was no difference in pre-operative levels of TNF-α, IL-6, and CRP between ERAT group and LA group, while the level of TNF-α, IL-6, and CRP in ERAT group was significantly lower than LA group after operating. However, we acknowledge that the timing of post-ERAT measurement of inflammatory factors is various across included studies, which may be one of the sources of heterogeneity.

Appendectomy has long been the most important method for the treatment of acute appendicitis. Although LA has faster recovery, less pain, and less wound infection compared with open surgery [48,49], there is still a certain risk of postoperative complications, and it has been reported [50,51] that the negative resection rate of appendix is as high as 8%-15%. Based on our meta-analysis, it is found that ERAT has its own unique advantages of being faster, more effective, and safer, compared with LA.

Limitation

First, the high heterogeneity across included studies was found, which could be attributed to different severities of the patients enrolled in each study, different mean ages of each study, different operating experience of ERAT of gastroenterologists and endoscopists in each study, and different study designs. Second, as little study compared LA with antibiotics treatment as well as compared adults with children, it is difficult to perform a meta-analysis regarding these outcomes. Third, limited studies were reported in other areas outside China.

CONCLUSION

Compared with LA treatment, ERAT reduces operation time, and results in fewer complications and shorter recovery time, with preserving the appendix and its immune and biological functions. However, given that only a limited number of studies were reported and most were conducted in China, more original studies with high quality in multi-centers from different countries and areas are still needed to further explore this novel modality of treatment for appendectomy.

ARTICLE HIGHLIGHTS

Research background

Evidence from previous studies shown that endoscopic retrograde appendicitis therapy (ERAT) is an effective treatment for acute appendicitis.

Research motivation

However, different studies reported conflicting outcomes regarding the effectiveness of ERAT in comparison with laparoscopic appendectomy (LA).
**Research objectives**

This meta-analysis was conducted to compare the effectiveness of ERAT with LA.

**Research methods**

Randomized controlled trials and retrospective studies of ERAT for acute uncomplicated appendicitis were searched in PubMed, Cochrane Library, Web of Science, Embase database, China National Knowledge Infrastructure (CNKI), the WanFang Database, and Chinese Scientific Journals Database (VIP).

**Research results**

10 randomized controlled studies (RCTs) and 2 case-control studies were included in the current systematic review. Firstly, the length of hospitalizations [WMD = -1.15, 95%CI: (-1.99, -0.31); P = 0.007] was shorter than LA group. Secondly, the level of post-operative CRP [WMD = -10.06, 95%CI: (-17.39, -2.73); P = 0.007], TNF-α [WMD = -7.70, 95%CI: (-8.47, -6.93); P < 0.001], and IL-6 Levels [WMD = -9.78, 95%CI: (-10.69, -8.88); P < 0.001; P < 0.001] in ERAT group was significantly lower than LA group. Thirdly, ERAT group had a lower incidence of intestinal obstruction than LA group. [OR = 0.19, 95%CI: (0.05, 0.79); P = 0.020].

**Research conclusions**

Based on our meta-analysis, it is found that ERAT has its own unique advantages of being more effective, safer compared with LA.

**Research perspectives**

As little study compared LA with antibiotics treatment, future study should focus on comparing the effectiveness between LA and antibiotics treatment.

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META-ANALYSIS

Prognostic value of ground glass opacity on computed tomography in pathological stage I pulmonary adenocarcinoma: A meta-analysis

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Author contributions: Li ZL and Wang Y designed the research; Pan XL, Liao ZL and Yao H conducted the literature search and collected and retrieved the data; Yan WJ, Wen DY and Wang Y analyzed the data; Pan XL wrote and revised the manuscript; All authors approved the final version.

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

PRISMA 2009 Checklist statement: This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) checklist.

Country/Territory of origin: China

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report’s scientific quality classification

Abstract

BACKGROUND

The clinical role of ground glass opacity (GGO) on computed tomography (CT) in stage I pulmonary adenocarcinoma patients currently remains unclear.

AIM

To explore the prognostic value of GGO on CT in lung adenocarcinoma patients who were pathologically diagnosed with tumor-node-metastasis stage I.

METHODS

A comprehensive and systematic search was conducted through the PubMed, EMBASE and Web of Science databases up to April 3, 2021. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were combined to assess the association between the presence of GGO and prognosis, representing overall survival and disease-free survival. Subgroup analysis based on the ratio of GGO was also conducted. STATA 12.0 software was used for statistical analysis.

RESULTS

A total of 12 studies involving 4467 patients were included. The pooled results indicated that the GGO predicted favorable overall survival (HR = 0.44, 95%CI: 0.34-0.59, P < 0.001) and disease-free survival (HR = 0.35, 95%CI: 0.18-0.70, P = 0.003). Subgroup analysis based on the ratio of GGO further demonstrated that the proportion of GGO was a good prognostic indicator in pathological stage I pulmonary adenocarcinoma patients, and patients with a higher ratio of GGO showed better prognosis than patients with a lower GGO ratio did.

CONCLUSION

This meta-analysis manifested that the presence of GGO on CT predicted
favorable prognosis in tumor-node-metastasis stage I lung adenocarcinoma. Patients with a higher GGO ratio were more likely to have a better prognosis than patients with a lower GGO ratio.

**Key Words:** Ground glass opacity; Stage I; Lung adenocarcinoma; Prognosis; Meta-analysis

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**Core Tip:** Our manuscript demonstrated that the ground glass opacity (GGO) predicted favorable overall survival \((P < 0.001)\) and disease-free survival \((P = 0.003)\). Subgroup analysis based on the ratio of GGO further demonstrated that the proportion of GGO was a good prognostic indicator in pathological stage I pulmonary adenocarcinoma patients and patients with a higher ratio of GGO showed better prognosis than patients with a lower GGO ratio did. This meta-analysis manifested that the presence of GGO on computed tomography predicted favorable prognosis in tumor-node-metastasis stage I lung adenocarcinoma. Patients with a higher GGO ratio were more likely to have a better prognosis than patients with a lower GGO ratio.

**INTRODUCTION**

Due to great advances in technology and the gradual popularity of high-resolution computed tomography (HRCT), many more cases of cancer can be screened and diagnosed at very early stages than previously possible[1,2]. Meanwhile, the proportion of different pathologic subtypes of lung cancer have changed significantly, and adenocarcinoma occupies a considerable proportion among non-small cell lung cancer[3,4]. With the increasing incidence of lung adenocarcinoma in recent years, a novel term, ground glass opacity (GGO), has been reported and received widespread attention. GGO refers to the increase in local density in the pulmonary nodules and blurred shadow that does not cover the blood vessels and bronchi in the lungs.

According to previous research, the presence of GGO in lung adenocarcinoma usually indicates the indolent nature of the lesions, and pure GGO nodules are related to pathologically preinvasive lesions[5-8]. In other words, the proportion of GGO reflects the malignant degree of pulmonary adenocarcinoma to a certain extent. Compared with pure GGO and subsolid lesions with a mixture of solid portion and GGO portion, lung adenocarcinomas representing as pure solid lesions are typically related with more aggressive behaviors and worse prognosis[9-13]. Therefore, the presence or absence of GGO and the specific ratio should be considered for the diagnosis and formulation of treatment.

Miao et al[14] conducted a meta-analysis by including 13 studies and demonstrated that the GGO ratio was significantly associated with overall survival (OS) [hazard ratio \((HR) = 0.8, 95\% \text{ confidence interval (CI): 0.78-0.93, } P = 0.009\)] and the GGO area measured on HRCT showed a good prognostic value in small lung adenocarcinoma. However, most of the studies included in their meta-analysis did not focus on stage I lung adenocarcinoma patients, and the clinical guiding significance of GGO in early stage lung adenocarcinoma is more important.

Thus, the aim of this meta-analysis was to explore the prognostic value of the presence of GGO on computed tomography (CT) in pathologic stage I lung adenocarcinoma patients, with the expectation that our findings will help with the clinical management and treatment of this group of patients.
MATERIALS AND METHODS

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) checklist.

Literature retrieval

The PubMed, EMBASE and Web of Science electronic databases were searched until April 3, 2020. The following key words were used: Adenocarcinoma, lung, pulmonary and GGO. A combination of medical subject heading terms and free words was applied. In detail, the specific search strategy was as follows: Adenocarcinoma AND (lung OR pulmonary) AND (ground glass opacity OR GGO). In addition, the references cited in included studies were also reviewed for availability.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Patients were pathologically diagnosed with lung adenocarcinoma and tumor-node-metastasis (TNM) stage I; (2) Patients received the radical operation; (3) Patients were divided into different groups according to the ratio of GGO on CT and the prognosis was compared between groups; (4) The endpoints in the studies included the OS and disease-free survival (DFS); and (5) The HR with 95%CI were reported, if not, the Kaplan-Meier survival curves were provided to calculate them.

The exclusion criteria were as follows: (1) The HR with 95%CI were not reported, and the survival curves were also not obtained; (2) Reviews, case reports, meeting abstracts, animal trials and editorials; and (3) Duplicated or severely overlapped data.

Data extraction and quality assessment

The following information was extracted from included studies: The author, publication year, country, sample size, ratio of GGO, TNM stage (IA or IB), endpoints and HR with corresponding 95%CI.

The quality of included studies were assessed according to the Newcastle Ottawa Scale (NOS), and studies with a NOS of 6 or higher were regarded as high-quality studies [15].

The literature retrieval, selection, data extraction and quality assessment were performed by two investigators independently (Xue-Lin Pan and Zi-Ling Liao), and any disagreement was resolved by team discussion.

Statistical analysis

All statistical analysis were conducted by STATA 12.0 software (College Station, TX, United States). The HR with 95%CI were combined to evaluate the association between the presence of GGO and prognosis. When the HR with corresponding 95%CI were not provided directly, they were calculated from the Kaplan-Meier survival curves using the method reported by Tierney et al [16]. The heterogeneity was evaluated by Cochran’s Q test and Higgins $I^2$ statistic; $P < 0.10$ and/or $I^2 > 50\%$ was defined as significant heterogeneity among studies, and the random-effects model was applied for the pooled effect estimates, otherwise the fixed-effects model was used [17]. Subgroup analyses stratified by the ratio of GGO (0% vs > 0%) were conducted. Sensitivity analysis for OS and DFS were performed by removing individual study from the meta-analysis each time.

RESULTS

Literature search and selection

Initially, 2899 records were yielded from the three databases. After removing 736 duplicated records, 105 publications were found to be potentially related with the topic of this meta-analysis. Then 35 records were excluded due to the following reasons: Conference abstracts ($n = 13$), case reports ($n = 12$), animal trials ($n = 5$) and reviews ($n = 5$). Seventy full tests were reviewed for eligibility, and 58 publications were excluded because of insufficient data ($n = 55$) and overlapping data ($n = 3$). Finally, a total of 12 studies were included in this meta-analysis for further analysis [18-29] (Figure 1).

Basic characteristics of included studies

Among the included 12 studies, a total of 4467 patients were enrolled, with a range of
sample size from 79 to 809. Most of included studies were from Asian countries, including Japan, China and Korea. Meanwhile, seven of the 12 studies divided patients into two groups according to the presence or absence of GGO in pulmonary nodules. All included studies were high-quality researches with a NOS of 6 or higher. Detailed information is presented in Table 1.

**Meta-analysis results**

Eight studies explored the association between the presence of GGO on CT and OS of stage I lung adenocarcinoma patients\[18,20-23,27-29\]. The pooled results indicated that GGO was significantly related with better OS (HR = 0.44, 95%CI: 0.34-0.59, \(P<0.001\); \(I^2 = 24.3\%\), \(P = 0.236\)) (Figure 2). Subgroup analysis based on the ratio of GGO demonstrated that the presence of GGO was an independent predictor for OS, and patients with a higher ratio of GGO had better OS than patients with a lower ratio of GGO did (Figure 3 and Table 2).

Eight studies investigated the relationship between the presence of GGO on CT and DFS\[19-21,23,24,26-28\]. The pooled results demonstrated that the presence of GGO was significantly related with improved DFS (HR = 0.35, 95%CI: 0.18-0.70, \(P = 0.003\); \(I^2 = 88.2\%\), \(P < 0.001\)) (Figure 4). Subgroup analysis stratified by the proportion of GGO in nodules also manifested that the presence of GGO was a significant predictive indicator for DFS, and patients with a higher ratio of GGO were more likely to experience a better DFS (Figure 5 and Table 2).

**Sensitivity analysis**

The results of sensitivity analysis for the OS (Figure 6A) and DFS (Figure 6B) indicated that the pooled results of this meta-analysis were stable and reliable.

**DISCUSSION**

The current meta-analysis demonstrated that the presence of GGO on CT was a predictive indicator for improved OS and DFS of pathologic stage I lung adenocarcinoma patients. In addition, the proportion of GGO played an essential role in predicting the survival of this group of patients.
GGO: Ground glass opacity; TNM: Tumor-node-metastasis; NOS: Newcastle-Ottawa quality assessment scale; OS: Overall survival; DFS: Disease-free survival.

Table 1 Basic characteristics of included studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country</th>
<th>Sample size</th>
<th>GGO ratio</th>
<th>TNM</th>
<th>NOS</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takamochi et al[18], 2004</td>
<td>Japan</td>
<td>189</td>
<td>0.8</td>
<td>IA + IB</td>
<td>7</td>
<td>OS</td>
</tr>
<tr>
<td>Nakayama et al[18], 2010</td>
<td>Japan</td>
<td>201</td>
<td>0.5</td>
<td>IA</td>
<td>6</td>
<td>DFS</td>
</tr>
<tr>
<td>Yanagawa et al[20], 2014</td>
<td>Japan</td>
<td>145</td>
<td>0.37</td>
<td>IA + IB</td>
<td>7</td>
<td>OS, DFS</td>
</tr>
<tr>
<td>Nakamura et al[21], 2015</td>
<td>Japan</td>
<td>113</td>
<td>0.5</td>
<td>IB</td>
<td>7</td>
<td>OS, DFS</td>
</tr>
<tr>
<td>Wang et al[22], 2016</td>
<td>United States</td>
<td>79</td>
<td>0</td>
<td>IA + IB</td>
<td>6</td>
<td>OS</td>
</tr>
<tr>
<td>Zhong et al[23], 2018</td>
<td>Japan</td>
<td>354</td>
<td>0.5</td>
<td>IA</td>
<td>7</td>
<td>DFS</td>
</tr>
<tr>
<td>Miyoshi et al[25], 2019</td>
<td>Japan</td>
<td>809</td>
<td>0</td>
<td>IA</td>
<td>7</td>
<td>OS</td>
</tr>
<tr>
<td>Kinoshita et al[24], 2019</td>
<td>Japan</td>
<td>274</td>
<td>0</td>
<td>IA + IB</td>
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<td>DFS</td>
</tr>
<tr>
<td>Zhong et al[26], 2021</td>
<td>China</td>
<td>620</td>
<td>0</td>
<td>IA + IB</td>
<td>6</td>
<td>OS, DFS</td>
</tr>
<tr>
<td>Han et al[28], 2020</td>
<td>Korea</td>
<td>544</td>
<td>0.5</td>
<td>IA</td>
<td>8</td>
<td>DFS</td>
</tr>
<tr>
<td>Phillips et al[27], 2020</td>
<td>United States</td>
<td>357</td>
<td>0</td>
<td>IA</td>
<td>7</td>
<td>OS, DFS</td>
</tr>
<tr>
<td>Shigefuku et al[29], 2021</td>
<td>Japan</td>
<td>782</td>
<td>0</td>
<td>IA + IB</td>
<td>7</td>
<td>OS</td>
</tr>
</tbody>
</table>

Table 2 Results of meta-analysis

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No. studies</th>
<th>HR</th>
<th>95%CI</th>
<th>P value</th>
<th>I² (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>8 [18,20-23,27-29]</td>
<td>0.44</td>
<td>0.34-0.59</td>
<td>&lt; 0.001</td>
<td>24.3</td>
<td>0.236</td>
</tr>
<tr>
<td>&gt; 0%</td>
<td>3 [18,20,21]</td>
<td>0.14</td>
<td>0.05-0.36</td>
<td>&lt; 0.001</td>
<td>0.0</td>
<td>0.943</td>
</tr>
<tr>
<td>0%</td>
<td>5 [22,23,27-29]</td>
<td>0.49</td>
<td>0.37-0.66</td>
<td>&lt; 0.001</td>
<td>0.0</td>
<td>0.583</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>8 [19-21,25,24,26-28]</td>
<td>0.35</td>
<td>0.18-0.70</td>
<td>0.003</td>
<td>88.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 0%</td>
<td>5 [19-21,25,26]</td>
<td>0.29</td>
<td>0.10-0.87</td>
<td>0.027</td>
<td>89.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>0%</td>
<td>3 [24,27,28]</td>
<td>0.42</td>
<td>0.23-0.75</td>
<td>0.004</td>
<td>49.8</td>
<td>0.136</td>
</tr>
</tbody>
</table>

*Subgroup analysis was conducted based on the cutoff values of ground glass opacity proportion. HR: Hazard ratio; CI: Confidence interval.

Although we conducted subgroup analysis based on the GGO ratio in pulmonary nodules and manifested that patients with a higher ratio of GGO on CT would experience better prognosis than patients with a lower ratio of GGO did, we still deemed that it was necessary to explore the association between the proportion of GGO and survival risk. Half of the included studies simply divided patients into the GGO group (presence of GGO) and non-GGO group (absence of GGO) and only identified the prognostic value of presence or absence of GGO on CT in stage I lung adenocarcinoma patients[22,24,25,27-29]. The other studies divided patients into the higher GGO ratio group and lower GGO ratio group, and most of them defined the 50% as the threshold ratio[18,21,25,26]. However, after combining the four studies comparing the DFS between the GGO dominant group and solid dominant group, no significant difference in the DFS was observed (HR = 0.47, 95% CI: 0.17-1.27, P = 0.136; I² = 85.4%, P < 0.001) [Supplementary Figure 1][19,21,23,26], which indicated that 50% may not be a reliable critical value in distinguishing the prognosis of patients with different ratios of GGO on CT. Besides, Takamochi et al[18] identified 80% as the threshold value and found that patients with a GGO ratio > 80% had improved OS than patients with a GGO ratio < 80% did (HR = 0.158, 95% CI: 0.045-0.554, P = 0.004)[18]. However, they did report the source of this threshold. Yanagawa et al[20] identified the optimal cutoff value of GGO proportion on CT according to the receiver operating characteristic analysis, and 37% was defined as the optimal threshold value[20]. Notably, in their study, GGO ratio < 37% was verified to be a strong predictive indicator for poor OS.
Pan XL et al. GGO in stage I lung adenocarcinoma

Figure 2 Funnel plot for the association between the presence of ground glass opacity on computed tomography and overall survival of stage I pulmonary adenocarcinoma patients. HR: Hazard ratio; CI: Confidence interval.

Figure 3 Funnel plot of subgroup analysis based on the ratio of ground glass opacity for the association between the presence of ground glass opacity on computed tomography and overall survival in stage I pulmonary adenocarcinoma patients. HR: Hazard ratio; CI: Confidence interval.

Thus, it is believed that a reliable statistical method is vital in dividing patients into different groups according to the ratio of GGO when exploring the prognostic value of GGO ratio on CT in future relevant studies. Besides, the study by Shigefuku et al[29] reported the association between the presence of GGO on CT and cancer-specific survival (CSS) of stage I lung adenocarcinoma patients and manifested that GGO was also a significant predictive indicator for improved CSS (HR = 0.509, 95%CI: 0.260-0.997, P = 0.049)[29]. Actually, we deemed that CSS was more valuable than OS in pathologic TNM stage I pulmonary adenocarcinoma. For lung adenocarcinoma patients without other malignancies, the 5-year OS rate exceeds 80%[3]. Thus, defining the CSS, as well as the DFS, as the endpoint might help with exploring the impact of pulmonary nodules and its components on the prognosis.
Although we demonstrated that the presence of GGO on CT predicted favorable prognosis in TNM stage I lung adenocarcinoma and patients with a higher GGO ratio had an improved prognosis than patients with a lower GGO ratio did, there are still many fields worthy of in-depth investigating about the GGO ratio in stage I lung adenocarcinoma patients. First, as mentioned above, the optimal cutoff value of GGO proportion in distinguishing survival risk of patients with different ratios of GGO on CT remains unclear. Second, a combination of GGO proportion and other imaging features such as the spiculation sign and lobulation sign should be better in predicting prognosis of lung adenocarcinoma patients. Third, the association of GGO ratio on CT with the therapeutic effect of targeted therapy or chemoradiotherapy is unclear, although most of patients with stage I lung adenocarcinoma do not received these adjuvant therapies. However, multiple primary lung adenocarcinomas are receiving
Figure 6 Sensitivity analysis. A: The association between the presence of ground glass opacity on computed tomography and overall survival in stage I pulmonary adenocarcinoma patients; B: The association between the presence of ground glass opacity on computed tomography and disease-free survival in stage I pulmonary adenocarcinoma patients. CI: Confidence interval.

increasing attention in recent years, and these adjuvant therapies might be applied in multiple primary pulmonary adenocarcinoma patients undergoing diagnostic pulmonary resection.

There are several limitations in this meta-analysis. First, all included studies are retrospective, which may cause some bias. Second, most of patients are from Asian countries, and there might be some regional heterogeneity. Third, due to the lack of detailed information about the age, sex and pathological subtype of adenocarcinoma, we failed to conduct subgroup analysis based on these parameters.

CONCLUSION

We demonstrated that the presence of GGO on CT predicted favorable prognosis in TNM stage I lung adenocarcinoma by combining 12 relevant studies involving 4467 patients. Patients with a higher GGO ratio were more likely to have a better prognosis
than patients with a lower GGO ratio. However, more prospective studies with high quality are still needed to verify our findings.

ARTICLE HIGHLIGHTS

Research background
The presence of ground glass opacity (GGO) in lung adenocarcinoma usually indicates the indolent nature of lesions, and the proportion of GGO reflects the malignant degree of pulmonary adenocarcinoma to a certain extent.

Research motivation
The prognostic role of GGO on computed tomography (CT) in stage I pulmonary adenocarcinoma patients remains unclear now.

Research objectives
To identify the prognostic value of GGO on CT in lung adenocarcinoma patients who were pathologically diagnosed with tumor-node-metastasis stage I.

Research methods
Several databases were searched for relevant studies. The hazard ratio and corresponding 95% confidence interval were combined to assess the association between the presence of GGO and prognosis, representing as the overall survival and disease-free survival. Subgroup analysis based on the ratio of GGO was also conducted.

Research results
GGO predicted favorable overall survival \((P < 0.001)\) and disease-free survival \((P = 0.003)\). Subgroup analysis based on the ratio of GGO further demonstrated that the proportion of GGO was a good prognostic indicator in pathological stage I pulmonary adenocarcinoma patients, and patients with a higher ratio of GGO showed better prognosis than patients with a lower GGO ratio did.

Research conclusions
The presence of GGO on CT predicted favorable prognosis in tumor-node-metastasis stage I lung adenocarcinoma.

Research perspectives
Patients with a higher GGO ratio were more likely to have a better prognosis than patients with a lower GGO ratio.

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Atrial fibrillation and concomitant left subclavian, axillary and brachial artery embolism after fiberoptic bronchoscopy: A case report

Cui-Lin Yang, Ran Zhou, Zhi-Xian Jin, Min Chen, Bao-Li Zi, Ping Li, Kai-Hua Zhou

CASE REPORT

Atrial fibrillation and concomitant left subclavian, axillary and brachial artery embolism after fiberoptic bronchoscopy: A case report

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Author contributions: Chen M and Jin ZX were the attending physicians for the patient, reviewed the literature, and contributed to writing the manuscript; Zi BL and Li P reviewed the literature and contributed to writing the manuscript; Zhou KH performed the bronchoscopy procedure and contributed to manuscript writing; Zhou R was responsible for revising the manuscript for important intellectual content; all authors approved the final submitted version of the manuscript.

Informed consent statement: Written informed consent was obtained from the patient for publication of this report and any accompanying images.

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

CARE Checklist (2016) statement:

Abstract

BACKGROUND
Fiberoptic bronchoscopy has been widely used in the diagnosis and treatment of respiratory diseases. Numerous major and minor complications have been reported following this procedure. The incidence of major postoperative complications is approximately 0.5% and includes respiratory depression, pneumothorax, pulmonary edema, pneumonia, airway obstruction and cardiorespiratory arrest. Minor complications include vasovagal reactions, cardiac arrhythmias, hemorrhage, pneumothorax, aphonia, nausea, vomiting and fever. However, to our knowledge, a case of atrial fibrillation (AF) concomitant with fatal arterial embolism in the upper extremities following diagnostic bronchoscopy has never been reported.

CASE SUMMARY
A 70-year-old female patient presented with a history of rheumatic heart disease beginning at 10 years of age and an approximately 10-year history of hypertension. The patient was transferred from the cardiology department to the respiratory department due to recurrent coughing, pneumonia, and fever. She underwent fiberoptic bronchoscopy in the respiratory department. Approximately 2 h after completion of bronchoscopy, she complained of left arm numbness and weakness. Physical examination detected cyanosis of the left upper extremity, grade III weakened limb muscle strength, and undetectable left brachial artery pulsation. Auscultation indicated A.F. B-mode ultrasound examination of the blood vessels showed hyperechoic material in the left subclavian, axillary and brachial arteries, and parallel veins. As our hospital has
no vascular surgery capability, the patient was transferred to a specialized hospital for emergency thrombectomy that day. A tracking investigation found that the patient’s conditions improved after successful thrombectomy.

**CONCLUSION**

Thromboembolism following bronchoscopy is rare, and only a few cases of cerebral air embolism after bronchoscopy have been reported.

**Key Words:** Fiberoptic bronchoscopy; Complications; Atrial fibrillation; Thromboembolism; Anticoagulant therapy; Case report

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**Core Tip:** This case highlights the fact that although fiberoptic bronchoscopy is generally a well-known and safe procedure, serious complications, such as arterial thrombosis may occur. The risk of developing arterial thrombosis following bronchoscopy is higher in patients with atrial fibrillation with mitral stenosis, highlighting the need for a rigorous risk assessment in these patients.

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**INTRODUCTION**

Fiberoptic bronchoscopy is a well-tolerated, minimally invasive surgical procedure, which has been widely used in the diagnosis and treatment of respiratory diseases[1]. For diagnostic purposes, bronchoscopy permits a visual inspection of the tracheobronchial tree and removal of tissue samples for biopsy. Therapeutically, bronchoscopy is used to remove secretions and to aspirate foreign bodies from the interior of the bronchi[2]. Although fiberoptic bronchoscopy is an established and commonly used procedure, there are several postoperative complications that may arise, including hemoptysis, bleeding, pneumothorax and bronchospasm[3]. Anecdotal evidence has been reported describing the occurrence of arterial cerebral air embolism following diagnostic flexible fiberoptic bronchoscopy[4-6]. However, to our knowledge, atrial fibrillation (AF) with concomitant embolism of the left subclavian artery, axillary artery, and brachial artery as a postoperative complication following fiberoptic bronchoscopy has not been reported.

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**CASE PRESENTATION**

**Chief complaints**

A 70-year-old female patient was admitted to the Department of Cardiology due to complaints of repeated dizziness over a 10-year period and shortness of breath and cough for 1 year. These symptoms progressed over a 1-mo period.

**History of present illness**

The patient was transferred from the Cardiology Department to the Respiratory Department due to recurrent cough, fever, and multiple lesions identified on computed tomography (CT) in both lungs. Physicians recommended fiberoptic bronchoscopy for further diagnosis. Two hours after completion of the operation, the patient complained of exacerbation of left arm numbness and weakness. The skin of the left upper extremity was found to be cyanotic, muscle strength decreased to grade 3, and the left brachial artery pulsation was not detectable. B-mode ultrasound examination of the blood vessels revealed hyperechoic material in the left subclavian...
artery, axillary artery, brachial artery, and parallel veins (Figure 1A, B). Based on the patient’s symptoms, history of rheumatic heart disease, and ultrasound images, we diagnosed embolism in the left upper extremity. As our hospital has no vascular surgery capability, the patient was transferred on the same day to a specialized hospital for an emergency thrombectomy. A tracking investigation found that the patient’s conditions improved after successful thrombectomy. The numbness in the left upper limb disappeared, and muscle strength and skin color returned to normal.

History of past illness
The patient had a history of rheumatic heart disease at age 10 years with hypertension as high as 160/110 mmHg, which was well controlled through oral amlodipine tablets.

Personal and family history
The patient had no pertinent family history.

Physical examination
Vital signs of the patient appeared stable during bronchoscopy, except for minor coughing. Blood pressure was 128/80 mmHg, heart rate was 80–105 beats/min with signs of AF, peripheral capillary oxygen saturation (SpO₂) was 95%–98%, respiratory rate was 20 breaths/min, and temperature was 36.5°C 2 h after the examination. The patient complained of numbness in the left arm and difficulty stretching the fingers of her left hand. Her skin in the left upper extremity was cyanotic; muscle strength decreased to grade 3; and the left brachial artery pulsation was not detectable.

Laboratory examinations
Five coagulation tests on the first day of admission revealed a prothrombin time (PT) of 13.6 s, an activated partial thromboplastin time (APTT) of 23.4 s, a thrombin time (TT) of 16.6 s, an international normalized ratio (INR) of 1.19, and fibrinogen (FIB) levels of 5.12 g/L. Emergency coagulation tests after bronchoscopy showed a PT of 12.3 s, an APTT of 22.7 s, a TT of 17.2 s, and an INR of 0.89. The FIB concentration was 6 g/L (reference range 2–4 g/L), D-dimer was 8.13 mg/L (reference range 0-0.55 g/L), te potassium level was 3.36 mmol/L (reference range 3.5–5.3 mmol/L), lactate dehydrogenase was 439 U/L (reference range 90–250 U/L), and troponin I was 0.216 g/L (reference range 0.006–0.06 g/L).

Imaging examinations
Color doppler ultrasound indicated the presence of rheumatic heart disease, moderate mitral valve stenosis, and moderate insufficiency, left atrium enlargement, decreased left ventricular diastolic and systolic function, moderate tricuspid valve regurgitation, severe pulmonary hypertension, and minor pericardial effusion. Chest CT detected multiple nodules and exudative lesions in both lungs, as well as local swelling of the left upper lung lobe. The bronchoscopy examination detected branch stenosis in the anterior segment of the right upper lobe, chronic inflammation in the right upper lobe, and inflammatory infiltration in the upper apicoposterior segment.

Final Diagnosis
Based on the patient’s symptoms, history of rheumatic heart disease, and ultrasound images, the patient was finally diagnosed with AF with concomitant left subclavian artery, axillary artery, and brachial artery embolism after fiberoptic bronchoscopy.

Treatment
Since our hospital is not equipped for vascular surgery, the patient was transferred on the same day to a specialized hospital for emergency thrombectomy.

Outcome and Follow-up
A tracking investigation found that the patient’s conditions improved after successful thrombectomy. Left upper limb numbness disappeared, while muscle strength and
Figure 1 B-mode ultrasound examination of blood vessels showed hyperechoic material. A: Brachial artery; B: Axillary artery.

skin color returned to normal.

DISCUSSION

The most likely cause behind the formation of an upper extremity embolism in the case presented was the detachment of an atrial embolus induced by AF combined with an accelerated heartbeat throughout the bronchoscopy procedure. Physical examination showed an AF rhythm after bronchoscopy. The patient had a long history of rheumatic heart disease, and echocardiography indicated moderate mitral stenosis with mild mitral regurgitation. Studies have shown that ~20% of patients with mitral stenosis had thromboembolism, and ~80% of patients with thrombosis had AF. Thus, AF, mitral stenosis, and thromboembolism are closely related.

AF is one of the most common arrhythmias and is the main complication in thromboembolism. The 2019 AHA/ACC/HRS updated guidelines for the management of patients with AF recognize the damage caused by thromboembolism due to AF and provide new recommendations for the prevention and treatment of thromboembolism. Valvular AF is defined in the guidelines as AF that occurs in the setting of moderate-to-severe mitral stenosis (potentially requiring surgical intervention) or in the presence of an artificial (mechanical) heart valve. Valvular AF also may be considered as an indication for long-term anticoagulation therapy with warfarin. Our patient had AF and moderate mitral stenosis (mitral valve area 1.1 cm²), which is defined as valvular AF requiring long-time warfarin anticoagulation therapy. However, since the patient did not receive anticoagulant therapy, the surgical procedure may have induced detachment of the embolus, leading to the formation of an embolism in the upper limb.

AF is not an absolute contraindication for fiberoptic bronchoscopy. According to the 2019 American AF guidelines, if a patient with AF or a mechanical heart valve requires temporary interruption of warfarin treatment during an elective invasive procedure or surgery, bridging therapy that includes unfractionated heparin or low molecular weight heparin is recommended. The decision on bridging therapy should balance the risks of stroke and bleeding.

CONCLUSION

This case highlights the importance of anticoagulation prior to fiberoptic bronchoscopy in patients with AF. Numerous guidelines recommend an oral anticoagulant, especially warfarin, as the first choice for patients with AF. To achieve optimum results and to reduce the risks of bleeding and thromboembolism, the recommended INR for warfarin treatment is between 2.0 and 3.0. At this dose, the relative risk of stroke is reduced by 64%, and all-cause mortality may be significantly reduced by 26%. However, the utilization rate of oral anticoagulants in China is lower than in western countries. The current utilization rate of warfarin-based antithrombotic therapy in Chinese patients with non-valvular AF is below 10%. Various
reasons have been attributed to the low utilization rate of anticoagulation therapy in Chinese patients with AF, including the narrow safety window of warfarin, which results in poor compliance and extra coagulation monitoring and dose adjustments required due to the constant INR variations. GARFIELD global research has shown that the lack of effective long-term management and safety concerns of anticoagulant therapy results in approximately half of all eligible patients not receiving anticoagulant therapy[11]. Therefore, physicians have an important role in improving the acceptance and usage of anticoagulation therapy in patients with AF.

ACKNOWLEDGMENTS

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Streptococcal toxic shock syndrome after hemorrhoidectomy: A case report

Chien-Yu Lee, Yuarn-Jang Lee, Chia-Che Chen, Li-Jen Kuo

Abstract

BACKGROUND
Streptococcal toxic-shock syndrome after hemorrhoidectomy is rare but may be catastrophic. Group A streptococci have produced various surface proteins and exotoxins due to genetic changes to fight the human body’s immune response. Though life threatening infection after hemorrhoidectomy rarely occurs, all surgeons should be aware of the potential complications of severe sepsis after hemorrhoidectomy and keep in mind their clinical presenting features in order to diagnose early and administer appropriate and effective therapeutic drugs early.

CASE SUMMARY
Here, we present a case of a 56-year-old man with a painful thrombotic external hemorrhoid who presented to our outpatient department for management. There was no history of systemic diseases or recent disease infection. Hemorrhoidectomy was suggested and performed. After surgery, the patient developed hypotension, tachycardia, fever with chills and renal function impairment on day 2 post-operation. The clinical condition progressed to severe septic shock and metabolic acidosis. The patient responded poorly to treatment and expired after 1 d even with use of extracorporeal membrane oxygenation. The results of the blood and wound cultures showed group A streptococcus pyogenes.
CONCLUSION
Although extremely uncommon, all surgeons should be aware of these potential life-threatening septic complications and alert to the presenting features for patients receiving hemorrhoidectomy.

Key Words: Hemorrhoid; Sepsis; Streptococcus pyogenes; Streptococcal toxic shock syndrome; Case report

INTRODUCTION
Streptococcal toxic shock syndrome (STSS) occurs as a serious complication of invasive group A streptococcus (GAS) and 30%-70% of patients die in spite of aggressive treatments[1-3]. The criteria to define STSS include the isolation of GAS from a normally sterile site, hypotension, and involvement of at least two organ systems (renal impairment, coagulopathy, abnormal liver function, acute respiratory distress syndrome, skin rash, or soft tissue necrosis)[4]. Though GAS infection and STSS rarely happen after hemorrhoid treatment, all surgeons should be aware of the potential complications of severe sepsis after hemorrhoidectomy and keep in mind their clinical presenting features in order to diagnose early and administer appropriate and effective therapeutic drugs early.

CASE PRESENTATION

Chief complaints
The 56-year-old man was seen in our outpatient department because of sudden onset severe anal pain.

History of present illness
The patient had a history of external hemorrhoids for 20 years and denied any systemic diseases. This time, he visited our outpatient department because of sudden onset severe anal pain and bleeding.

History of past illness
The patient had a free previous medical history.

Personal and family history
No significant personal or family history was identified.
Physical examination
Rectal examination showed a thrombosed external protruding hemorrhoid and surgery was suggested because of acute pain. Preoperative blood pressure was 108/96 mmHg, the pulse was 59 beats per minute, the oxygen saturation was 100% under ambient air at rest and other examination results were normal.

Laboratory examinations
Routine laboratory examinations were within normal limits.

Imaging examinations
Routine chest X-ray examination was normal.

FINAL DIAGNOSIS
Acute thrombotic hemorrhoids with bleeding and severe anal pain.

TREATMENT
The patient received hemorrhoidectomy immediately after his outpatient department visit.

OUTCOME AND FOLLOW-UP
The patient received hemorrhoidectomy immediately after his outpatient department visit. Hemorrhoidectomy was performed smoothly. After the operation, the patient was sent back to the ward of general surgery and vital signs were similar to those from preoperative examination. On the morning of day 1 post-operation, his temperature was 36.4 °C, blood pressure was 85/50 mmHg, and pulse was 83 beats per minute. On examination, the patient had good spirits and fair activity without any discomfort except for moderate wound pain (VAS = 5). The wound showed mild swelling and no pus or bloody discharge. Mefenamic acid 250mg QID PO and Pethidine 50mg PRN were prescribed for pain relief. Increased pulse rates to 108 beats per minute and persistent hypotension (76/54 mmHg) were noted on day 2 post-operation. The patient appeared well and denied having dizziness, chills, weakness, poor appetite or low urine output. Sepsis, stress ulcer induced gastrointestinal bleeding and dehydration were first considered but the patient denied tarry stool and epigastric discomfort. Due to the hypotension, we planned to give intravenous fluid, but the patient refused to establish an intravenous line because of fear of pain; thus, water intake was encouraged and vital signs were closely monitored. On the morning of day 3 post-operation, the patient had fever to 38.6 °C with mention of chills. His blood pressure was 70/42 mmHg, his pulse was 124 beats per minute, and his oxygen saturation was 97% under ambient air. Two sets of blood cultures and laboratory tests were immediately obtained. The laboratory result revealed leukocytosis (white blood cell, 13100/µL), elevated C-reactive protein (33.12 mg/dL), blood urea nitrogen (40.6 mg/dL), creatinine (2.6 mg/dL) and decreased platelets (81000/µL). Intravenous fluid and antibiotics (Cefmetazole, 1g, Q8H) were given due to suspected sepsis. We rechecked vital signs after 2 h, and found his blood pressure was 155/110 mmHg, his pulse was 88 beats per minute, and his oxygen saturation was 95% under ambient air. The patient started to complain of general soreness and discomfort. After 6 h, the patient underwent a consciousness change, as noted by his family. On examination, we found a body temperature of 36.1 °C, blood pressure of 68/51 mmHg, pulse of 144 beats per minute, respiratory rate of 27 per minute and oxygen saturation of 95% under ambient air. Immediate intravenous fluid resuscitation was performed and artery blood gas analysis revealed pH 7.32, pCO\(_2\) 16.9 mmHg, pO\(_2\) 118.9 mmHg, and HCO\(_3\) 8.5 mmol/L. The patient was sent to the intensive care unit and an endotracheal tube was put in place because of low oxygen saturation and tachypnea. Sodium bicarbonate was given and due to persistent metabolic acidosis, continuous venous-venous hemofiltration was arranged. Sudden cardiac arrest happened after continuous venous-venous hemofiltration. Cardiopulmonary resuscitation was performed and emergent extracorporeal membrane oxygenation (ECMO) was applied to sustain
circulation and tissue perfusion. Although there was neither significant swelling nor pus discharge of the anal wound, a swab culture from the deep wound was obtained. The patient experienced cardiac arrest again 2 h after ECMO placement and expired. The blood and wounds culture both yielded *Streptococcus pyogenes*.

### DISCUSSION

Hemorrhoids are a common disease with the prevalence of 4.4%-11% throughout the population[5,6]. Hemorrhoidectomy is an efficient and advantageous way to cure hemorrhoids, especially when patients fail to respond to conservative measures[7]. The postoperative complications of hemorrhoidectomy include fecal impaction, infection, urinary retention, bleeding and anus stenosis. The overall postoperative complications rate is approximately 3% and septic complication following treatment of hemorrhoids is rare[8-10]. The predominant organisms isolated in those patients with septic complications are Escherichia coli and Bacteroides[9,10]. Only one study to date has reported *Streptococcus pyogenes* induced necrotizing fasciitis and toxic shock syndrome after hemorrhoidectomy similar to the case we presented[11].

Group A *Streptococcus* (GAS; *Streptococcus pyogenes*) causes a broad spectrum of infections, including skin and soft tissue infections, tonsillitis, postpartum endometritis, puerperal sepsis, necrotizing soft tissue infection, and toxic shock syndrome (TSS)[12]. Invasive group A streptococcal (invasive GAS) disease is relatively rare but is often complicated by shock and multiorgan failure and is associated with high mortality and morbidity[1-3]. The incidence of invasive GAS diseases is high in adults > 50 years of age and young children and most patients are not immunocompromised[2,3,13]. Streptococcal TSS (STSS) occurs as a serious complication of invasive GAS disease in approximately one-third of cases and 30% to 70% of patients die in spite of aggressive treatments[14,15]. The criteria to define STSS includes the isolation of GAS from a normally sterile site, hypotension, and involvement of at least two organ systems (renal impairment, coagulopathy, abnormal liver function, acute respiratory distress syndrome, skin rash, or soft tissue necrosis) (Table 1)[4]. Our patient fulfilled the diagnostic criteria of confirmed STSS, without the presentation of necrotizing fasciitis. The pathogenic mechanisms of STSS are not completely understood because each is the culmination of complex interactions between the defense abilities of the human host and specific virulence factors of GAS[16]. Streptococcal pyrogenic exotoxins and other proteins act as superantigens and trigger excessive T cell response and secretion of massive inflammatory cytokines producing capillary leakage and arterial hypotension[17]. Predisposing factors for invasive GAS are minor trauma, including injuries resulting in hemotoma, bruising, muscle strain, recent surgery, viral infection (*e.g.*, influenza, varicella, *etc.*), alcohol abuse, immunosuppression, chronic lung disease, intravenous drug use, heart disease, diabetes, cancer, and recent child birth[18]. Risk factors identified in our patient included thrombosed hemorrhoid, recent surgery (hemorrhoidectomy) and age > 50 years.

Bacteria do colonize anal wounds following open hemorrhoidectomy[19]. *E. coli*, followed by *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most dominant organisms[19]. However, overt wound infection after routine hemorrhoid surgery is rare (1.4%) and routine prophylactic antibiotic use is unnecessary[20,21]. In thrombosed hemorrhoid and septic complications after hemorrhoid treatment, *E. coli* and anaerobes are the predominant pathogens[10,11,22]. In our patient, a thrombosed hemorrhoid and open hemorrhoidectomy provided a portal of entry for GAS. This could explain local or indeed distant sepsis.

The systemic review of McCloud et al[9] reported 38 patients with life threatening sepsis following treatment for hemorrhoids. Of these, all were well prior to surgery with the exception of two (one was a case of human immunodeficiency virus infection and the other had drug-induced agranulocytosis). The predominant organisms isolated in these patients were *Escherichia coli*, *Bacteroides fragilis*, and *Staphylococcus aureus*. Only one study to date reported *Streptococcus pyogenes* induced STSS after hemorrhoidectomy[11], similar to the case presented here. In the literature reviewed by McCloud et al[9], 10 patients died and seven of them had initial presentations of septic shock; conversely, only 2 of the 28 survival cases developed septic shock at initial presentation. In our case, the most important presentation was septic shock without local wound necrosis. The fierce progression of GAS infection related to TSS calls for early aggressive intervention due to the high mortality and morbidity rate[14,15].
**Isolation of group A streptococcus**

Laboratory criteria for diagnosis:

1. Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene
2. A generalized erythematous macular rash that may desquamate
3. Evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
4. Acute respiratory distress syndrome: defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
5. In patients with preexisting liver disease, a > twofold increase over baseline levels of fibrinogen level, and the presence of fibrin degradation products
6. Coagulopathy: platelets ≤ 100000/mm³ and/or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products
7. Liver abnormalities: alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels ≥ twice the upper limit of normal for the patient’s age. In patients with preexisting liver disease, a > twofold increase over baseline levels
8. Acute respiratory distress syndrome: defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
9. A generalized erythematous macular rash that may desquamate
10. Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene
11. Laboratory criteria for diagnosis:
12. Isolation of group A streptococcus

**Table 1 Clinical criteria for streptococcal toxic-shock syndrome**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Hypotension defined by a systolic blood pressure less than or equal to 90 mmHg</td>
<td>for adults or less than the fifth percentile by age for children aged less than 16 years</td>
</tr>
<tr>
<td>Multiple organ involvement characterized by two or more of the following:</td>
<td>Renal impairment: creatinine ≥ 2 mg/dL (≥ 177 μmol/L) for adults or ≥ twice the upper limit of normal for age. In patients with preexisting renal disease, a &gt; twofold elevation baseline creatinine levels</td>
</tr>
<tr>
<td>Renal impairment: creatinine ≥ 2 mg/dL (≥ 177 μmol/L) for adults or ≥ twice the upper limit of normal for age. In patients with preexisting renal disease, a &gt; twofold elevation baseline creatinine levels</td>
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</tr>
<tr>
<td>Coagulopathy: platelets ≤ 100000/mm³ (≤ 100 × 10¹²/L) and/or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products</td>
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<tr>
<td>Liver abnormalities: alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels ≥ twice the upper limit of normal for the patient’s age. In patients with preexisting liver disease, a &gt; twofold increase over baseline levels</td>
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<tr>
<td>Acute respiratory distress syndrome: defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia</td>
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</table>

**CONCLUSION**

Though GAS infection and STSS rarely happen after hemorrhoid treatment, catastrophic complications indeed do occur. All surgeons should be aware of the potential complications of severe sepsis after hemorrhoidectomy. The GAS infection following hemorrhoidectomy should be considered even when there is little to find on examination and the presenting features of STSS should be kept in mind.

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Subsequent placenta accreta after previous mifepristone-induced abortion: A case report

Peng Zhao, Ying Zhao, Jing He, Xiao-Xia Bai, Jian Chen

BACKGROUND
Mifepristone-induced abortion (MIA) has been used worldwide to terminate pregnancies. However, the association between placenta accrete (PA) and MIA has seldom been reported.

CASE SUMMARY
A 26-year-old pregnant woman presented with painless vaginal bleeding at 35 wk of gestation. She had a medical abortion (mifepristone followed by misoprostol) 1 year ago at the sixth week of gestation. Her personal history for previous surgery was negative. Abdominal ultrasonography showed a normal foetus with complete placenta previa. The foetal membrane ruptured with massive vaginal bleeding and severe abdominal pain. An emergency Caesarean section was performed, and the newborn was delivered. The placenta failed to expel and manual extraction was carried out. A large defect was noted in the uterine fundus and repair of the uterine rupture was conducted immediately. The postoperative pathology report showed placenta accreta.

CONCLUSION
The evidence suggests a possible etiologic role of MIA in PA, as the incidence of PA after MIA is much higher than general population. Millions of pregnancies are complicated by PA each year, some of which result in fatality. To prevent subsequent placental complications after MIA, hormonal supplementation might be a promising therapeutic options. However, further studies are needed to identify the high-risk factors and to confirm the effectiveness of estrogen supplement therapy.
Key Words: Mifepristone-induced abortion; Placenta accreta; Uterine rupture; Placental complications; Hormonal supplementation; Case report

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INTRODUCTION

Considered as the most popular abortion choice, mifepristone-induced abortion (MIA) has been used to terminate unwanted pregnancies. It has been estimated that 3 million women received mifepristone in combination with misoprostol in France, Sweden, the United Kingdom, and China in 2000 [1]. Since then, the worldwide use of MIA has expanded. By 2003, the estimated number of induced abortions has reached 46 million [2]. The immediate side effects of MIA have been well studied and the long term outcomes still need full evaluation. There have been published findings of placental complications, such as retained placenta [3], placental abruption [4], and placenta previa [5] associated with MIA. However, placenta accreta (PA) has been seldom reported. The aim of this study was to (1) report a case of PA after a previous MIA; (2) review the literature; and (3) evaluate the risk factors and therapeutic strategies for preventing placental complications.

CASE PRESENTATION

**Chief complaints**

A 26-year-old (gravida 2, parity woman presented at our emergency department at 33 wk of gestation with a chief complaint of painless vaginal bleeding for 5 h.

**History of present illness**

There was no fever, vaginal bleeding, vaginal discharge, or any other symptoms.

**History of past illness**

She had a medical abortion (mifepristone followed by misoprostol) 1 year ago at the sixth week of gestation. Her personal history for previous surgery, including cervical and uterine surgery, was negative.

**Personal and family history**

No significant personal history or hereditary family history was noted.

**Physical examination**

The patient’s vital signs were normal on admission. Vaginal spotting was noted. No abdominal sharp tenderness or rebound pain were present. Vaginal examination revealed that the cervix was closed and its length was in the normal range. There was no vaginal fluid.
Zhao P et al. Placenta accreta after previous mifepristone-induced abortion

Figure 1 A large uterine defect was noted in the fundus after manual removal of the placenta.

Laboratory examination
She was hemodynamically stable with normal liver function tests, normal coagulation profile and a haemoglobin level of 10.8 mg/dL. Cardiotocography, C-reactive protein, and fetal non-stress test results were normal.

Imaging examination
Abdominal ultrasonography showed a normal foetus with the placenta located in the anterior uterine wall. The fundus and the lower margin of the placenta completely covered the internal orifice of the cervix (complete placenta previa). No fluid was detected in the pouch of Douglas.

FINAL DIAGNOSIS
The patient was diagnosed with complete placenta previa at week 33 of gestation.

TREATMENT
Dexamethasone was administered instantly to the mother to promote foetal lung maturation. The patient stayed hospitalized for recurrent vaginal bleeding and tocolytics were given accordingly. 12 d later at 35 wk of gestation, the foetal membranes ruptured with massive vaginal bleeding and severe abdominal pain. An emergency Caesarean section was performed and a newborn was delivered with a birth weight of 2500 g and an Apgar score of 9 at 5 min and 10 at 10 min. The placenta failed to expel and manual extraction was carried out. The placenta was tightly attached and was difficult to remove. A large 5 cm × 3 cm defect was noted in the uterine fundus after manual removal of the placenta (Figure 1). Repair of the uterine defect was conducted immediately. The surgery went well with an estimated blood loss of 1000 mL.

OUTCOME AND FOLLOW-UP
The pathology report showed placenta accreta. The patient was discharged 6 d after surgery and recovered uneventfully during follow-up.

DISCUSSION
This preliminary study showed that there was a potential association between PA and MIA. In theory, the use of mifepristone to induce abortion is associated with endometrial haemorrhage and extracellular matrix degradation, which may cause irreversible injury to the endometrium[6]. If the severity of injury exceeds the self-repair capacity of the uterus, long term adverse effects are likely to occur. PA, defined as the invasion of chorionic villi into the myometrium, is one of the clinical manifest-
Zhao P et al. Placenta accreta after previous mifepristone-induced abortion

Table 1: Studies of estrogen administration following mifepristone-induced abortion

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Hormone regimen</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al</td>
<td>Post-operation, oral contraceptive</td>
<td>Ethinyl oestradiol 30 µg; levonorgestrel 150 µg</td>
<td>Start on the day of abortion, daily for 21 d</td>
</tr>
<tr>
<td>[12], 1988</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tang et al</td>
<td>Post-operation, oral contraceptive</td>
<td>Ethinyl oestradiol 30 µg; levonorgestrel 150 µg</td>
<td>Start 1 d after the administration of misoprostol, daily for 21 d</td>
</tr>
<tr>
<td>[13], 2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu et al</td>
<td>Post-operation, estrogenic supplementation</td>
<td>Oestradiol valerate 1mg</td>
<td>Start 1 d after abortion, daily for 14-18 d</td>
</tr>
<tr>
<td>[14], 2006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al</td>
<td>Post-operation, oestrogenic-progesterone sequential administration</td>
<td>Oestradiol valerate 2 mg; Medroxyprogesterone 10 mg</td>
<td>Oestradiol valerate, start 1 d after abortion, daily for 21 d; Medroxyprogesterone, daily for the last 5 d</td>
</tr>
<tr>
<td>[15], 2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farhi et al</td>
<td>Post-operation, oestrogenic-progesterone sequential administration</td>
<td>Oestradiol valerate 2 mg; Norgestrel 0.5 mg</td>
<td>Oestradiol valerate, start 1 d after abortion, daily for 21 d; Norgestrel, daily for the last 10 d</td>
</tr>
<tr>
<td>[16], 1993</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luo et al</td>
<td>Pre-operation, oestrogen supplementation</td>
<td>Oestradiol valerate 5 mg</td>
<td>Oestradiol valerate, daily for 3 d before abortion</td>
</tr>
<tr>
<td>[17], 2012</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This study also demonstrated that the prevalence of PA after MIA has been neglected and underestimated for a long time. It has been reported that the incidence of PA after MIA was 0.5% [7], which is twelve-fold higher than the 0.04% estimated in pregnant women in the general population [8]. Between 2010 and 2014, an estimated 55.9 million induced abortions were performed worldwide [9], with 65.1% of the women having subsequent pregnancies [10]. To put the above estimates into real-world terms, there would be 0.2 million pregnancies complicated by PA. Moreover, the misuse of over-the-counter or black market mifepristone by self-administration potentially poses a serious danger. For example, in India, 5 million unsafe abortions are performed each year, and 31.25% of the patients had a history of self-administration of abortion pills [11]. Therefore, the actual number of pregnancies complicated by PA after MIA can be assumed to be much higher than the estimated number.

The prevention of PA after MIA is a major concern of physicians during clinical practice. Sporadic studies have shown hormonal supplementation to be one of the promising options to prevent endometrial injury after MIA [12-16]. Administration of estrogen before or after MIA increases endometrial proliferation and reduces the risk of endometrial injury. The details of studies of post-[12-16] and pre-MIA hormonal supplementation [17] are shown in Table 1. However, the previously described effectiveness of estrogen supplementation needs to be verified by a larger and more suitable clinical trial. Additionally, prescribing estrogen for every patient would lead to a significant financial burden and consumption of precious resources. Therefore, it is important to identify the risk factors that increase the risk of PA associated with MIA. Several observational studies [7,18,19] showed that multiple MIA's, prolonged duration of vaginal bleeding after MIA, gestational age more than 6 wk at MIA, and an interpregnancy interval longer than 18 mo might be associated with placental complications. In this report, the patient had one clinical feature that could be identified as a risk factor, and that was a gestational age of more than 6 wk at MIA. Further study should be conducted to confirm the risk factors.

CONCLUSION

In conclusion, there is evidence of a possible etiologic role of MIA in PA, as the incidence of PA after MIA is much higher than it is in the general population. Millions of pregnancies are complicated by PA each year, some of which result in fatality. Hormonal supplementation might effective for preventing placental complication subsequent to MIA. However, further studies needed to identify risk factors and to confirm the effectiveness of estrogen supplementation therapy.

ACKNOWLEDGEMENTS

We would like to thank Dr. Joynauth Jyotsnav for his critical review and language editing of this study.
References


Autosomal dominant tubulointerstitial kidney disease with a novel heterozygous missense mutation in the uromodulin gene: A case report

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Author contributions: Zhang LL, Lin JR, Zhu TT and Zhang DM contributed to the study design; Zhang LL, Liu Q, Gan LW and Li Y collected data during the study; Li Y and Ou ST developed the first draft of the manuscript, which was then reviewed and intensively revised by the other authors; all authors read and approved the manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Abstract

BACKGROUND
Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a progressive chronic disease that is inherited in an autosomal dominant fashion. Symptoms include hyperuricemia, gout, interstitial nephritis, renal cysts, and progressive renal damage that can lead to end-stage renal disease. Mutations in the uromodulin gene (UMOD) characterize the ADTKD-UMOD clinical subtype of this disease. To date, > 100 UMOD mutations have been identified. Early diagnosis of ADTKD-UMOD is important to treat the disease, slow down disease progression, and facilitate the identification of potentially affected family members.

CASE SUMMARY
We report a 40-year-old man harboring a novel heterozygous missense mutation in UMOD (c.554G>T, p. Arg185Leu). The patient had hyperuricemia, gout, and chronic kidney disease. The same mutation was detected in his daughter, aunt and cousin.

CONCLUSION
A single nucleotide substitution in exon 3 of UMOD was responsible for the heterozygous missense mutation (c.554G>T, p.Arg185Leu).

Key Words: Autosomal dominant tubulointerstitial kidney disease; Hyperuricemia; Uromodulin gene; Mutation; Case report

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Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a set of heritable renal disorders that are characterized by autosomal dominant inheritance and clinical findings of tubulointerstitial disease in affected individuals. Most patients present with hyperuricemia, gout, arthritis, interstitial nephritis, and progressive renal damage, whereas some patients develop end-stage renal disease (ESRD) within 10–20 years\cite{1}. Renal biopsy of patients with ADTKD often indicates interstitial fibrosis, tubular atrophy, and renal cysts\cite{2}. Pathogenic mutations associated with ADTKD are present in the uromodulin gene (UMOD) in 40% of cases, whereas mutations in either renin or hepatocyte nuclear factor-1β genes are detected in 2.5% of cases\cite{3,4}. UMOD mutations are considered under the clinical ADTKD-UMOD disease subtype, and most UMOD mutations are localized to exons 3–5 of this gene in the chromosome 16p11–p13 region\cite{5,8}.

Uromodulin is the most abundant protein in urine and is released from epithelial cells via proteolytic cleavage within the loop of Henle\cite{9,10}. Missense mutations in this gene lead to misfolding of the protein and its accumulation within the endoplasmic reticulum of affected cells, thereby impairing urinary excretion\cite{11}. These mutations also lead to disrupted trafficking of Na⁺-K⁺-2Cl⁻ cotransporters in the luminal membrane of affected cells\cite{12}. This ultimately leads to impaired urine concentration, increased rates of proximal tubular sodium and urate reabsorption, hyperuricemia, and gout, which are the clinical characteristics of ADTKD.

Owing to changes in diets and other factors, the rates of hyperuricemia are increasing annually and the age of ADTKD onset is decreasing continuously, similar to ADTKD-UMOD. However, the risk factors, pathogenesis and prognosis of these two disease isoforms differ considerably. Early diagnosis of ADTKD-UMOD is important to treat the disease, slow down disease progression, and facilitate the identification of potentially affected family members. Identification of potentially affected family members can facilitate decision-making about donors and family planning. In the present study, we report the case of a 40-year-old Chinese man harboring a novel heterozygous missense mutation in UMOD, which was also detected in his seven family members.

### CASE PRESENTATION

#### Chief complaints

The patient was a 40-year-old man who was admitted to hospital because of increased pain in the metatarsal joints and renal impairment.

#### History of present illness

Around 15 years previously, the patient was diagnosed with gout.
History of past illness
The patient had a free previous medical history.

Personal and family history
The proband had a family history of hyperuricemia as his grandmother, father, two of his aunts, and two of his female cousins were diagnosed with hyperuricemia and gout. The grandmother, father, one aunt, and one female cousin had been undergoing hemodialysis and died between the ages of 30 and 50 years. In addition, the patient’s 9-year-old daughter had also been diagnosed with hyperuricemia based on her 5.6 mg/dL serum uric acid level (normal range for children aged 1-10 years: < 5.3 mg/dL) [13] (Figure 1).

Physical examination
The patient’s temperature was 36.7 °C, heart rate 88 bpm, respiratory rate 14 breaths/min, blood pressure 132/78 mmHg, and oxygen saturation in room air 100%. Physical examination indicated the presence of a mildly painful nodule behind the auricle, slight pain and swelling of the knee joints, serious pain and deformity of the interphalangeal joints, and gout stones on the 1 s metatarsal joints in the feet of the patient (Figure 2).

Laboratory examinations
The patient had respective blood urea nitrogen and serum creatinine levels of 50.5 mg/dL and 6.2 mg/dL (normal ranges: 7.30–21.06 mg/dL and 0.46–0.82 mg/dL, respectively). The patient had a serum uric acid level of 13.2 mg/dL (normal range: 2.6–6.0 mg/dL), whereas fractional uric acid excretion was reduced by 3.43%. Other laboratory test results were within normal ranges.

Imaging examinations
Renal ultrasonography showed that the patient’s kidneys were relatively atrophic (longitudinal image; 8.1 and 8.7 cm in the major axis of right and left kidneys), indicating the presence of cysts and suggestive of ESRD (Figure 3). Analysis of the knee joints by computed tomography showed high bone density, the presence of high-density shadows, narrowing of the joint space, and soft tissue swelling, which were consistent with the patient’s gout/arthritis symptoms (Figure 4).

Further diagnostic work-up
Considering the family history of kidney disease, juvenile-onset of hyperuricemia, symptoms of gout/arthritis, and progressive renal impairment beginning at an early age, ADTKD-UMOD was considered highly probable. After receiving written informed consent from the four affected living members of the patient’s family, DNA analyses, clinical data collection, and image publication were performed for these individuals. The peripheral blood was sent to CIPHER gene to perform the whole exome sequencing by Illumina HiSeq (the specific method can be consulted in the Supplementary Material). Genetic analyses revealed the presence of a novel heterozygous missense mutation in UMOD exon 3 of the patient, his daughter, aunt, and younger female cousin (Figure 5). The conclusion of the genetic test was variants of unknown clinical significance. According to the American College of Medical Genetics and Genomics genetic variation classification standards and guidelines, the variation site was heterozygous, and the zygote type could explain the patient’s disease. Furthermore, this missense mutation was the result of nucleotide exchange at position c.554 (c.554G>T), in which leucine was replaced by arginine at position 185 in the final protein (p.Arg185Leu). This resulted in abnormal folding of uromodulin protein, leading to its accumulation within the endoplasmic reticulum and impaired trafficking through the cell.

**FINAL DIAGNOSIS**
The final diagnosis of the present case was ADTKD with a mutation in UMOD.
Zhang LL et al. Novel heterozygous mutation in the UMOD

**Figure 1** Pedigree for the family of the patient, indicating individuals affected by familial hyperuricemia and chronic kidney diseases. (1) Black and gray symbols corresponding to the affected individuals, with the patient described in this case report marked with an arrow; and (2) Lines under individuals indicate people who provided DNA samples, while the two underlines denote couples with no children.

**Figure 2** Swelling, gout stones, and deformity of the interphalangeal joints, with two large gout stones affecting the 1s metatarsal joints of the feet in the patient.

**TREATMENT**

Medication aimed at controlling uric acid levels was administered to the patient but was not efficacious in controlling the gradually increasing serum creatinine and uric acid levels. Recently, the glomerular filtration rate for this patient decreased to 6.3 mL/min/1.73 m². Hence, we recommended arteriovenous fistula surgery for hemodialysis preparation. Moreover, his affected family members do not currently require dialysis but should maintain a healthy lifestyle and preventatively take uric acid medication to control the onset of hyperuricemia.
Figure 3 Renal ultrasound findings of the patient, revealing relatively atrophic kidneys with multiple secondary cysts.

Figure 4 Computed tomography scans demonstrating joint space narrowing, soft tissue swelling, and high density urate crystal deposition in the patient.

OUTCOME AND FOLLOW-UP

The patient received regular blood dialysis and medications, and gout was controlled.

DISCUSSION

ADTKD is a condition also referred to as medullary cystic kidney disease, familial juvenile hyperuricemic nephropathy, and UMOD-associated kidney disease. Recently, ADTKD has been proposed as a collective term to refer to the aforementioned progressive kidney diseases[3]. Most cases of ADTKD present with mutations in the UMOD, REN, MUC1, TCF2, or SEC51A1 genes[14,15]. ADTKD-UMOD disease subtype is the most common, and the clinical features of all disease subtypes differ based on the mutated gene.
Zhang LL et al. Novel heterozygous mutation in the UMOD

Uromodulin is the most abundant protein in urine and is the primary component of urinary casts that are encoded by chromosome 16p11-p13 [7]. Mutations in UMOD gene can result in defective sodium transport in the thick ascending limb, leading to natriuresis that results in secondary proximal tubular sodium and urate uptake. This abnormal sodium and urate uptake further leads to hyperuricemia and gout. In addition, misfolded uromodulin deposits accumulate in the endoplasmic reticulum of affected epithelial cells [11]. Owing to these molecular mechanisms, UMOD mutations can result in conditions such as progressive distal tubular dysfunction, hyperuricemia [11,16], hyperuricemic nephropathy [17], urinary tract stone formation [18], salt-sensitive hypertension, and kidney damage [19]. However, uromodulin excretion is reduced even in ADTKD patients without UMOD mutations [20], and UMOD-knockout mice do not have hyperuricemia [21]. Other recent studies have suggested that mutated uromodulin in the kidneys may elicit an immune response that is specific to this protein, ultimately leading to the observed tubular injury and interstitial fibrosis [22]. Hence, further work is needed to elucidate the underlying mechanisms of ADTKD-UMOD in detail.

ADTKD-UMOD can be diagnosed based on UMOD sequence analyses or immunostaining for misfolded uromodulin protein. However, misfolded uromodulin staining is not routinely performed in pathology laboratories, and only a limited number of institutions can perform this specialized test. In addition, many patients are not eligible for a kidney biopsy at the time of diagnosis, similar to the case reported here.

Currently, whether treatment of this condition with allopurinol or febuxostat can effectively reduce blood uric acid levels, relieve gout symptoms, and slow down progressive kidney impairment is unclear. The patient in the present report did not achieve disease remission after receiving medication aimed at controlling uric acid level, and eventually developed ESRD at an early age. However, whether dialysis or renal transplantation can help patients achieve long-term remission requires further study.

CONCLUSION
When a young adult individual presents with hyperuricemia and has a family history of hyperuricemia, ADTKD-UMOD should be considered and UMOD DNA analyses are necessary. Identification of the pathogenic mutations governing this condition can help facilitate the presymptomatic diagnosis of this rare condition, in addition to genetic counseling and family planning for relatives of affected individuals.
ACKNOWLEDGMENTS

The authors are grateful to the patient and her relatives for allowing publication of this rare case report.

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Novel KDM6A mutation in a Chinese infant with Kabuki syndrome: A case report

Hong-Xian Guo, Bao-Wei Li, Mei Hu, Shao-Yan Si, Kai Feng

BACKGROUND
Kabuki syndrome (KS) is a rare syndrome characterized by multisystem congenital anomalies and developmental disorder. KMT2D and KDM6A mutations were identified as the main causative genes in KS patients. There are few case reports and genetic analyses, especially of KDM6A gene mutation, in China.

CASE SUMMARY
This study reports a de novo KDM6A mutation in a Chinese infant with KS. A 2-month-old Chinese baby was diagnosed with KS, which manifested as hypoglycemia, congenital anal atresia at birth, feeding difficulties, hypotonia, and serious postnatal growth retardation. He died of recurrent respiratory infections at age 13 mo. DNA sequencing of his blood DNA revealed a novel KDM6A frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19).

CONCLUSION
We present a Chinese KS patient with a novel KDM6A frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19), broadening the mutation spectrum.

Key Words: Kabuki syndrome; KDM6A; Gene mutation; Chinese; Case report

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Kabuki syndrome (KS), also termed Kabuki make-up syndrome or Niikawa–Kuroki syndrome, is a congenital anomaly/mental retardation syndrome characterized by five main clinical features: a distinctive face, skeletal anomalies, dermatoglyphic abnormalities, mental retardation, and postnatal growth retardation. The incidence of KS is approximately 1 in every 32000 births, and to date, there have been a number of cases reported in PubMed, showing that KS affects all ethnic populations without preference of gender or race, although it was originally reported in Japan (https://rarediseases.org/rare-diseases/kabuki-syndrome/). Nevertheless, due to misdiagnoses and missed diagnoses, the actual number of KS cases is underestimated.

In China, there have been only a few cases reported, while the KS type II cases were even rarer (i.e. KDM6A mutations). The whole-exome sequencing of KS DNA samples has shown that KS development is mainly caused by mutations of KMT2D and KDM6A. It includes KMT2D-associated, autosomal-dominant KS type I (KS-1) and KDM6A-associated, X-linked-dominant KS type II (KS-2) and 56%-70% and 3%-8% of KS patients have mutations in KMT2D and KDM6A, respectively, whereas 25%-30% are diagnosed clinically without any known gene mutations.

In this case report, we identified and diagnosed a 2-month-old Chinese male baby with KS. DNA sequencing of his blood revealed a novel KDM6A frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19), which clinically led to hypoglycemia, congenital anal atresia at birth, feeding difficulties, hypotonia, and serious postnatal growth retardation, and he died of recurrent respiratory infections at age 13 mo.

CASE PRESENTATION

Chief complaints
A 2-month-old boy was admitted to our hospital due to persistent feeding difficulties, poor weight gain and weak crying for 2 mo.

History of present illness
The patient was the second child of his mother and was born via spontaneous vaginal delivery. The gestational age was 34 wk. Apgar score was 10 points. There were no abnormalities in the placenta and umbilical cord except for oligohydramnios (100 mL). At birth, the infant had the following birth parameters: 31.5 cm head circumference, 2.5 kg body weight, and 46 cm length, placing him in the 25–50th percentile in Chinese newborns. Ten minutes later, he was immediately admitted to the neonatal intensive care unit because of transient respiratory difficulty, and was diagnosed with neonatal hypoglycemia and congenital anal atresia. He was thereafter treated with respiratory support, glucose rehydration, and surgical correction of the anal atresia. Three weeks later, he was discharged from the hospital except feeding difficulty and poor weight gain.

History of past illness
The patient was the second child of Chinese parents who were healthy and non-consanguineous. He was born at 34 weeks’ gestation from a healthy 32-year-old woman via spontaneous vaginal delivery. Prenatal ultrasound imaging showed that the mother had reduced amniotic fluid level since 32 weeks’ gestation and the...
amniotic fluid index was 7.0 cm. The ultrasound imaging also suggested mild hydrenephrosis with dilatation of the upper ureteral diameter (0.6 cm) on the right kidney. There were no other abnormalities identified. The mother had irregular vaginal bleeding 8 h before delivery. His mother did not suffer from fever or use tobacco, alcohol, or illicit drugs during the entire pregnancy.

**Personal and family history**
The infant was born at 34 weeks’ gestation from a healthy 32-year-old woman via spontaneous vaginal delivery and the father was aged 34 years. The parents were healthy and unrelated. The infant had a healthy 4-year-old brother. Family history was unremarkable.

**Physical examination**
He had severe malnutrition and poor skin elasticity with stable vital signs, but his growth and development level was below the normal range with the 3rd centiles, e.g., his height was 50.0 cm, weight 3.05 kg and head circumference 35.0 cm, and according to the WHO (2006) child growth standards, he was indicated as having postnatal onset of growth retardation. He also had distinctive body features, namely a long palpebral fissure, arched eyebrow, lateral sparse of the eyebrow, long eyelashes, and high-arched palate, but short nasal columella with a broad and depressed nasal tip (Figure 1). His palms had a simian crease. He also showed weak crying, muscle hypotonia, and motor delay and could not lift his head and accomplish a test of audio and visual tracking.

**Laboratory examinations**
Routine blood analyses revealed mild anemia (hemoglobin, 98 g/L), blood sugar level was low (2.31 mmol/L; normal range, 3.9–6.1 mmol/L) and his blood ammonia level was high (76 μmol/L; normal range, < 60 μmol/L). The level of insulin-like growth factor 1 was low (< 25 ng/mL) and growth hormone (GH) level was in the normal range. Liver, kidney and thyroid functions and electrolyte level were normal. Laboratory tests of urine and blood samples did not show any amino acid or aliphatic acid metabolic disorders. Furthermore, his chromosome count was normal (46, XY).

**Imaging examinations**
Cardiac ultrasound revealed patent foramen ovale and ductus arteriosus, and urological ultrasound indicated mild hydrenephrosis and dilatation in the right kidney. Brain magnetic resonance imaging revealed corpus callosum hypoplasia, enlarged ventricles, and white matter dysplasia. Chest X-ray and abdominal ultrasound showed no apparent abnormality. Ophthalmological examination revealed hypoplasia of the optic nerve and retina with hearing loss in both ears (Table 1).

**Further diagnostic work-up**
As this infant showed peculiar facial features, multisystem anomalies, persistent feeding difficulties, hypoglycemia, and serious postnatal growth deficiency, KS diagnosis was indicated. Thus, the venous blood samples from both patient and parents were collected for whole-exome sequencing to confirm the diagnosis. Data from the infant’s sample showed a novel KDM6A frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19), whereas blood samples from his parents showed no abnormality (Figure 2).

**FINAL DIAGNOSIS**
The final diagnosis of the presented case was KS due to a novel KDM6A frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19).

**TREATMENT**
There are no curable treatment options for KS currently available. At age 6 mo, the patient’s physical development parameters were as follows: weight 5.0 kg, head circumference 37.5 cm and body length 61.5 cm, (all < 3rd percentiles). The patient was started on GH replacement therapy. At the same time, rehabilitation training was carried out.
<table>
<thead>
<tr>
<th>Organ</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>(1) Long palpebral fissure, arched eyebrow, long eyelashes; and (2) sparse lateral eyebrows, optic nerve, and retina hypoplasia</td>
</tr>
<tr>
<td>Ear</td>
<td>Hearing loss</td>
</tr>
<tr>
<td>Nose</td>
<td>Short columella with depressed nasal tip, wide nasal bridge</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>High-arched palate</td>
</tr>
<tr>
<td>Dermatoglyphic</td>
<td>Simian crease</td>
</tr>
<tr>
<td>Limbs and joints</td>
<td>Joint laxity</td>
</tr>
<tr>
<td>Head</td>
<td>High forehead and hairline</td>
</tr>
<tr>
<td>Heart</td>
<td>Patent ductus arteriosus, patent foramen ovale</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Anal atresia, persistent feeding difficulties</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Mild hydronephrosis and dilatation on the right kidney</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Persistent hypoglycemia, mild high blood lactic acid levels</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Immune dysfunction, frequent pulmonary infections</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Hypotonia, weak crying</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>Corpus callosum hypoplasia, enlarge ventricles, and white matter dysplasia</td>
</tr>
<tr>
<td>Growth delay</td>
<td>Normal growth parameters at birth, postnatal growth retardation, motor delay</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>Low insulin-like growth factor 1 deficiency</td>
</tr>
</tbody>
</table>

**OUTCOME AND FOLLOW-UP**

The therapeutic effects were unsatisfactory. There was no improvement in growth and development. At age 7 mo, the patient had recurrent respiratory tract infection. He died of pulmonary infection at age 13 mo after failure of treatment and rescuing.

**DISCUSSION**

KS, a rare congenital disorder, was first reported in 1981 by two groups of Japanese physicians\[^4,5\]. The estimated prevalence in Japan is approximately 1/32000 versus 1/86000 in Australia and New Zealand or in Europe and America\[^14,15\]. KS cases have also been reported in China and our PubMed search showed that only six KS-2 cases have been so far reported in Mainland China\[^6-9\], indicating that our current case is the seventh. The typical KS features include facial abnormality (long palpebral fissures with eversion of the lateral third of the lower eyelid; arched and broad eyebrows; sparse lateral eyebrows; short columella with depressed nasal tip; large, prominent, or cupped ears); postnatal growth retardation; mild to moderate intellectual impairment; scoliosis deformity; short and small fifth finger; susceptibility to infection; visceral deformity; dermatoglyphic abnormalities; blue sclera; hearing impairment; hypotonia; lack of GH; and other abnormalities\[^16\]. \[^17\]. KMT2D and KDM6A are two pathogenic genes that have been identified in KS. KMT2D gene mutation leads to KS type I, which is autosomal dominant; \[^13\]. KMT2D gene encodes the lysine specific methyltransferase 2D, a methyltransferase that specifically modifies the lysine residue at the fourth acid lysine (H3K4) on histone H3 and catalyzes H3K4 from unmethylation to mono-, di- and/or tri-methylation. The set domain of KMT2D protein is responsible for the activity of this part of methyltransferase, type I is common. In contrast, KDM6A gene mutations leads to KS II, an X-linked dominant inherited disease. KDM6A gene encodes the lysine demethyltransferase 6A. The differences between KS type I and II are that: (1) KS I has obvious facial features, and is more likely to have kidney disease, joint dislocation, and palatal abnormalities; and (2) KS II is more likely to have hypoglycemia due to hyperinsulinism, hypertrichosis, long halluces, and large central incisors\[^13\]. Furthermore, KS II is characterized by clinical manifestations of feeding difficulties, hypotonia, retarded growth, and short stature.
Guo HX et al. Kabuki syndrome in Chinese infant

Figure 1 Facial features of the patient. At age 3 mo, he had a long palpebral fissure (A), arched and broad eyebrows with the lateral third displaying sparseness (B), long eyelashes (A), but short columella with depressed nasal tip (C), wide nasal bridge, and high-arched palate as well as a high forehead and hairline (D).

In terms of developmental delay and cognitive impairment, male patients are more affected than females[13]. Both KDM6A and KMT2D are components of the activation signal cofactor complex whose function is to remove inhibitory epigenetic markers and deposit activated methylation markers on the chromatin, and then recruit RNA polymerase II complex to activate chromatin[19]. A previous study demonstrated that the KDM6A KS variants might impair functions of the histone demethylase through various mechanisms, including alteration of the protein integrity, local environment, molecular interactions and protein dynamics[20]. KDM6A protein plays a critical role in cell differentiation, development, and cancer, and is also important in differentiation of embryonic stem cells and development of various tissues, and alteration of KDM6A protein functions and expression results in developmental defects, growth retardation, multiple congenital organ malformations, and hematological and immunological anomalies[21].

In our current case, the patient was diagnosed with early-stage disease, possibly because of his serious symptoms that caused his early death. This patient had most of the KS clinical manifestations and the diagnosis was established based on these clinical findings (i.e., preterm at age 34 wk), transient respiratory difficulty at birth, persistent hypoglycemia, and congenital anal atresia in the neonatal period. Moreover, the patient had persistent feeding difficulty, weak crying, hypotonia, and postnatal growth retardation, as well as distinctive facial features, multiple congenital internal malformations and increased infection susceptibility, which are consistent with KS diagnostic criteria [13]. Our current case report confirmed that KS is associated with novel KDM6A frameshift mutation (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19). Taken together, the data show that KS is genetically heterogeneous. Further studies with a larger number of KS cases will provide a better understanding of KS pathogenesis, and provide novel strategies to prevent and control KS.

Previous Chinese studies[8,9] have reported that KS patients have typical facial features, including the long palpebral fissures, sparse lateral or notched eyebrows, depressed nasal tip and large ears. However, the microcephaly, cleft lip/palate, and cardiac defects occurred less frequently in Chinese KS patients. Moreover, these studies[8,9] also showed the brain abnormalities, such as thinning of the pituitary and
myelination of the cerebral white matter in Chinese KS patients, suggesting a strong association between various brain abnormalities and KS.

It is worth noting that KS is a congenital multiple organ dysplasia and to date, there is no unique and specific perinatal diagnostic methodology. Long et al reported two infants who presented with prenatal hydrops/ascites, who were subsequently diagnosed with KS[22]. Guo showed the final diagnosis KS II of a 3-month-old patient with congenital hydrocephalus and suggested that congenital hydrocephalus was closely associated with KS II[7], while Rosenberg et al[23] collected retrospective data from 49 individuals with KS and over one third had complications of polyhydramnios, and reduced placental weight also complicated KS pregnancies, suggesting that the differential diagnosis for polyhydramnios in the absence of intrauterine growth retardation should include KS. A Chinese study[24] reported that a 24-week-old fetus was diagnosed with KS II using the chromosomal microarray analysis plus growth retardation and cardiovascular and musculoskeletal abnormalities using routine color Doppler ultrasonography. Another previous study[25] retrospectively reviewed 11 patients and showed that prenatal ultrasound was an important tool, while a molecular technique was also important in KS diagnosis. The most frequent ultrasound features observed were cardiac anomalies (49.4%), followed by polyhydramnios or oligohydramnios (28.9%), genitourinary anomalies (26.5%), single umbilical artery (15.7%), intrauterine growth restriction (14.5%) and hydrops fetalis/pleural effusion/ascites (12.0%); 50.6% of which had more than one abnormal antenatal ultrasound finding. These enlighten us that there are no distinct signs in fetuses to suggest the KS diagnosis prenatally. More and more investigators have suggested that prenatal phenotypic heterogeneity is associated with KS. If fetal ultrasound abnormalities show one or more deformities, KS should be considered. We need to complete a relevant gene analysis as soon as possible to realize early diagnosis and early intervention.

**CONCLUSION**

This case report identified a de novo frameshift KDM6A mutation localized on chromosome Xp11 (c.704_705delAG, p. N236Sfs*26) (GRCh37/hg19) in a Chinese male.
infant with KS. After literature review, we believe that his severe clinical manifestations were part of the KS II phenotype spectrum. Our data support the investigation of a genotype-phenotype correlation, which explains the phenotypic variability of KS II. This case provides more information about the mutational spectrum of KS II.

ACKNOWLEDGMENTS
We thank the patient’s family who agreed to this case report.

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Pancreatic cancer with synchronous liver and colon metastases: A case report

Yuan-Mei Dong, Hong-Nian Sun, De-Cong Sun, Mu-Hong Deng, Yong-Gang Peng, Yan-Yun Zhu

Abstract

BACKGROUND
Metastasis of pancreatic cancer to the colon is rare and the features need to be further elucidated. Herein, we report a rare case of pancreatic cancer with simultaneous liver and colon metastases.

CASE SUMMARY
A 48-year-old man with intrahepatic space-occupying lesions based on a computed tomography scan was admitted to our hospital for further treatment. Abdominal magnetic resonance imaging revealed a 6.4 cm × 4.2 cm mass in the tail of the pancreas and multiple low-density masses in the liver parenchyma. In addition, a mass of 2.2 cm × 1.6 cm with surface congestive erosions in the sigmoid colon was detected by colonoscopy. Histopathological examination of biopsies from both the liver and colon lesions revealed a moderately to poorly differentiated adenocarcinoma. Immunohistochemical staining of the colon tumor was positive for cytokeratin (CK) 7 and CK, but negative for colorectal adenocarcinoma-related markers CK 20, CDX2, and SATB2, thus indicating that the metastasis originated from the pancreas. Next-generation sequencing for genomic profiling of the liver and colon metastases both found mutations in KRAS (p.G12D) and TP53 (c.376-1delG), with microsatellite stable and low tumor mutational burden without actionable or cancer-predisposing gene mutations detected. The patient was subsequently treated with 12 cycles of FOLFIRINOX which led to a sustainable response, followed by ongoing maintenance treatment with irinotecan plus fluorouracil.
CONCLUSION
For this rare case, careful evaluation of histopathological and immunohistochemical staining results are required. The genomic profiling of colon lesions was revealed for the first time, and FOLFIRINOX showed good treatment efficacy in this patient.

Key Words: Pancreatic cancer; Colonic metastasis; Immunohistochemical staining; Genomic profiling; Next-generation sequencing; Case report

INTRODUCTION
Pancreatic cancer is reported to be the fourth most common cause of cancer-related death in the United States, with a low 5-year survival rate of 9% [1]. Given the lack of early signs or symptoms of pancreatic cancer, the majority of patients are diagnosed at advanced stages (53%) with metastases to the liver, lungs, or peritoneum, and their 5-year survival is only 3% [2]. However, colon metastasis from pancreatic cancer is extremely rare, with several cases reported in literature and the majority being metachronous [3,4]. Herein, we report a case with synchronous liver and colon metastases of pancreatic cancer and review the literature regarding colon metastases of pancreatic cancer.

CASE PRESENTATION

Chief complaints
A 48-year-old man with intrahepatic space occupying lesions, as shown by abdominal computed tomography, was admitted to our hospital for further treatment in June 2020.

History of present illness
The patient visited a local hospital due to high blood sugar level and loss of appetite in October 2019. The local doctor administered metformin symptomatic treatment, but after three months of treatment, the patient lost four kilograms of weight and had poor blood sugar regulation. Subsequently, acarbose was administered and the blood sugar level was normalized. However, in April 2020, the patient developed anorexia and heartburn and continued to lose weight and this was followed by back pain and abdominal distension.

History of past illness
The patient had no previous medical history.
Personal and family history
The patient had a history of drinking, but had no family history of malignant tumors.

Physical examination
Upon arrival, physical examination of the patient revealed a body temperature of 36.3 °C, blood pressure of 129/77 mmHg, heart rate of 78 beats/min, and respiratory rate of 20 breaths/min. No jaundice or palpable masses were observed. The patient’s Karnofsky performance status (KPS) score was 90.

Laboratory examinations
Complete blood count of the patient showed a slight reduction in hemoglobin (116 g/L; normal range: 137-179 g/L) and red blood cells (3.72 × 10^{12}/L; normal range: 4.3-5.9 × 10^{12}/L). Blood chemistry tests showed an increase in total bilirubin (32.3 μmol/L; normal range: 0-21.0 μmol/L), direct bilirubin (19.9 μmol/L; normal range: 0-8.6 μmol/L), γ-glutamyltransferase (785.1 U/L; normal range: 0-50 U/L), alkaline phosphatase (380.7 U/L; normal range: 45-125 U/L) and lactate dehydrogenase (481.2 U/L; normal range: 40-250 U/L), but demonstrated normal values for alanine aminotransferase (20.6 U/L; normal range: 0-40 U/L), and aspartate aminotransferase (23.5 U/L; normal range: 0-40 U/L). The level of serum tumor marker was significantly elevated for carcinoembryonic antigen (CEA) (198 ng/mL; normal range: 0-5.0 ng/mL), CA125 (204.2 U/mL; normal range: 0.1-35 U/mL), CA15-3 (285.5 U/mL; normal range: 0.1-30 U/mL), CA72-4 (65.69 U/mL; normal range: 0.1-10 U/mL), CYFRA21-1 (18.35 ng/mL; normal range: 0.1-4.0 ng/mL), NSE (50.39 ng/mL; normal range: 0-24 ng/mL), and alpha fetoprotein (2.08 ng/mL; normal range: 0-20 ng/mL, respectively).

Imaging examinations
Abdominal magnetic resonance imaging (MRI) scan revealed a hypovascular lesion in the tail of the pancreas (6.4 cm × 4.2 cm in size) and multiple hypovascular nodules in the liver parenchyma (Figure 1A and 1B). Colonoscopy was performed due to the high CEA level and a mass 2.2 cm × 1.6 cm in size with surface congestive erosions in the sigmoid colon was found, which occupied a quarter of the intestinal cavity and was 33 cm from the anus (Figure 1C).

Further diagnostic work-up
Given the difficulty in performing endoscopic ultrasound-guided fine-needle aspiration of the pancreas mass, biopsy of the left lobe of the liver was obtained and pathologically presented as moderately to poorly differentiated degenerative adenocarcinoma within large areas of necrosis (Figure 2A). Histopathological examination of biopsies from the colon mucosal lesions revealed moderately to poorly differentiated adenocarcinoma, which was compatible with liver metastasis from the primary pancreas (Figure 2B). Immunohistochemical staining of the colon tumor was positive for cytokeratin (CK) 7 and CK, which were expressed particularly in epithelial cells, but negative for colorectal adenocarcinoma-related markers, such as CK 20, CDX2, and SATB2 (Figure 3). A targeted comprehensive genomic profiling assay was performed on the liver and colon metastases using a next-generation sequencing (NGS) panel containing 654 cancer-related genes (Berryoncology, Beijing, China), which detected KRAS p.G12D (27.04%), TP53 c.376-1delG (18.07%), EP300 p.R1462* (5.13%), and CD244 p.M2995fs*17 (5.51%) in the liver lesion and KRAS p.G12D (6.49%), and TP53 c.376-1delG (5.91%) in the colon biopsy; In addition, microsatellite stable (MSS) and low tumor mutational burden (TMB) were seen in both liver and colon metastases.

FINAL DIAGNOSIS
The final diagnosis in this case was pancreatic cancer with synchronous liver and colon metastases.
Figure 1 Radiological images at the time of diagnosis. A: Abdominal magnetic resonance imaging showed a hypovascular mass present in the tail of the pancreas 6.4 cm × 4.2 cm in size; B: Multiple hypovascular nodules of no more than 7.1 cm × 5.5 cm scattered in the liver parenchyma; C: Colonoscopy image showing a 2.2 cm × 1.6 cm mass with surface congestive erosions, which was 33 cm from the anus.

Figure 2 Results of pathologic diagnosis. A: Fine-needle aspiration biopsy of the left lobe of the liver; B: Biopsy from colonoscopy. Magnification: 40 ×; scale bar: 100 μm.

**TREATMENT**

After comprehensive diagnostic evaluations, the patient was administered 12 cycles of FOLFIRINOX and subsequently maintained with ongoing irinotecan plus fluorouracil.

**OUTCOME AND FOLLOW-UP**

Abdominal MRI showed partial response in the pancreas and liver lesion after treatment with three cycles of FOLFIRINOX, thus the patient continued to receive this chemotherapy. Abdominal MRI scans showed that the tumor had shrunk in the tail of the pancreas (Figure 4A) and liver (Figure 4B) after receiving 12 cycles of FOLFIRINOX. Colonoscopy was performed after receiving nine cycles of FOLFIRINOX and no protuberant or new mucosal lesions were found (Figure 4C). Serum tumor markers, including CEA and CA125, all returned to normal levels. Since then, the patient has been receiving maintenance treatment with irinotecan plus fluorouracil. The patient’s KPS score was 90.

**DISCUSSION**

Metastasis of pancreatic cancer to the colon is extremely rare, with less than ten cases reported in the literature (Table 1), to the best of our knowledge. The median age of these cases was 70 years (range: 45-91 years; male: 4, female: 3). Lesions in the pancreas and colon were identified simultaneously in four of these cases, but only one pancreatic cancer patient presented with synchronous colon and liver metastases[5-8]. However, our case is the only one reported with complete pathology, treatment, and
Table 1 Literature review of the characteristics of pancreatic cancer patients with colon metastasis

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Metastatic site</th>
<th>Timing of metastasis</th>
<th>Immunohistochemical staining</th>
<th>Treatment</th>
<th>OS from CM Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charles et al [21]</td>
<td>45</td>
<td>Male</td>
<td>Colon</td>
<td>NA</td>
<td>CA19-9 (+), CK (+), EMA (+), CEA (+), CDX2 (-), CK20 (-), CK7 (-), CD10 (-), vimentin (-), TTF-1 (-)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Woogyeong et al [3]</td>
<td>64</td>
<td>Male</td>
<td>Colon</td>
<td>Metachronous</td>
<td>CK7 (+), CK20 (-), CK19 (+)</td>
<td>Hemicolecotomy + gemcitabine</td>
<td>6+</td>
</tr>
<tr>
<td>Giuseppe et al [5]</td>
<td>70</td>
<td>Female</td>
<td>Liver, colon</td>
<td>Synchronous</td>
<td>CK7 (+), CK20 (-)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ryan et al [6]</td>
<td>91</td>
<td>Female</td>
<td>Colon</td>
<td>Synchronous</td>
<td>CK7 (+), CK20 (-), CDX2 (-)</td>
<td>Palliative care</td>
<td>NA</td>
</tr>
<tr>
<td>Deborah et al [7]</td>
<td>73</td>
<td>Female</td>
<td>Colon</td>
<td>Synchronous</td>
<td>CK7 (+), CK20 (-), CDX2 (-), SATB2 (-)</td>
<td>Gemcitabine + nab-paclitaxel</td>
<td>7 mo</td>
</tr>
<tr>
<td>Rohan et al [8]</td>
<td>71</td>
<td>Male</td>
<td>Colon</td>
<td>Synchronous</td>
<td>CK7 (+), CK20 (-)</td>
<td>Gemcitabine + nab-paclitaxel</td>
<td>NA</td>
</tr>
</tbody>
</table>

CM: Colon metastasis; NA: Not available; EMA: Epithelial membrane antigen; CEA: Carcinoembryonic antigen; TTF-1: Thyroid transcription factor-1; CK: Cytokeratin; OS: Overall survival.

Figure 3 Histopathological analysis of biopsy from the colon lesion. A: CK 7 positive; B: CK positive; C: CK 20 negative; D: CDX2 negative; E: SATB2 negative. Magnification: 10 ×.

follow-up data.

As the majority of metastases from pancreatic cancer occurs in the liver, lung, abdomen, regional lymph nodes, and peritoneum, such cases are easily misdiagnosed as primary colon cancer, which influences treatment decision-making. The presence of masses in both the colon and pancreas could be a result of metastasis from the pancreas to the colon, metastasis from the colon to the pancreas, or synchronous primary cancers. The majority of previously reported cases were identified by histological examination and immunohistochemical staining of colon biopsies, most of which were based on CK 7 and CK 20 expression (Table 1). Cytokeratins are proteins of keratin-containing intermediate filaments, which are found in epithelial tissues. The expression of CK 7 is observed in the majority of cases of carcinoma, except in those carcinomas derived from the colon, prostate, kidney, and thymus. Positive CK 20 was seen in virtually all cases of colorectal carcinomas and Merkel cell tumors; CK 20-positive staining has also been seen in some cases of pancreatic carcinomas (62%)[9].
Figure 4 Radiological images of response assessment to FOLFIRINOX treatment. A: Abdominal magnetic resonance imaging after 12 cycles of FOLFIRINOX treatment showing the size of the hypovascular mass in the tail of the pancreas had shrunk to 4.2 cm × 2.0 cm; B: Multiple hypovascular nodules in the liver parenchyma were also reduced to less than 3.5 cm; C: A colonoscopy after 9 cycles of FOLFIRINOX showing that the mucosa of the original lesion site was slightly rough and red, and that no protuberant or new mucosal lesions were found.

Besides these two tumor markers, CDX2 expression was demonstrated to be an exquisitely sensitive marker, but incompletely specific for intestinal adenocarcinomas [10], SATB2 was shown to be highly expressed in the epithelium of the lower gastrointestinal tract[11] and CK was also included by us to further improve the diagnostic accuracy of the colon lesion. In this case, immunohistochemical staining of the colon tumor was positive for CK 7 and CK, but negative for CK 20, CDX2, and SATB2, thus suggesting that the lesion originated from the pancreas. Interestingly, KRAS p.G12D and TP53 c.376-1delG were detected in both the liver and colon lesions, thus indicating the same histopathological origin, which was typical of an advanced stage of pancreatic cancer[12]. How the pancreatic cancer in the present case metastasized to the colon remains unclear. Since the lymph nodes near the colon lesion were negative, cancer cells from the pancreas may have traveled to the colon through the bloodstream and this was presumed to be the most probable pathway.

It has been reported that 5%-10% of all pancreatic cancers are estimated to be attributable to inherited risk factors and some patients who had no family history of this cancer harbor at least one known inherited pancreatic cancer-predisposing genetic alteration[13,14]. Therefore, the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend that all patients diagnosed with pancreatic cancer should consider germline testing[14,15]. Genomic profiling of our patient was performed using a 654 gene panel containing 102 cancer-susceptibility genes, and pathogenic or likely pathogenic gene mutations associated with increased risk for pancreatic cancer were not found, which was consistent with the fact that the pancreatic cancer patient had no family history of this cancer.

Furthermore, efforts to translate the latest advances in the molecular characterization of pancreatic cancer into targeted therapeutics are in progress. The Know Your Tumor program is a collaboration between industry and academia to determine whether targeted therapy based on actionable mutations can improve outcomes in pancreatic cancer patients[16,17]. In addition to target therapy, immunotherapy has emerged as an exciting treatment alternative for patients with TMB-high or MSI-high tumors. Unfortunately, actionable mutations were not observed in the patient, which was accompanied by low TMB and MSS; thus, systemic chemotherapy was considered. FOLFIRINOX was compared with the previous standard-of-care (gemcitabine) in a randomized phase 3 trial of 342 patients as first-line therapy for patients with untreated metastatic disease and an Eastern Cooperative Oncology Group performance status score of 0 or 1[18]. The median overall survival was improved from 6.8 mo in the gemcitabine group to 11.1 mo in the FOLFIRINOX group [hazard ratio for death: 0.57; 95% confidence interval (CI): 0.45 to 0.73; P < 0.001]. Two years later, the results of another first-line phase 3 trial of the efficacy and safety of gemcitabine plus nab-paclitaxel vs gemcitabine monotherapy were published, reporting a median overall survival of 8.5 mo in the nab-paclitaxel–gemcitabine group, as compared with 6.7 mo in the gemcitabine group (HR for death: 0.72; 95%CI: 0.62 to 0.83; P < 0.001) [19]. Although first-line therapy with FOLFIRINOX and gemcitabine plus nab-paclitaxel have never been compared in a head-to-head clinical trial, real-world retrospective analyses indicate that FOLFIRINOX improved overall survival when compared with gemcitabine plus nab-paclitaxel or others among younger patients, with better performance status[20]. However, gemcitabine monotherapy remains a standard treatment for patients with poor performance status or comorbidities that preclude combination chemotherapy. Considering that our patient showed a good
Herein, we present a rare case of primary pancreatic cancer with synchronous liver and colon metastases. Immunohistochemical staining of CK, CK7, CK20, CDX2, and SATB2 on the colon biopsy distinguished the metastatic and primary tumors. Comprehensive NGS profiling of the liver and colon lesions at diagnosis was performed to identify cancer susceptibility gene variants and therapies. FOLFIRINOX, which was administered as first-line systemic therapy, improved the patient’s outcome. To the best of our knowledge, this is the first case report that reveals the genomic profiles of pancreatic cancer with colon metastasis using a multigene NGS panel, which is a step forward for clinical pathology.

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performance status, he was administered FOLFIRINOX. The patient showed sustainable response during the treatment with FOLFIRINOX for a total of 12 cycles, thus suggesting that the regimen is a good option for pancreatic cancer with colon metastasis. Since then, the patient has been maintained with irinotecan plus fluorouracil.
Pancreatic cancer with colon metastasis


Veno-venous-extracorporeal membrane oxygenation treatment for severe capillary leakage syndrome: A case report

Wei-Xin Nong, Qing-Jie Lv, Ye-Sheng Lu

Abstract

BACKGROUND
Capillary leak syndrome (CLS) is characterized by the leakage of large amounts of fluid and plasma proteins into the interstitial space, resulting in hypoalbuminemia, hypovolemic shock, elevated blood concentration, systemic progressive edema, and multiple serosal cavity effusion. Clinical syndromes such as cavity effusion pose a grave threat to the life and health of the patient.

CASE SUMMARY
A 58-year-old female patient was admitted to the hospital after being in a coma for 6 h following accidental ingestion of a pesticide. She was treated with phenycyclidine hydrochloride and pralidoxime iodide for detoxification, mechanical ventilation to maintain oxygen supply, continuous renal replacement therapy to maintain the internal environment, and hemoperfusion to promote the excretion of toxins. She also received a transfusion of red blood cells and massive fluid resuscitation. However, her blood pressure was not maintained. The patient was diagnosed with CLS due to pesticide poisoning. Oxygenation was difficult to maintain under full ventilator support; therefore, veno-venous-extracorporeal membrane oxygenation (VV-ECMO) treatment was given 13 h after admission. Her oxygenation level improved, but a large amount of ascites and pleural effusion soon became apparent. We continued drainage with an indwelling drainage tube, and the ECMO flow stabilized. The leakage gradually decreased, and ECMO was discontinued 3 d later. On the 6th day, the patient recovered from unconsciousness, but on gastroscopic evaluation, severe erosions were found in her entire stomach. With the family’s consent, treatment was stopped, and the patient was discharged from the hospital on the 7th day.

CONCLUSION
ECMO, liquid resuscitation and management, and improvement in plasma colloidal osmotic pressure, circulation, and tissue oxygen supply are crucial in treating CLS.
Key Words: Capillary leakage syndrome; Pesticide poisoning; Liquid resuscitation; Hypoxia index; Extracorporeal membrane oxidation; Case report

Core Tip: The case of a patient with severe capillary leak syndrome who was successfully treated by veno-venous-extracorporeal membrane oxygenation (VV-ECMO) is reported, which reflects the positive role of VV-ECMO in the treatment of capillary leak syndrome (CLS), and reflects the key elements of clinical treatment of CLS, such as increasing plasma colloidal osmotic pressure, improving circulation, and ensuring tissue oxygen supply.

INTRODUCTION

Capillary leakage syndrome (CLS) refers to a group of clinical syndromes such as hypoproteinemia, hypovolemic shock, blood concentration, systemic progressive edema, and multiple serosal cavity effusion caused by leakage of a large amount of fluid and plasma proteins into the interstitial space resulting from injury of capillary endothelial cells and increased vascular permeability[1-4].

CLS is most likely to cause harm to the alveoli and limit gas exchange, leading to tissue hypoxia that aggravates the capillary injury, resulting in respiratory and circulatory failure. Subsequently, it leads to systemic multiple organ dysfunction syndrome and increases mortality[5]. Since CLS is difficult to treat effectively, it can easily develop into multiple organ dysfunction syndrome. Hence, early recognition and active treatment (including control of the primary disease, liquid resuscitation and management, increasing the plasma colloid osmotic pressure, improving circulation, and enhancing oxygen supply in the tissues) and prevention of deterioration are the crucial elements in the clinical treatment of critical illnesses resulting from CLS. We herein present a case of severe CLS that was successfully treated by veno-venous-extracorporeal membrane oxygenation (VV-ECMO) at our department.

CASE PRESENTATION

Chief complaints
A 58-year-old female patient was admitted to the hospital after being unconscious for 6 h following accidental ingestion of a pesticide.

History of present illness
The patient was unconscious for 6 h.

History of past illness
The patient had a prolonged history of schizophrenia.

Personal and family history
The patient received endotracheal intubation and gastric lavage at a local health center and was then referred to the electronic intensive care unit of our hospital.

Physical examination
Physical examination revealed the following: Temperature, 35 °C; pulse, 150 beats/min; heart rate, 30 beats/min; blood pressure, 75/50 mmHg; shallow coma;
bilateral pupil diameter, 3 mm; light reflection disappearance; wet and cold skin; moist rales in both lungs; soft abdomen; disappearance of intestinal sounds. The Acute Physiology and Chronic Health Evaluation II score was 22 points, and the Sequential Organ Failure Assessment score was 11 points.

**Laboratory examinations**

Arterial blood gas analysis revealed the following: pH, 7.28; blood partial pressure of carbon dioxide, 24 mmHg; partial pressure of blood oxygen (PaO₂), 57 mmHg; oxygenation index (PaO₂/FiO₂), 145 mmHg; lactic acid, 6.7 mmol/L; HCO₃⁻, 18.2 mmol/L; cholinesterase (urgent check), 183 U/L. Specific information on the ingested pesticide was not obtained.

**FINAL DIAGNOSIS**

The final diagnosis included acute organophosphorus pesticide poisoning, acute respiratory failure, aspiration pneumonia, and schizophrenia.

**TREATMENT**

After admission, the patient was treated with phencyclidine hydrochloride and pralidoxime iodide to detoxify, ventilator support to maintain oxygen supply, continuous renal replacement therapy to maintain the internal environment, hemoperfusion to promote the excretion of toxins, transfusion of red blood cells, and massive fluid resuscitation. However, her blood pressure could hardly be stabilized despite a large dose of hypertensive drugs. Subsequently, ultrasonography combined with pulse contour cardiac output (PICCO) monitoring was carried out to check the hemodynamics. Cardiopulmonary ultrasound showed the following: Ejection fraction, 45%; good performance of both lungs; PICCO cardiac index, 2.9 L/min/m²; global end-diastolic volume index, 439 mL/m²; systemic vascular resistance index, 1458 dyn.s.cm⁻².m⁻²; increased extravascular lung water index (EVLWI), 16 mL/kg; pulmonary vascular permeability index (PVPI), 4.3; central venous pressure, 16 mmHg. The findings suggested severe capacity loss and fluid reactivity in continuous expansion. Moreover, the intravascular volume was being lost rapidly, the patient gradually developed systemic edema, and the findings deteriorated further: PICCO EVLWI, 22 mL/kg; PVPI, 8.7; and bladder pressure, 30 mmHg. The patient was diagnosed with CLS caused by pesticide poisoning.

Considering the pathophysiology of CLS, colloid fluid, plasma, and albumin were selected for expansion. However, the patient’s leakage continued to worsen, with difficulties in maintaining oxygenation under full ventilator support (Positive end-expiratory pressure, 15 cm H₂O; PPLAT, 35 cm H₂O; PICCO, EVLWI, 32; oxygenation index, 54 mmHg). Hence, the patient received VV-ECMO treatment at the 13th hour after admission with the consent of the family members. After ECMO, the patient’s oxygenation level improved, but soon a low-flow alarm appeared. On performing bedside ultrasonography, the patient was found to have a large amount of ascites and pleural effusion. Abdominal puncture and pleural puncture were performed, and the protein level in pleural hydroperitoneal fluid was found to be significantly high. An indwelling drainage tube was placed for continuous drainage, and the ECMO flow recovered to a stable level.

**OUTCOME AND FOLLOW-UP**

After the above active treatments, the leakage of the patient gradually decreased. The cholinesterase level had recovered to 4917 U/L, and the patient was taken off the machine successfully after 3 d of ECMO. Under ventilator support, the oxygenation index was 180 mmHg, and the bladder pressure was 12 mmHg. On day 6, the patient became lucid, and her muscle strength was at grade 2. A jejunal tube was placed under endoscopic visualization for enteral nutrition, but the whole stomach was found to be severely eroded; the mucosa in the gastric bulb and descending part covered a large area of coke, with a small amount of bleeding, and a very small amount of normal tissue was functional (Figure 1). The prognosis was very poor, and after the family members learned about the condition, they consented to stop the treatment, and the
DISCUSSION

CLS is a rare condition[6,7] associated with increased capillary permeability due to endothelial damage, resulting in leakage of plasma and protein into interstitial spaces[2,5,9]. It is characterized by rapidly developing edema, hypotension, and hypoproteinemia[10,11]. CLS has been observed in a variety of diseases[12,13], with the most common being sepsis. The pathogenesis of CLS is complex and has not been fully elucidated. Some scholars believe that the pathophysiology of CLS includes capillary endothelial injury from the influence of inflammatory mediators. The capillary semipermeability barrier is composed of endothelial cells and the basement membrane. Under normal physiological conditions, only small molecules such as water and electrolytes are allowed to pass through and enter the tissue gap to complete substance exchange. Meanwhile, the passage of large molecules such as toxins, metabolites, and albumin is restricted. When the body is stimulated by a variety of pathogens and stressors, endothelial cells become injured, necrosis or cell gaps increase, and the capillary semi-permeability barrier is seriously damaged. This reduces the capillary filtration rate of macromolecular substances and increases vascular permeability, leading to CLS. Under the stimulation of various pathogenic factors, monocytes and macrophages are activated to release various proinflammatory cytokines. This further activates effector cells such as granulocytes and endothelial cells, and accelerates the metabolism of arachidonic acid and the release of free radicals, thrombotin A2, prostaglandins, and other inflammatory mediators, forming the ‘inflammatory cascade effect’ that mediates the immune response and causing systemic inflammatory response syndrome and immune disorders[14]. The release of a large number of inflammatory mediators can directly damage capillary endothelial cells, leading to vascular endothelial cell injury, apoptosis, deformation, cell connection separation, or even fracture and resulting in endothelial cell dysfunction and cell membrane destruction. Further, cadherin deposition in microvascular endothelial cells leads to the formation of actin stress fibers, ultimately leading to increased capillary permeability[15]. In addition, the paracrine release of histamine and bradykinin from the mast cells in damaged tissues may further promote the occurrence of CLS[16].

Currently, there are many studies on the treatment of CLS[17]. However, there is still a lack of specific treatment measures, and the treatment of the primary disease is time-consuming[18]. In the leakage stage of CLS, small molecular proteins in the plasma leak out of the blood vessels, the plasma colloid osmotic pressure decreases, the effective circulating blood volume decreases, and the blood pressure drops progressively. The key to treatment is to maintain the effective circulating blood volume and to prevent or treat shock. Whether crystalloid or colloid treatment should be provided for CLS is still controversial[19]. Due to the high capillary permeability and low molecular weight of the crystal liquid phase, most of the crystal liquid is exudated to the tissue space, leading to increased systemic edema after infusion.
Therefore, the amount of crystal liquid should be limited for ensuring an effective circulating blood volume to avoid inter-tissue edema and cell edema. Thus, colloidal fluids were provided during fluid and albumin resuscitation (Table 1). Despite this, the fluid infusion inevitably aggravated leakage, and edema occurred in all organs. A large amount of fluid leakage from capillaries into the interstitium of the lung led to decreased pulmonary compliance, increased airway resistance, and decreased ventilation function. Severe hypoxemia occurred, and oxygenation was hardly maintained despite full ventilator support \[20\]. Therefore, VV-ECMO was used for oxygenation. The patient also presented with abdominal space syndrome; therefore, we relieved the compression symptoms of internal edema using an external minimally invasive drainage, such as puncture, to maintain oxygen supply and to obtain time for the treatment of the primary disease. The pathophysiological process of CLS can be observed from the intake and output volume of patients, as shown in Table 1.

CONCLUSION

In summary, CLS has a complex etiology with a quick onset. Specific treatment methods are often lacking, and it can easily develop into multiple organ dysfunction syndrome. In this regard, early identification, active treatment of primary disease, fluid resuscitation and management, increasing plasma colloidal osmotic pressure, improving circulation, and ensuring tissue oxygen supply are key elements in the clinical treatment of critical diseases due to CLS. ECMO plays an important and positive role in the treatment of CLS.

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Anticoagulant treatment for pulmonary embolism in patient with cerebral hemorrhage secondary to mechanical thrombectomy: A case report

Xiang-Ting Chen, Qian Zhang, Chang-Qing Zhou, Yu-Fu Han, Qing-Qing Cao

Abstract

BACKGROUND
Cerebral hemorrhage secondary to cerebral embolism after mechanical thrombectomy is characterized by high morbidity, disability and mortality. If the patient also has severe pulmonary embolism (PE) at the same time, the treatment becomes more complex. This report describes the treatment strategy for a patient with PE and cerebral hemorrhage secondary to cerebral embolism after mechanical thrombectomy.

CASE SUMMARY
A 70-year-old woman presented to our emergency department with right-sided hemiplegia and mixed aphasia of 2.5 h duration. She was diagnosed with left cerebral embolism, left internal carotid artery occlusion, PE and left calf intramuscular vein thrombosis. Following mechanical thrombectomy, brain magnetic resonance imaging showed cerebral infarction with basal ganglia hemorrhage. We observed changes in cerebral hemorrhage on serial monitoring of brain computed tomography and adjusted the dose of anticoagulant drugs. After 3 wk of treatment, the patient’s neurological and respiratory symptoms significantly improved, and a favorable prognosis was obtained.

CONCLUSION
Anticoagulation could be a potential option for PE accompanied by hemorrhagic transformation of an ischemic infarct.

Key Words: Pulmonary embolism; Brain embolism; Cerebral hemorrhage; Mechanical thrombectomy; Anticoagulation; Case report

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Core Tip: Pulmonary embolism accompanied by cerebral hemorrhage secondary to cerebral embolism after mechanical thrombectomy is characterized by high disability and mortality. To manage this situation, we adopted a treatment strategy that involved adjustment of anticoagulant drugs according to the changes in cerebral hemorrhage after mechanical thrombectomy. The patient had a favorable prognosis.

INTRODUCTION
Cerebral hemorrhage secondary to cerebral embolism after mechanical thrombectomy is characterized by high morbidity, disability and mortality[1]. If the patient also has severe pulmonary embolism (PE) at the same time, the prognosis may be poor. In this situation, the treatment choice is critical. We report a patient with PE and cerebral hemorrhage secondary to cerebral embolism after thrombectomy who was treated with anticoagulant drugs and her neurological and respiratory symptoms significantly improved. As far as we know, this complex situation has not been described in the literature.

CASE PRESENTATION
Chief complaints
A 70-year-old woman presented to our emergency department with right-sided hemiplegia and mixed aphasia.

History of present illness
This patient had a history of pulmonary hypertension for approximately 2 mo, but her shortness of breath was not relieved. Her right-sided hemiplegia and mixed aphasia started 2.5 h ago.

History of past illness
This patient had no history of allergies, denied tobacco and alcohol use, and was healthy with no history of hypertension, diabetes, coronary heart disease, hyperlipidemia, stroke, or cardiac risk factors.

Personal and family history
This patient has no relevant family history in particular of clotting disorders.

Physical examination
On arrival, her blood pressure was 118/88 mmHg, heart rate was 93 bpm, and respiratory rate was 25 breaths/min. No pathological breath sounds or heart murmurs were noted and no edema in the lower extremities was observed. Neurological examination revealed mixed aphasia, right hemiplegia, and hypoesthesia. Right-side extremity weakness was noted and was graded 0/5 on the Medical Research Council Scale. Her National Institutes of Health Stroke Scale (NIHSS) score was 25.

Laboratory examinations
Laboratory tests revealed high levels of N-terminal pro-brain natriuretic peptide (2308 pg/mL). Her D-dimer level was also elevated (6.23 mg/L). Results of arterial blood gas analysis indicated obvious hypoxemia (PaO₂, 65 mmHg; PaCO₂, 36 mmHg; pH, 7.44). Protein C, protein S, antithrombin III, lupus anticoagulant, and factor V Leiden, prothrombin gene mutation as well as anti-β2-glycoprotein-1 antibodies were within normal limits. Twelve-lead electrocardiography showed a normal sinus rhythm.
Brain computed tomography angiography (CTA) showed occlusions of the intracranial segment of the left internal carotid artery and the M1 segment of the left middle cerebral artery. The Alberta Stroke Program Early CT Score was 12. Brain magnetic resonance imaging (MRI) revealed acute multiple cerebral infarctions in the bilateral centrum semiovale, left lateral ventricle, and basal ganglia (Figure 1A). Pulmonary angiography showed that both main trunks and partial branches of bilateral pulmonary arteries were embolized (Figure 2A, 2C). Digital subtraction angiography (DSA) was performed and confirmed the CT findings (Figure 1C). Transesophageal echocardiography did not show any abnormalities. Ultrasound of both lower extremities showed thrombosis in the left muscle calf venous thrombosis (MCVT).

**FINAL DIAGNOSIS**

Based on these findings, she was diagnosed with left cerebral embolism, left internal carotid artery occlusion, PE, and left MCVT.

**TREATMENT**

Mechanical thrombectomy was performed, and a large number of thrombi were aspirated with a Penumbra ACE suction catheter, and 100 000 U urokinase was administered locally for thrombolysis. Postoperative angiography showed that the left internal carotid artery, distal middle cerebral artery, and anterior cerebral artery were recanalized (Figure 1D), and the distal blood flow was significantly improved (thrombolysis in cerebral infarction; TICI 2b). After surgery, 4000 U enoxaparin solution was administered.

On the first day after surgery, the patient’s consciousness and symptoms of right hemiplegia improved (NIHSS 15 points). Postoperative brain MRI (Figure 1B) and follow-up brain CT (Figure 3A) showed that the left frontotemporal, occipital, parietal, insula, basal ganglia, and hippocampus had subacute large areas of cerebral infarction with basal ganglia hemorrhage. Anticoagulant therapy was stopped. On the second day after surgery, the follow-up CT scans showed that the cerebral hemorrhage had not enlarged markedly (Figure 3B) and the patient was given a subcutaneous injection of enoxaparin 2000 U twice daily as anticoagulant treatment. On the fourth day after surgery, brain CT scans showed that the cerebral hemorrhage had not enlarged and enoxaparin was changed to 4000 U twice daily. On day 20 after surgery, D-dimer, N-terminal pro-brain natriuretic peptide and blood gas analysis returned to normal levels. Dyspnea gradually resolved. There was no new evidence of cerebral infarction or hemorrhage on repeat CT of the brain (Figure 3C, 3D). Pulmonary angiography showed that the PE had improved (Figure 2B, 2D). Because the patient had left MCVT, combined with PE and cerebral hemorrhage, we suggest considering temporary inferior vena cava filter (IVCF) placement, but the patient’s family refused this treatment.

**OUTCOME AND FOLLOW-UP**

The patient was discharged to a rehabilitation center 3 wk after admission. The last brain CT scan showed no evidence of new cerebral infarction or hemorrhage. At the time of discharge, the patient showed slight fluid aphasia with right hemiplegia. There was right-sided upper extremity weakness graded 2/5 and lower extremity weakness graded 3/5 on the Medical Research Council Scale. Her NIHSS score was 9 and Modified Rankin Scale was 4. Dyspnea was not observed. The patient was discharged to an oral anticoagulant, namely warfarin, and no recurrence of cerebral infarction or cerebral hemorrhage was found after 6 mo of follow-up.

**DISCUSSION**

We present the unique case of a patient with PE and cerebral hemorrhage secondary to
Figure 1 MRI and digital subtraction angiography imaging before and after surgery. A: Axial brain MRI (DWI) on admission showed acute cerebral infarction in the basal ganglia; B: Postoperative brain MRI (DWI) showed subacute large areas of cerebral infarction with basal ganglia hemorrhage; C: Angiogram of the left internal carotid artery showed proximal occlusion of the left middle cerebral artery before mechanical thrombectomy; D: Postoperative angiography showed complete recanalization of the left internal carotid artery and middle cerebral artery. DWI: Diffusion-weighted imaging; MRI: Magnetic resonance imaging.

Cerebral embolism after mechanical thrombectomy. However, after anticoagulant treatment, the neurological deficit and dyspnea symptoms gradually resolved, and the patient had a good prognosis. As far as we know, there are no similar case reports.

In this study, MRI revealed that the bilateral brain showed mostly scattered lesions, and the diagnosis of multiple cerebral infarctions was made. However, neither CTA nor DSA showed obvious atherosclerotic plaques. Therefore, it is unlikely that atherosclerotic plaques were present. In addition, the patient did not have common risk factors for stroke, such as diabetes, hyperlipidemia, or hypertension. She was diagnosed with pulmonary hypertension in the other hospital, but because they did not further investigate the cause, this led to subsequent aggravation of the patient’s condition. The patient had cerebral embolism and PE, and both the venous and arterial systems were affected at the same time. Therefore, the patient may have had rare causes leading to chronic PE and further pulmonary hypertension. Pulmonary hypertension may cause a brief right-to-left shunt and emboli from pulmonary arteries to enter the left heart system, finally causing paradoxical cerebral embolism. Although the patient’s cardiac examination showed no abnormal passage between the right heart and left heart, abnormal passages such as patent foramen ovale may be closed or healed as the PE improves. This may be related to the pressure change between the right and left atria.

Based on these findings, combined with the patient’s lower extremity ultrasound, the possibility of PE caused by the left MCVT was considered. MCVT is a peripheral type of deep vein thrombosis (DVT) of the lower extremities and is considered to be the most common origin of DVT. There are related reports that MCVT can spread to the deep veins to form more serious DVT and cause chronic PE, or embolus may become detached and cause chronic PE, so we considered this possibility. At present, there is still a lack of robust evidence-based medical evidence to guide standardized treatment of MCVT; therefore, we still recommended the use of IVCFs to prevent the occurrence of another PE for this patient. It should be noted that the
Figure 2 Changes in pulmonary embolism before and after anticoagulation. A, C: Pulmonary angiogram showed multiple repletion defects in both the pulmonary artery trunks and its branches before anticoagulation; B, D: Pulmonary angiogram showed the thrombus was eliminated after 20 d of treatment.

The purpose of IVCF is to prevent PE and therefore to reduce associated morbidity and mortality, although randomized trials are needed[7,8]. In patients undergoing anticoagulation for DVT or PE in whom a contraindication to anticoagulation develops, many guidelines and expert consensus suggest[9] that an IVCF be considered in the setting of ongoing significant clinical risk for PE. Furthermore, we have not found the cause of venous thrombosis, so rare causes of venous thrombosis could not be excluded[10].

This patient had a large area of cerebral embolism caused by acute occlusion of the internal carotid artery and was treated with emergency mechanical thrombectomy. Postoperative CT showed hemorrhagic transformation of an ischemic infarct. However, the patient also had multiple emboli in both pulmonary aortic trunks, and both blood gas analysis and dyspnea indicated severe PE. Anticoagulation is indicated for the treatment of PE[11], but it may aggravate cerebral hemorrhage. However, if anticoagulation is not administered, PE may gradually worsen and threaten the patient’s life. Furthermore, the recanalized blood vessel may be occluded again. Cerebral hemorrhage secondary to mechanical thrombectomy is not always aggravated after anticoagulation[12,13], and PE would not improve without anticoagulation. Therefore, the following treatment strategy was adopted. On the first day after surgery, brain CT scan showed hemorrhage in the left basal ganglia area and anticoagulant treatment was stopped. On the second day after surgery, a half-dose of low-molecular-weight heparin was administered twice daily. To adjust the dose of anticoagulant drugs, consecutive brain CT examinations were performed to observe whether the cerebral hemorrhage was progressively aggravated. On the fifth day after surgery, when half-dose anticoagulation therapy did not aggravate cerebral hemorrhage, a full dose was administered. The patient’s neurological symptoms and respiratory symptoms subsequently showed significant improvement.

CONCLUSION

It is unlikely that a specific treatment regimen will work for all patients. In patients with PE combined with cerebral embolism, especially those with cerebral hemorrhage...
Figure 3 Changes on brain CT scan after surgery. A: Postprocedural brain CT showed large areas of cerebral infarction and hemorrhage in the left basal ganglia area; B–D: Follow-up brain CT showed no new evidence of cerebral infarction or hemorrhage. CT: computed tomography.

secondary to mechanical thrombectomy, the benefit of anticoagulation and the risk of bleeding should be carefully evaluated to implement an individualized treatment strategy. Disease evolution should be closely monitored to adjust the treatment strategy at any time.

REFERENCES


CASE REPORT

Complete restoration of congenital conductive hearing loss by staged surgery: A case report

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Author contributions: Yoo JS conceived the report; Lee EJ and Yoo JS wrote the first draft with input from all authors; Lee CM and Yang YN carried out the literature search and provided the figures; Lee EJ and Yoo JS revised the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

Informed consent statement: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript has been prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: South Korea

Specialty type: Otorhinolaryngology

Abstract

BACKGROUND
Stapedial tendon ossification is a rare disease, with only a few reports. The stapedial tendon originates from the apex of the pyramidal eminence and is attached to the neck of the stapes. In stapedial tendon ossification, the stapes is fixed, causing conductive hearing loss. In most cases, complete hearing restoration is achieved by dividing the stapedial tendon after exploratory tympanotomy.

CASE SUMMARY
A 28-year-old woman presented to our hospital with the major complaint of bilateral hearing loss that started during childhood. Exploratory tympanotomy was performed due to suspicion of otosclerosis or middle ear anomalies. We found bilateral conductive hearing loss due to stapedial tendon ossification with a middle ear anomaly during surgery. There have been several reports of complete recovery of hearing after resection of the stapedial tendon. However, in this case, recovery of hearing was insufficient, even with the division of the stapedial tendon. In the second surgery, the stapes anomaly and footplate fixation were confirmed, and hearing was completely recovered after stapedotomy. Therefore, we report this case with a review of the relevant literature.

CONCLUSION
This is the first case of stapedial tendon ossification and fixation of the footplate surgically diagnosed on both sides. With surgical treatment, successful results are expected.
INTRODUCTION

Stapedial ankylosis is a congenital or an acquired ossification of the stapes, which causes conductive hearing loss through disturbance of the sound transmission system. The main cause is fixation of the footplate along with the normal superstructure, such as otosclerosis, tympanic sclerosis, and congenital stapes fixation. However, since 1957, cases with limited movement of the stapes due to ossification of the stapedial tendon have been reported[1-14]. The stapedial tendon originates from the apex of the pyramidal eminence, attaches to the neck of the stapes, and is involved in the acoustic reflex. Due to this anatomical location, stapedial tendon ossification was also referred to as the elongation of the pyramidal eminence or bony bar[2-4]. When the stapes is fixed, this causes conductive hearing loss. In most cases, complete hearing improvement is achieved by division of the stapedial tendon after exploratory tympanotomy[2-6]. According to the literature, it can be diagnosed by computed tomography (CT) and tympanotomy. In addition, it is easily mistaken for otosclerosis, and thus discrimination is essential[7]. In the case described herein, surgical division was performed after diagnosing stapedial tendon ossification through exploratory tympanotomy, but hearing recovery was insufficient. Therefore, we performed stapedotomy as the second surgery and achieved complete hearing recovery after stapedotomy. Here, we report this case along with a review of relevant literature.

CASE PRESENTATION

Chief complaints
Bilateral hearing loss.

History of present illness
A 28-year-old woman visited our clinic with bilateral hearing loss. She had poor hearing since childhood.

History of past illness
There was no previous history of infection or trauma, and there were no other medical symptoms.

Personal and family history
She had no family history of hearing loss.

Physical examination
On otoscopy, both eardrums were normal.
Laboratory examinations
On the patient’s first visit to our clinic, laboratory test results were within the normal ranges.

Imaging examinations
Temporal bone CT showed normal middle ear and ossicular chain.

Hearing tests
As per pure tone audiometry, the air-conduction threshold was 50 dB on the right and 45 dB on the left, and bilateral conductive hearing loss was found, showing a 40 dB air-bone gap (Figure 1A). The speech discrimination scores on both sides were 92% each.

FINAL DIAGNOSIS
The patient was diagnosed with stapedial tendon ossification and fixation of the footplate on both sides.

TREATMENT
Right-sided stapes surgery was planned due to suspicion of bilateral otosclerosis. When we scanned the temporal bone CT before surgery, the bilateral stapedial tendon showed a slightly thicker appearance than normal, but was overlooked (Figure 2). An exploratory tympanotomy was performed on the right side under general anesthesia. Entire fixed ossicle mobility was also identified. After separating the incudostapedial joint (I-S joint), it was found that the stapedial tendon was ossified. It looked like a bony bar between the pyramidal eminence and the stapes neck. The posterior crura and footplates of the stapes were invisible and appeared in the form of a monopod. After division of the stapedial tendon with a fine burr, we noted that the movement of the stapes became hypermobile, and that it was misdiagnosed as otosclerosis. The separated I-S joint was connected with fibrin glue, and the surgery was terminated. The hearing test after surgery showed that the air-bone gap (ABG) on the right side decreased by 5 dB. One month later, an exploratory tympanotomy was performed on the contralateral side, and the same stapedial tendon ossification was observed; only the stapedial tendon was divided with a fine burr without any other treatment (Figure 3). After dividing only the stapedial tendon on the left side, the mobility of the stapes improved. Because the patient was under general anesthesia, we ended the operation in anticipation of proper hearing recovery. The hearing test after surgery showed that the ABG on the left side decreased by approximately 15 dB (Figure 1B). Even if the right side was separated from the I-S joint incorrectly and the improvement was insufficient, the ABG on the left side improved by only 15 dB; therefore, we considered the possibility of an accompanying abnormality and planned a second surgery on the right side. During the second surgery, the stapes were observed in the form of a rod, and it was found that the footplate was fixed. Therefore, stapedotomy was planned. After measuring the length between the incus and the stapes, a small hole was made with a perforator, and a window was made on the posterior side of the footplate using a Skeeter drill. A piston wire (0.4 mm × 5 mm) was hung over the long process of the incus and fixed using a crimper. The operation was subsequently terminated.

OUTCOME AND FOLLOW-UP
There were no postoperative complications. One year after surgery, her hearing in the right ear had markedly improved (Figure 1C). Therefore, we are considering a left-sided stapedotomy and expecting the same improvement; however, due to the coronavirus disease 2019, it is planned in the next few years.

DISCUSSION
The major cause of isolated stapedial ankylosis is stapedial footplate fixation with
normal stapes suprastructure due to otosclerosis, congenital stapedial fixation, and tympanosclerosis as reported by Henner [15]. In addition to stapedial tendon ossification, there are various types of ankylosis caused by elongation of the pyramidal eminence, stapes promontory fixation, and stapes pyramidal bony bar with normal stapedial tendon. Ossification of the stapedius tendon rarely occurs due to congenital causes. If it occurs due to an acquired cause, such as infection, it can be accompanied by tympanosclerosis. This disease, which needs to be differentiated, is otosclerosis and is often misdiagnosed. Stapedial tendon ossification has been reported in only a few studies [1-14]. Most previous reports have shown bilateral conductive hearing loss without trauma or past history. Here, on otoscopy, the eardrum was almost normal, and the patient did not complain of any other symptoms. From previous reports showing the same findings over different generations, a congenital cause was found, and it was thought to have an autosomal recessive inheritance [4,9].

Stapedial tendon ossification can be diagnosed using preoperative CT and exploratory tympanotomy. On temporal bone CT, it can be diagnosed as a linear image from the pyramidal eminence to the stapes superstructure [7]. Based on these findings, it can be differentiated from otosclerosis [16]. A definitive diagnosis is to directly confirm ossification of the stapedius tendon that fixes the stapes through tympanotomy. The treatment involves dividing the tendon between the stapes and the pyramidal eminence. After securing a sufficient surgical field, it is carefully performed using a microdrill or laser. Hearing was significantly restored following division of the stapedial tendon. The average ABG before surgery was 30 dB, which closed after the surgery [2-6,10] (Table 1).

Our patient had no history of ear infection or degenerative change in the middle ear; thus, the stapedial tendon ossification might have originated from a congenital lesion. Our patient was misdiagnosed with bilateral otosclerosis, and at the time of the first right side surgery, we made a mistake in separating the right I-S joint. However, on the left side, even though only the stapedial tendon was divided because the lesion...
Table 1 Changes in hearing before and after surgery in stapedial tendon ossification patients

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Ears</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Average of air-bone gaps [pre OP/post OP/△ (pre OP-post OP)]</th>
</tr>
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<tr>
<td>Schuknecht et al[1], 1957</td>
<td>1</td>
<td>PE elongation</td>
<td>Division</td>
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</tr>
<tr>
<td>Patel[5], 1972</td>
<td>1</td>
<td>ST ossification</td>
<td>Division and stapedectomy</td>
<td>51.67 dB/15 dB/36.67 dB</td>
</tr>
<tr>
<td>Cremers et al[2], 1986</td>
<td>2</td>
<td>PE elongation</td>
<td>Division</td>
<td>22.5 dB/0 dB/22.5 dB</td>
</tr>
<tr>
<td>Grant et al[4], 1991</td>
<td>4</td>
<td>ST ossification</td>
<td>Division</td>
<td>31.67 dB/2.5 dB/29.17 dB</td>
</tr>
<tr>
<td>Jecker et al[8], 1992</td>
<td>2</td>
<td>ST ossification</td>
<td>Division</td>
<td>NA/NA/NA</td>
</tr>
<tr>
<td>Kinsella et al[3], 1993</td>
<td>3</td>
<td>Bony bar</td>
<td>Division</td>
<td>29.44 dB/0 dB/29.44 dB</td>
</tr>
<tr>
<td>Kurosaki et al[7], 1995</td>
<td>8</td>
<td>ST ossification</td>
<td>Division and stapedectomy</td>
<td>NA/NA/NA</td>
</tr>
<tr>
<td>Thies et al[4], 1996</td>
<td>5</td>
<td>Bony bar</td>
<td>Division</td>
<td>25.83 dB/NA/NA</td>
</tr>
<tr>
<td>Hara et al[9], 1997</td>
<td>3</td>
<td>ST ossification</td>
<td>Division</td>
<td>NA/NA/NA</td>
</tr>
<tr>
<td>Lee et al[11], 2009</td>
<td>1</td>
<td>ST ossification</td>
<td>Division</td>
<td>30 dB/13.33 dB/16.67 dB</td>
</tr>
<tr>
<td>Wetmore et al[12], 2011</td>
<td>6</td>
<td>Bony bar</td>
<td>Division</td>
<td>NA/NA/NA</td>
</tr>
<tr>
<td>Ulkù[13], 2011</td>
<td>2</td>
<td>ST ossification</td>
<td>Division</td>
<td>NA/NA/NA</td>
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<tr>
<td>Wasano et al[10], 2014</td>
<td>2</td>
<td>ST ossification</td>
<td>Division</td>
<td>25 dB/2.5 dB/22.5 dB</td>
</tr>
<tr>
<td>Chan[14], 2016</td>
<td>1</td>
<td>Bony bar</td>
<td>Division</td>
<td>NA/NA/NA</td>
</tr>
</tbody>
</table>

Air-bone gaps: Calculated using the American Academy of Otolaryngology recommendations. NA: Not available; PE: Pyramidal eminence; ST: Stapedial tendon.

was the same, hearing improvement after surgery was insufficient. Therefore, we suspected an accompanying malformation and performed the second surgery, wherein we found an anomaly of the stapes in the form of a monorod and fixation of the footplate. Thus, a window was made on the posterior side of the fixed footplate using a Skeeter drill, and a piston wire (4 mm × 0.5 mm) was hung on the incus long process and inserted into the window. Hearing on the right side showed marked improvement after the stapedotomy. Previously, one case of stapedial tendon ossification and fixation of the footplate on both sides was reported. At that time, only one side was diagnosed and treated with stapedectomy[7]. This is relevant because our case is the first to have been surgically diagnosed on both sides. In addition, successful results are expected after surgical treatment.

Congenital stapedial footplate fixation (CSFF) is a rare cause of congenital conductive hearing loss. Nevertheless, this is a common congenital ossicle abnormality. It has been reported that approximately 9% of newborns to 13-year-olds have congenital abnormal stapes footplate[17]. Pathophysiologically, in CSFF, the annular ligament of the oval window is misdeveloped and the footplate is fixed as a result. In some cases, it is accompanied by abnormalities of the ossicle or facial nerve[18]. Symptoms initially appear as conductive hearing loss on audiometry with no signs of effusion or infection. In all cases where exploratory tympanotomy is performed, preoperative imaging is required, and the diagnosis is confirmed during surgery when a fixed footplate is observed. Stapedotomy has been proven to be safe and effective in improving auditory outcomes.

**CONCLUSION**

Stapedial tendon ossification is a very rare disease that results in bilateral conductive hearing loss. If stapedial tendon ossification is found, good progress can be expected following division. In most previously reported case reports, the ABG was completely restored after surgery. However, as in our case, when hearing improvement after surgery is insufficient, the possibility of accompanying malformations should be
considered. Thus, secondary surgery may be necessary, and successful results can be obtained when the comorbid anomaly is resolved.

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Blastic plasmacytoid dendritic cell neoplasm with skin and bone marrow involvement: Report of three cases

Jiang-Hong Guo, Hong-Wei Zhang, Li Wang, Wei Bai, Jin-Fen Wang

Abstract

BACKGROUND

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and highly aggressive hematopoietic malignancy. BPDCN is difficult to diagnose because of the overlap in morphologic and immunophenotypic features with various cutaneous lymphatic hematopoietic tumors.

CASE SUMMARY

We report on three BPDCN cases, all characterized by skin nodules and examined by histology, immunohistochemical detection, in situ hybridization for Epstein-Barr virus, and follow-up. We also review the relevant literature. All patients were positive for CD56 and negative for Epstein-Barr encoded small RNA. Two patients had bone marrow involvement. Chemotherapy is the main treatment for BPDCN, but case 1 showed bone marrow suppression and case 2 developed recurrence after chemotherapy. Case 1 survived for 7 mo, case 2 for 17 mo, and case 3 for 9 mo.

CONCLUSION

An accurate pathological diagnosis is a precondition for treatment, and the diagnosis of BPDCN should be based on a combination of clinical symptoms, pathological characteristics, immunophenotype, and other auxiliary examinations. It is necessary to clarify the clinicopathological features and biological behavior of BPDCN to improve its understanding by both clinicians and pathologists. Case 2 survived significantly longer than the other two cases, suggesting that the treatment received by case 2 was more effective.

Key Words: Blastic plasmacytoid dendritic cell neoplasm; Diagnosis; Immunohistochemistry; Skin lesion; Follow-up; Case report
Core Tip: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is difficult to diagnose because of the overlap in morphologic and immunophenotypic features with various cutaneous lymphatic hematopoietic tumors. We report the clinical symptoms, pathological characteristics, immunophenotype, treatment, and follow-up (from diagnosis until death) for three patients with BPDCN. It is necessary to clarify the clinicopathological features and biological behavior of BPDCN to improve the understanding of the disease by both clinicians and pathologists. The survival time of case 2 was significantly longer than usual, suggesting that the treatment received by this case was suitable for clinical application.

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INTRODUCTION
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a highly aggressive lymphoid hematopoietic system tumor derived from precursors of plasmacytoid dendritic cells, with no racial or ethnic predisposition. BPDCN is difficult to diagnose because of the overlap in morphologic and immunophenotypic features with various cutaneous lymphatic hematopoietic tumors. We retrospectively report the clinicopathological data, histological and morphological characteristics, immunophenotype, and differential diagnosis in three cases of BPDCN, in order to raise awareness of the condition and provide evidence for its clinical treatment and prognosis. In addition, we briefly review previous cases of BPDCN.

CASE PRESENTATION

Chief complaints
Case 1 was a 59-year-old man who was admitted to the Department of Hematology of Shanxi Cancer Hospital in February 2013, with a complaint of skin nodules all over his body.
Case 2 was a 15-year-old girl who was admitted to the Department of Hematology of Shanxi Cancer Hospital in July 2016, with a complaint of nodules on her back.
Case 3 was a 70-year-old woman who was hospitalized in another hospital, but she came to our hospital for consultation and examination of pathological samples.

History of present illness
Case 1 found a nodule in his right inner thigh in November 2012, and unequal nodules gradually appeared on his trunk and limbs, followed by multiple tender enlarged lymph nodes in his neck, armpits, and groin. The tumors grew rapidly.
Case 2 inadvertently found scattered hard subcutaneous nodules on her back in May 2016.

History of past illness
Case 1 had a 3-year history of hypertension, but his blood pressure was controlled with oral nifedipine sustained-release tablets.
Cases 2 and 3 had no relevant medical histories.

Personal and family history
All the three cases had no relevant medical histories.
Physical examination
Case 1 had a temperature of 36.3 °C, heart rate of 81 bpm, respiratory rate of 20 breaths per minute, and blood pressure of 153/89 mmHg. Dense reddish-brown, slightly protruding, macular papules were scattered over his whole body, accompanied by ulceration. Multiple tender lymph nodes measuring about 1-5 cm in diameter were palpable in the bilateral neck, armpit, and groin regions. The clinical consideration was lymphoma.

The temperature of case 2 was 36.3 °C, her heart rate was 116 bpm, respiratory rate was 20 breaths per minute, and blood pressure was 107/63 mmHg. Multiple subcutaneous dark red, tender nodules were present under the skin, with the largest being about 4 cm in diameter. The clinical consideration was lymphoma.

Laboratory examinations
All patients underwent skin biopsy. The biopsy tissues were stained with hematoxylin and eosin, immunohistochemically stained for antigens including CD56, CD4, CD123, and CD68, and used for in situ hybridization to detect Epstein-Barr virus [EBV; Epstein-Barr encoded small RNA (EBER)].

Case 1: Lactate dehydrogenase (LDH) level was normal (156 U/L). A 2.0-cm lymph node biopsy from the right upper arm showed the absence of normal lymph node structure, and medium-sized diffuse lymphoid cells. Immunohistochemically, lymphocytes were positive for CD56, CD123 (Figure 1A), CD38, LCA, CD43, CD99, and Ki67 (60%), and negative for CD4, CD68, myeloperoxidase (MPO), CD3, CD20, CD21, CD10, CD5, CyclinD1, CD23, CD15, CD30, CD138, S-100, Pax-5, MUM1, CD34, Granzyme B, TIA-1, and TdT. The EBER test was negative. Bone marrow biopsy revealed diffuse lymphoid cells between the bone trabeculae, with medium-sized heterotypic nuclei (Figure 1B). Immunohistochemical analysis of lymphocytes indicated positivity for CD56, CD123, CD43, and Ki67 (30%), and negativity for CD4, CD68, MPO, CD3, CD20, TIA-1, and TdT.

Case 2: LDH level increased to 348 U/L. Biopsy showed dense heteromorphic lymphoid cells throughout the dermis (Figure 2A). Immunohistochemically, the lymphocytes were positive for CD56, CD4 (Figure 2B), CD123, Bcl-2, and Ki67 (80%), but negative for CD68, MPO, CD3, CD20, CD30, CD43, CD5, MUM-1, CD34, TIA-1, Granzyme B, and CD10. An EBER test was negative. Posterior iliac puncture revealed diffuse lymphoid cells between the bone trabeculae and bone marrow, with medium-sized heterotypic nuclei, and bone marrow infiltration. Immunohistochemistry revealed that the lymphocytes were positive for CD56, CD4, CD123, and Ki67 (20%-30%), and negative for CD68, MPO, CD3, CD20, and CD38.

Case 3: Immunohistochemical and in situ hybridization examinations were performed in the Department of Pathology of Shanxi Cancer Hospital. A biopsy from her inner left thigh demonstrated diffuse infiltrating plasmacytoid cells with nuclear deviation. Immunohistochemically, the lymphocytes were positive for CD56, CD68, and Ki67 (10%), and negative for CD4, CD123, CD3, CD20, CD10, MUM1, AE1/AE3, Desmin, S-100, and CD30. The main test results are shown in Table 1.

Imaging examinations
Case 1: Computed tomography (CT) revealed multiple lymph nodes in bilateral areas I and IV of his neck, bilateral axilla, anterior inferior mediastinum, and bilateral iliac and inguinal regions. The largest lymph node was about 2.6 cm × 2.2 cm. A 1.25-cm pleural nodule in the right lower lung was considered as an inflammatory lesion, and most of the lymph nodes were solid.

Case 2: CT scans revealed multiple lymph nodes in the perivascular spaces in her neck, mediastinum, bilateral axilla, abdominal aorta, and bilateral iliac and inguinal regions, and a 0.9-cm subcutaneous nodule on her right lower back.

FINAL DIAGNOSIS
The final diagnosis in all three cases was BPDCN.
Table 1 Main test results in the three patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Site</th>
<th>CD56</th>
<th>CD4</th>
<th>CD123</th>
<th>CD68</th>
<th>MPO</th>
<th>CD3</th>
<th>CD20</th>
<th>Ki67</th>
<th>EBER</th>
<th>LDH</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Skin</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>60%</td>
<td>-</td>
<td>156 U/L</td>
<td>7 mo</td>
</tr>
<tr>
<td></td>
<td>Bone marrow</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30%</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Skin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>80%</td>
<td>-</td>
<td>348 U/L↑</td>
<td>17 mo</td>
</tr>
<tr>
<td></td>
<td>Bone marrow</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20%-30%</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Skin</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10%</td>
<td>-</td>
<td>Not checked</td>
<td>9 mo</td>
</tr>
</tbody>
</table>

EBER: Epstein-Barr encoded small RNA; LDH: Lactate dehydrogenase.

Figure 1 Case 1. A: Tumor cells were strongly and uniformly positive for CD123 with a membranous pattern; B: Diffuse lymphoid cells between the bone trabeculae, with medium-sized heterotypic nuclei (magnification, 400 ×). H&E: Hematoxylin and eosin.

Figure 2 Case 2. A: Neoplastic cells in the skin infiltrated mainly into the dermis, but not into the epidermis (magnification, 50 ×). B: Tumor cells were positive for CD4, with a membranous pattern.

TREATMENT

Case 1
Chemotherapy was administered as the main treatment for BPDCN, but the patient developed bone marrow suppression after treatment with the VDLD regimen (vincristine 2 mg, intravenous injection, days 1, 8, 15, and 22 [1.4 mg/m², ≤ 2 mg each time]; daunorubicin 40 mg/m², intravenous drip, days 1-3 and 15-16; L-asparaginase 6000 IU/m², intravenous drip, days 11, 14, 17, 20, 23, and 26; dexamethasone 1
mg/kg/d, orally, for 14 consecutive days, reduced by 1/3 on days 15-28). One month later, he was treated with the CAM regimen (cytoxan 750 mg/m², intravenous drip, days 1 and 8 [uromitexan rescue]; cytosine arabinoside 100 mg/m²/d, intravenous drip, days 1-3 and 8-10; 6-mercaptopurine 60 mg/m²/d, oral, days 1-7), and again showed bone marrow suppression.

Case 2
The subcutaneous nodules subsided after anti-infective treatment but subsequently reappeared and became more severe, gradually involving the limbs and body. She was treated with the CHOP (cytoxan 750 mg/m², vincristine 1.4 mg/m², doxorubicin 50 mg/m², all by intravenous drip on day 2, prednisone 100 mg, oral, days 2-6; repeated every 21 d) and VDCLP (vincristine 2 mg, intravenous injection, days 1, 8, 15, and 22 [1.4 mg/m², ≤ 2 mg each time]; daunorubicin 40 mg/m², intravenous drip, days 1-3 and 15-16; cytoxan 750 mg/m², intravenous drip, days 1 and 15 [uromitexan rescue]; L-asparaginase 6000 IU/m², intravenous drip, days 11, 14, 17, 20, 23, and 26; prednisone 1 mg/kg/d, oral, for 14 consecutive days, reduced by 1/3 on days 15-28) regimens for BPDCN, with improvement of the subcutaneous nodules and a complete bone marrow response.

Case 3
Case 3 was treated in another hospital. She knew that she had received chemotherapy but did not know the chemotherapy regimen.

OUTCOME AND FOLLOW-UP
Case 1 subsequently developed pulmonary infection in May 2013 and central infiltration on August 8, and finally died 7 mo after his diagnosis.
Case 2 was followed for 17 mo from diagnosis to death, after stopping treatment for economic reasons.
Case 3 died 9 mo after her diagnosis.

DISCUSSION
BPDCN accounts for only 0.7% of primary lymphatic hematopoietic tumors of the skin [1]. It can occur in any age group [2,3], but is most common in the elderly. The male:female ratio is 3.3:1. Jegalian et al [2] reported that children and young patients had a relatively good prognosis. About 76%-85% of cases [4] have skin involvement, with asymptomatic isolated or multiple nodules, plaques, or bruises. In some cases only the skin is involved, but multiple parts may be affected. The current cases of BPDCN included one man and two women, and although two were elderly, case 2 was unusually only 15 years old, and she had a relatively good prognosis (17 mo). In the present study, all three cases were characterized by skin nodules.

The diagnosis of BPDCN is based on pathological biopsy. Kerr et al [5] showed tumor cells invading the dermis and adipose tissue of the skin, with no tumor cells in the epidermis. When the lesion involves the bone marrow, it may show as an interstitial infiltration or as a mass of tumor cells, like infiltrating leukemia, often accompanied by hematopoietic tissue dysplasia [6]. In the current study, the pathological features of all three patients showed no tumor cells invading the epidermis, and a morphology consistent with that reported in the literature. In addition, the bone marrow was involved in cases 1 and 2, and numbers of diffuse lymphoid cells could be observed.

The immunological phenotype of BPDCN is important. Julia et al [7] proposed five specific immunological markers for BPDCN: CD56, CD4, CD123, TCL1, and CD303, and suggested that positivity for at least four of these indicated a diagnosis of BPDCN. Overexpression of CD123 or interleukin-3 receptor subunit alpha occurs in essentially all cases of BPDCN [8-10]; however, a few atypical cases have been reported which did not express CD4 or CD56 [11], and individual CD123-negative cases of BPDCN have also been reported [12]. CD68 is expressed in 50% of tumor cells, and such patients are prone to leukemic transformation [2]. In contrast, the cytotoxic markers CD23, CD30, and CD138 are negative. In this study, tumor cells expressed CD56 in all three cases, CD4, CD123, and CD68 were positive in one, two, and one case, respectively. Tumor cells were positive for CD68 expression in case 3, but she did not develop acute
leukemia. Laboratory examinations are also essential for diagnosing BPDCN, and LDH was significantly elevated in case 2.

Clinicopathologically, the differential diagnosis of BPDCN includes myeloid sarcoma or leukemia, T-lymphoblastic lymphoma, and natural killer (NK)/T cell lymphoma. Both myeloid sarcoma or leukemia and BPDCN can show skin, lymph node, and bone marrow involvement. However, applying a series of markers (such as CD56, CD4, CD123, and TCL-1) can better distinguish these diseases[12]. MPO is a specific immunological marker of acute myeloid leukemia (AML). In the current study, MPO was negative in cases 1 and 2, and BPDCN could be confirmed by a combination of morphology and immunological positivity for CD56, CD4, and CD123 and MPO negativity. Compared with BPDCN, T-lymphoblastic lymphoma usually occurs in adolescents or young adults, with more frequent mediastinal involvement. It is important to note that patients with BPDCN without skin involvement may have a younger onset age, and may have mediastinal involvement and CD34-positive tumor cells, which may be more easily confused with T-lymphoblastic lymphoma. Although case 2 was an adolescent, all three patients had skin involvement and no mediastinal involvement; furthermore, CD34 was negative in cases 1 and 2, and T-lymphoblastic lymphoma could thus be excluded. BPDCN and NK/T cell lymphoma can be distinguished by morphology, immunohistochemistry, and EBER testing. Tumor cells in NK/T cell lymphoma have various forms, often invade the vascular wall and are accompanied by necrosis, and cytotoxic markers such as TIA-1 and Granzyme B are often positive. Furthermore, NK/T cell lymphoma is associated with EBV infection, and the EBER test is thus positive in patients with NK/T cell lymphoma. Although CD56 was expressed in BPDCN, serum EBV and in situ hybridization for detection of EBER were negative, indicating that BPDCN was not related to EBV infection[1]. In this study, TIA-1 and Granzyme B were negative in cases 1 and 2, and all three patients were EBER-negative, thus excluding a diagnosis of NK/T cell lymphoma.

Given the lack of consensus, BPDCN has been treated with regimens used for other acute leukemias. Most case reports indicated that the majority of patients who received initial treatment with acute lymphoblastic leukemia, AML, or lymphoma CHOP chemotherapy achieved complete remission but had a high recurrence rate[13,14]. In this study, case 1 received successive VDLD treatment and CAM chemotherapy, but both caused significant bone marrow suppression. VCDCLP has since been used to replace VDLD. Notably, CHOP and VCDCLP resulted in improvement of the subcutaneous nodules and complete bone marrow response in case 2. Case 2 survived significantly longer than case 1, suggesting that case 2’s treatment was more effective. New treatment options have recently been developed. A cytotoxin directed against CD123 (tagraxofusp, formerly DT-IL3 and SL-401) has received United States Food and Drug Administration approval specifically for BPDCN in adults and in children aged 2 years or older[15].

CONCLUSION

In summary, BPDCN is a rare and highly aggressive hematopoietic malignancy. Skin involvement is the most common initial clinical manifestation, but it is not specific, and the bone marrow can also be affected. CD56, CD4, and CD123 are important diagnostic makers for BPDCN. The diagnosis of BPDCN should thus be based on a combination of clinical symptoms, pathological characteristics, and other auxiliary examinations, to minimize the risk of a missed or delayed diagnosis. These cases highlight the need to improve the understanding of BPDCN by both clinicians and pathologists.

REFERENCES


CONCLUSION

In summary, BPDCN is a rare and highly aggressive hematopoietic malignancy. Skin involvement is the most common initial clinical manifestation, but it is not specific, and the bone marrow can also be affected. CD56, CD4, and CD123 are important diagnostic makers for BPDCN. The diagnosis of BPDCN should thus be based on a combination of clinical symptoms, pathological characteristics, and other auxiliary examinations, to minimize the risk of a missed or delayed diagnosis. These cases highlight the need to improve the understanding of BPDCN by both clinicians and pathologists.

REFERENCES


Extracranial multiorgan metastasis from primary glioblastoma: A case report

Xing-Zhao Luan, Hao-Run Wang, Wei Xiang, Shen-Jie Li, Haiping He, Li-Gang Chen, Jian-Mei Wang, Jie Zhou

Abstract

BACKGROUND
Glioblastoma has a high degree of malignancy and poor prognosis. It is common to have in situ recurrence and intracranial metastasis, while extracranial metastasis is rare, and extracranial multiorgan metastasis is extremely rare. We report a case of glioblastoma with extracranial multiorgan metastasis, which will strengthen clinicians’ attention to the extracranial metastasis of glioblastoma and its treatment.

CASE SUMMARY
A male patient visited our hospital for treatment of dizziness and headache. Magnetic resonance imaging of the brain revealed a space-occupying lesion in the right temporoparietal occipital region. Chest computed tomography and abdominal ultrasound were normal, and no space-occupying lesions were observed in other organs of the body. The patient underwent surgery and diagnosed with glioblastoma. Postoperative concurrent radiotherapy and chemotherapy were completed. During the follow-up, the tumor was found to have metastasized to the scalp and neck, and a second tumor resection was performed. Postoperative follow-up revealed extracranial metastases to multiple extracranial organs including skull, scalp, ribs, spine, liver and lung. His family
manuscript was prepared and revised according to the CARE Checklist (2016).

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Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicted article; Externally peer reviewed.

Peer-review report’s scientific quality classification
Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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members refused further treatment, and requested only symptomatic treatment such as pain relief, and the patient died of systemic multiple organ failure. Survival time from diagnosis to death was 13 mo and from extracranial metastasis to death was 6 mo.

CONCLUSION
Glioblastoma extracranial metastasis is extremely rare, clinicians should always pay attention to its existence. The mechanism of glioblastoma extracranial metastasis is still unclear, and genetic and molecular studies are required.

Key Words: Glioblastoma; Extracranial metastasis; Multiple organ metastasis; Primary glioblastoma; Case report

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INTRODUCTION
Glioblastoma is the most common primary malignant tumor of the central nervous system (CNS). It often recurs in situ and rarely metastases, especially extracranially. Extracranial multiorgan metastasis is even rarer. We report a case of extracranial multiple organ metastasis of glioblastoma, reviewed relevant literature, and discussed the related mechanism and treatment plan. This report may provide more possibilities for the related mechanism and treatment of extracranial metastasis of glioblastoma.

CASE PRESENTATION

Chief complaints
A 47-year-old man presented with dizziness for 1 mo and headache for 1 wk without other discomfort.

History of present illness
The patient developed dizziness without obvious cause 1 mo ago, and was obviously dizzy and uncomfortable when squatting and suddenly standing up. The head distension and pain occurred 1 wk ago, and the symptoms persisted, but there was no relief after rest.

History of past illness
The patient had a history of right elbow injury caused by a car accident 20 years ago.

Personal and family history
Denial of personal and family history.

Physical examination
Physical examination showed no obvious abnormality and blood pressure was 130/80 mmHg.
Laboratory examinations
Blood analysis revealed mild leukocytosis $12.5 \times 10^9/L$, with predominant neutrophils (80%) with normal hematocrit and platelet count. Other tests were within the normal range.

Imaging examinations
Magnetic resonance imaging (MRI) of the brain revealed a space-occupying lesion of 62 mm × 40 mm × 43 mm in the right temporoparietal occipital region. T1-weighted and T2-weighted images showed high signal. The contrast-enhanced scan showed irregular annular enhancement, and the cerebral line shifted about 0.8 cm to the left (Figure 1A). Chest computed tomography (CT) and abdominal ultrasound were normal, and no space-occupying lesions were observed in other organs of the body.

Further diagnostic work-up
After admission, the lesion was extensively excised and the ventricle was opened intraoperatively (Figure 1B). The pathological results of the patient suggested that hematoxylin-eosin staining showed a large amount of necrosis and scattered heteromorphic cells, considering high-grade glioblastoma (Figure 1C), glial fibrillary acidic protein (+) (Figure 1D), Ki67 (+20%) (Figure 1E). Furthermore, pathological examination revealed that immune phenotype IDH1 wild type, IDH2 wild type, MGMT unmethylated, and the diagnosis was glioblastoma (World Health Organization grade IV).

FINAL DIAGNOSIS
The patient was diagnosed with glioblastoma (IDH-wild type).

TREATMENT
Postoperative concurrent chemoradiotherapy with the following regimen was administered: Radiotherapy (daily fractions of 2 Gy given 5 d/wk for 6 wk, for a total of 60 Gy) plus continuous daily temozolomide (75 mg/m² body-surface area per day, 7 d/wk from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150-200 mg/m² for 5 d during each 28-d cycle, and regular follow-up.

OUTCOME AND FOLLOW-UP
Six months after surgery, the patient had a mass at the site of surgical incision (Figure 2A), and intracranial recurrence and subcutaneous metastasis were considered in the re-examination of enhanced MRI (Figure 2B). Family members required temporary observation and simultaneous radiotherapy and chemotherapy. Nine months postoperatively, the patient was readmitted due to enlargement of the scalp incision and a new neck mass (Figure 2C). After the second admission, the patient underwent maximum lesion resection and scalp mass resection. Pathological examination of the scalp mass revealed glioblastoma, which was confirmed as extracranial metastasis (Figure 2D-F). Ultrasound indicated that the cervical mass was cervical lymph node enlargement, and we performed excision of the mass (Figure 2G). The pathological examination was consistent with glioblastoma metastasis to the cervical lymph nodes (Figure 2H). Follow-up head and chest CT showed metastases in the skull, scalp, ribs, spine, liver and lungs, and the patient died of systemic organ failure (Figure 3A-F). We suggested that the patient complete positron emission tomography/CT examination and further surgical treatment, but the patient and his family members refuse further examination and surgery, and only palliative treatment. Survival time from diagnosis to death was 13 mo and from extracranial metastasis to death was 6 mo.

DISCUSSION
Postoperative recurrence of glioblastoma is common, but metastasis is rare and
extracranial multiorgan metastasis is extremely rare[1].

Weiss[2] proposed the diagnostic criteria for extraencephalic metastasis of malignant tumors in 1955: (1) The histological features of the CNS neoplasm must be demonstrated to be unitary; (2) The initial symptoms must be caused by the tumor in the clinical history; (3) A full autopsy is necessary and there is sufficient evidence to rule out the possibility of other tumors; and (4) The pathomorphology of distant metastases and CNS neoplasm must be consistent, and appropriate degrees of difference can be considered. In view of the histological features of brain glioblastoma and the pathological manifestations of scalp and neck lymph nodes, the present case met the diagnostic criteria proposed by Weiss (except autopsy).

To further explore the characteristics of glioblastoma extracranial metastases, we reviewed cases of intracranial tumors with extracranial metastases reported in the past 5 years (Table 1). We found the following features: (1) Glioblastoma is the most common intracranial tumor with extracranial metastasis, although astrocytomas and diffuse glioblastoma have also been reported; (2) The most common site of the disease is the temporal lobe, and the frontal and occipital lobes have also been reported; (3) The most common site of extracranial metastasis is the spinal canal, followed by liver, lungs, lymph nodes and other sites, while extracranial multiorgan metastasis is relatively rare; and (4) The average time from diagnosis to death for intracranial tumors was 15.2 mo, and the discovery of extracranial metastases was approximately 4 mo. Our patient had glioblastoma located in the right temporal lobe with extracranial metastases to the skull, scalp, ribs, spine, liver and lungs. The survival time from diagnosis to death was 13 mo, and the survival time from extracranial metastases to death was 6 mo.

The mechanisms of glioblastoma extracranial metastasis are still not well known. Many reports of extracranial glioblastoma metastases show a strong correlation between these lesions and preceding intracranial operation such as aggressive surgical resection, biopsy, and ventriculopleural shunting, in particular, the intraoperative opening of the ventricle. Extracranial metastases have been attributed commonly to tumor cells depositing into the bloodstream or to surgical defects in the dura and skull [3]. However, Anzil[4] found that > 10% of all cases occurred in the absence of prior surgical intervention. He believed that aggressive operations are not prerequisites for
Table 1: Review the literature on extracranial metastases of malignant gliomas in the past five years

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/sex</th>
<th>Location primary</th>
<th>Location metastasis</th>
<th>Diagnose</th>
<th>Interval</th>
<th>Survival</th>
<th>Adjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65/M</td>
<td>R occipital lobe</td>
<td>Bones (femur, ilium, sacrum)</td>
<td>GBM</td>
<td>13</td>
<td>11</td>
<td>Concurrent radiochemotherapy</td>
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<tr>
<td>2</td>
<td>20/W</td>
<td>L temporal lobe</td>
<td>Lung, lymph gland</td>
<td>GBM</td>
<td>NS</td>
<td>NS</td>
<td>Chemotherapy (temozolomide)</td>
</tr>
<tr>
<td>3</td>
<td>75/W</td>
<td>L temporal lobe</td>
<td>Lung, pleura</td>
<td>Diffuse astrocytoma</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>4</td>
<td>48/W</td>
<td>L temporal lobe</td>
<td>Bone, lung, pleura, liver, mesentery</td>
<td>GBM</td>
<td>13</td>
<td>11</td>
<td>Concurrent radiochemotherapy</td>
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<tr>
<td>5</td>
<td>43/W</td>
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<td>Lung, pleura</td>
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<td>38</td>
<td>2</td>
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<tr>
<td>6</td>
<td>49/M</td>
<td>R temporal lobe</td>
<td>Lung, cerebrospinal fluid</td>
<td>GBM</td>
<td>12</td>
<td>10</td>
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<tr>
<td>7</td>
<td>56/W</td>
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<td>Parotid, lymph node, lung</td>
<td>GBM</td>
<td>14.5</td>
<td>11</td>
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<tr>
<td>8</td>
<td>32/M</td>
<td>L basal ganglia region</td>
<td>Lymph nodes, bones (ribs, scapula, spine)</td>
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<td>3</td>
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</tr>
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<td>10</td>
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<td>R temporal lobe</td>
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<td>Lung, multiple bone metastases</td>
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<td>13</td>
<td>47/M</td>
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<td>Scalp, lymph gland ribs, spine, liver, lungs</td>
<td>GBM</td>
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<td>Concurrent radiochemotherapy</td>
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Interval: Time from diagnosis of primary to diagnosis of metastasis in months; Survival: Survival after diagnosis of metastasis in months. R: Right; L: Left; M: Male; F: Female; NS: Not stated or not known; GBM: Glioblastoma multiforme.

Extracranial metastasis of glioblastoma, also suggesting that early hematogenous spread may be a mechanism. While intracranial operations are not necessary in the development of extracranial glioblastoma metastases, such operations provide opportunities for vascular invasion and cerebrospinal fluid dissemination of tumor cells, thereby increasing the risk of systemic spread and extracranial tumor metastasis [5,6]. The most common mechanism of glioblastoma metastasis outside the CNS/neuraxis is likely vascular invasion, which indicates the existence of circulating tumor cells in the bloodstream. Therefore, the tumor-free principle becomes especially important during surgery and ensures dura mater integrity. In addition, the fraction of tumor cells in the circulation may provide an opportunity for early detection and genetic analysis of the intracranial glioblastoma [7]. In our patient, the ventricle was opened and the dura was destroyed during the operation. The opening of the ventricular system led to tumor invasion into the ventricular system, coupled with the destruction of the dura and invasion of the epidural blood vessels, leading to the systemic metastasis of multiple organs. However, beyond these factors, is there a deeper genetic connection to extracranial metastasis?

Our case suggests that MGMT is not methylated, and whether extracranial diffusion is affected by MGMT methylation status remains unknown. A significant study by HEGI et al[8] suggested that MGMT promoter methylation is an independent prognostic factor, and adjuvant TMZ can be beneficial in glioblastoma patients treated with methylated MGMT promoter. It has been reported that MGMT status is potentially in contact with extracranial metastasis, and distant metastasis of oligoendrocytes and melanoma in tumors has been reported [9,10]. MGMT promoter methylation is closely associated with distant metastasis, and there is considerable heterogeneity. However, whether MGMT promoter methylation status is associated with poor prognosis in GBM has not been found. MGMT promoter status with glioblastoma extracranial metastasis merits further research.
Currently, the standard initial approach for most primary glioblastomas is maximum safe surgical resection followed by postoperative concurrent radiotherapy and chemotherapy[11]. The same is true of our patient treatment regimens. In the case of extracranial metastases, there is no standard treatment; surgery, radiation and systemic chemotherapy or bevacizumab are all potential options, depending on the patient’s condition[11]. Studies have suggested a possible beneficial pairing between immunotherapy and TMZ therapy, and radiation-driven evolution may have therapeutic implications for recurrent GBM[12,13]. Moreover, Draaisma et al.[14] found that MGMT promoter methylation had a prognostic effect in tumor recurrence, and the high-mutated phenotype only occurred in 6%-8% of TMZ-treated IDH WT GBMs. Therefore, for patients with extracranial multiple organ metastasis of glioblastoma, simultaneous radiotherapy and chemotherapy combined with immunotherapy is worth a try, and the study of targeted genes is a direction worthy of profound exploration.
CONCLUSION

Malignant glioblastoma with extracranial multiorgan metastasis is rare, and survival is short. Surgeons should always be alert to its occurrence. At present, surgical treatment and concurrent chemoradiotherapy are still the primary options for glioblastoma, so attention should be paid to achieving tumor-free status during surgery to reduce the possibility of extracranial metastasis. The mechanism of extracranial metastasis of glioblastoma is still not clear, thus genetic and molecular pathology is still worthy of further exploration.

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Transverse myelitis after infection with varicella zoster virus in patient with normal immunity: A case report

Daehun Yun, Soo Young Cho, Wan Ju, Eun Hyoung Seo

Abstract

BACKGROUND
Varicella zoster virus (VZV) is a human neurotropic and double-stranded DNA alpha-herpes virus. Primary infection with VZV usually occurs during childhood, manifesting as chickenpox. Reactivation of latent VZV can lead to various neurological complications, including transverse myelitis (TM); although cases of the latter are very rare, particularly in newly active VZV infection.

CASE SUMMARY
We report here an unusual case of TM in a middle-aged adult immunocompetent patient that developed concomitant to an active VZV infection. The 46-year-old male presented with painful vesicular eruption on his left chest that had steadily progressed to involvement of his back over a 3-d period. Cerebrospinal fluid testing was denied, but findings from magnetic resonance imaging and collective symptomology indicated TM. He was administered antiviral drugs and corticosteroids immediately but his symptom improvement waxed and waned, necessitating multiple hospital admissions. After about a month of repeated treatments, he was deemed sufficiently improved for hospital discharge to home.

CONCLUSION
VZV myelitis should be suspected when a patient visits the outpatient pain clinic with herpes zoster showing neurological symptoms.

Key Words: Herpes zoster; Postherpetic neuralgia; Transverse myelitis; Varicella zoster virus; Motor weakness; Vesicular; Pain; Case report

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Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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**Core Tip:** The occurrence of transverse myelitis (TM) secondary to varicella zoster virus (VZV) in immunocompetent patients is very rare. VZV-TM should be suspected when a patient visits an outpatient pain clinic with herpes zoster and presents neurological symptom(s). VZV-TM must be diagnosed early, by magnetic resonance imaging and/or cerebrospinal fluid analysis, since delayed intervention may allow for serious complications to develop. Also, early administration of a combination of antiviral drugs and corticosteroids may help resolve the condition and relieve the associated pain experienced by patients with TM secondary to VZV.

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**INTRODUCTION**

Among the outpatient population of the pain clinic, a significant number of patient visits are prompted by pain caused by herpes zoster (HZ). Rarely, that pain is accompanied by neurological symptoms; however, in such cases, concomitant transverse myelitis (TM) should be suspected. We describe herein an unusual case of TM shortly following infection by the varicella zoster virus (VZV) and in conjunction with the usual symptomology in immunocompetent patient.

VZV infection is very common and causes chickenpox and HZ\[1\]. The VZV infection itself is often complicated by postherpetic neuralgia (the most common neurologic complication), VZV vasculopathy, cerebellitis, meningoradiculitis, meningoencephalitis, myelitis, and ocular disease\[2\]. However, very few cases of VZV-TM have been reported, particularly in an immunocompetent patient. In order to accurately determine VZV as the cause of TM, cerebrospinal fluid (CSF) analysis is required, despite it being technically difficult to isolate VZV from CSF in VZV patients who have developed myelitis\[3\]. Additional evaluation of the neurological symptoms by magnetic resonance imaging (MRI) is important for accurate diagnosis, which allows for the timely initiation of treatment and improves prognosis.

**CASE PRESENTATION**

**Chief complaints**

A 46-year-old male presented to our hospital with complaint of painful vesicular eruption that had begun 3 d prior on his left chest and steadily progressed to involvement of his back.

**History of present illness**

The patient characterized the pain as ‘stinging’ and reported that it had begun after he participated in strenuous outdoor activities. He noted that the pain was accompanied by the vesicle eruption. He denied any history of trauma.

**History of past illness**

The patient denied VZV infection (i.e. chickenpox or any form of HZ) in his medical history.

**Personal and family history**

The patient’s other personal and family medical history was unremarkable for this case.

**Physical examination**

Vesicular eruption was present on the left chest to the axillary side, being limited within the T5-T8 dermatome (Figure 1). Using the visual analogue scale (VAS), the
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Figure 1 Multiple vesicles on the axillary side of the left chest.

patient classified the stinging pain intensity of the vesicle eruption as 7.

**Laboratory examinations**

Blood tests for serum VZV immunoglobulin (Ig) M and VZV IgG were positive.

**Imaging examinations**

Chest computed tomography (CT) findings were nonspecific.

**First diagnosis and treatment**

The patient was diagnosed with HZ and ordered treatment with an antiviral drug (Clovir tablet, famciclovir at 250 mg bid; Dong Wha Pharm, Seoul, Korea), steroid (dexamethasone at 5 mg bid; Daewon Pharm, Busan, Korea), and nonsteroidal anti-inflammatory drugs (Naxozole tablet, esomeprazole strontium 24.6 mg/naproxen 500 mg bid (Hanmi Pharm, Seoul, Korea); Valentac, diclofenac sodium at 75 mg/mL intramuscular injection (WhanIn Pharm, Seoul, Korea). After 1 wk, the patient showed improvement (Figure 2), with pain score reducing to VAS 2, and was discharged to home.

However, 10 d after discharge, the patient returned to the hospital with complaint of pain recurrence (VAS 7-8) and was referred to our pain clinic. The same dermatome region showed re-eruption of the vesicles. Upon readmission, we administered ultrasound-guided erector spina plane block (commonly referred to as ESPB) and prescribed Lyrica Capsules (pregabalin at 75 mg bid; Pfizer, New York, NY, United States) and Targin prolonged-release (oxycodone at 5 mg/naloxone at 2.5 mg bid; Mundipharma, Seoul, Korea) for pain control. After the ESPB, the patient reported his pain reduced to VAS 2 and he was again discharged. At 2 d later, however, his pain worsened (VAS 6–7), and he returned to hospital and was again readmitted for pain control. This time, we inserted a patient-controlled epidural analgesia (PCEA) port. First, with the patient in prone position, an 18-G Tuohy needle was advanced using the paramedian approach at the thoracic spine level 9–10 under C-arm guidance. The epidural space was identified using loss-of-resistance technique and the contrast medium was injected. After confirming loss-of-resistance using C-arm, a flexible epidural catheter was passed cranially for about 2–3 cm and secured with the skin. Initially, the port was used to administer 300 mL of 0.1% ropivacaine at a continuous infusion rate of 4 mL/h via a disposable silicone balloon infuser (AutoFuser; ACE Medical, Beverly Hills, CA, United States). During the maintenance of PCEA, the patient reported his pain to be reduced to VAS 3. However, that night, the patient began to experience difficulty urinating as well as mild motor weakness (motor grade 4) and paresthesia in the bilateral distal lower extremities. The epidural catheter was
Figure 2  After 1 wk of hospitalization with antiviral and corticosteroid treatment, the vesicular eruption showed improvement.

removed immediately.

**Further diagnostic work-up**

A catheter tip culture was ordered but revealed no microorganism. To rule-out central nervous system infection, a T-spine MRI was performed. The T2-weighted images showed high signal intensity within the left spinal cord level T2-8 (Figure 3). The neurologic examination revealed mild paresthesia and normal motor strength at the bilateral distal lower-half extremities and hyperactive deep tendon reflex on the left side. The need for a CSF study was explained, but the patient’s guardian refused consent.

**FINAL DIAGNOSIS**

Based on the patient’s overall clinical presentation profile and imaging findings, he was diagnosed with VZV and myelitis.

**TREATMENT**

A 1-wk course of Clovir (acyclovir 250 mg tid; Myung-In Pharm), Maxipime (cefeprime at 1 g bid; Boryung, Seoul, Korea) and Solondo tablet (prednisolone at 5 mg tid; Yuhan, Seoul, Korea) was initiated; in addition, the patient was administered Targin prolonged-release (oxycodone at 5 mg/naloxone at 2.5 mg bid; Mundipharma) and Lyrica Capsules (pregabalin at 75 mg bid; Pfizer) for pain control. The patient reported his pain to remain at about VAS 3 with these medications. The acyclovir as discontinued after the 1-wk course. A follow-up MRI was performed 3 wk later, and did not show any significant changes (Figure 4). At this time, the patient reported his pain to be well controlled (VAS 2) and findings from neurological examination were normal, allowing for discharge to home.

**OUTCOME AND FOLLOW-UP**

At the outpatient follow-up visit, conducted 1 mo after discharge, the patient had no neurologic symptoms but residual pain (VAS 2) that involved the area from the chest to the axillary side of the T5-T8 dermatome.
DISCUSSION

VZV is a human neurotropic and double-stranded DNA alpha-herpesvirus—the primary infection of which usually occurs during childhood and manifests as chickenpox[1]. After the primary infection, VZV becomes latent in the cranial root ganglia or dorsal root ganglia and can remain so for several decades; however, in elderly or immunocompromised individuals, it can become reactivated and recur as HZ[3,4].

HZ itself is associated with a variety of complications, such as HZ vasculitis and ophthalmic, neurologic or visceral disease. The most common neurological complication is postherpetic neuralgia, a chronic neuropathic pain that persists after resolution of the HZ skin rash. Other complications include cranial nerve or peripheral nerve palsy, myelitis, meningoencephalitis, and stroke[2].
Only 0.3% of patients reported with HZ manifestation experience TM[5]. In general, about 25%-50% of TM cases are caused by viral infections, including herpes virus or poliovirus. Though HZ infection is common, even in immunocompetent patients, it rarely progresses to TM. In Korea, in particular, only a few cases of TM secondary to VZV have been reported. Thus, TM secondary to VZV is an abnormal inflammatory finding; yet, the literature indicates that it can involve all parts of the spinal cord and that the pathogenesis may be related directly to the viral invasion and consequent axonal degeneration[6].

Symptoms of TM usually develop over a period of hours to days and sometimes progress gradually over weeks. Mostly, it involves both sides of the body below the affected area of the spinal cord, but there are cases wherein it appears to affect only one side. Common signs and symptoms include pain (back, abdomen, chest), abnormal sensation, weakness in arms or legs, and bladder and bowel problems[7]. TM is diagnosed based on the patient’s signs and symptoms, medical history, and clinical assessment of nerve function. If several diagnostic workups, including MRI, CSF analysis and complete blood count, provide evidence of inflammation, TM can be diagnosed after ruling out of other causes. MRI is one of the most effective diagnostic tools for TM secondary to VZV. In MRI, VZV myelitis is shown as hyperintensity in the spinal cord on T2-weighted images[8]. CSF analysis can then be done as a confirmatory test. Unfortunately, however, the procedure of CSF analysis is actually quite complicated; the VZV must first be separated from the CSF sample (invasively acquired) and must then demonstrate presence of VZV antigen via immunofluorescence assay. Indeed, in some cases reported in the literature, the VZV antibody was not found in the CSF sample and patient was diagnosed by MRI findings alone[3,9]. Likewise, no CSF study was conducted for our patient and the diagnosis was made according to the collective profile of clinical symptoms and MRI findings.

In TM, early therapeutic intervention is essential to minimize complications and pain extent and duration suffered by the patient. The intervention must be tailored to the patient’s symptoms, since there is yet no standardized treatment regimen for TM secondary to VZV. Currently, the accepted treatment regimen should include an antibiotic, antiviral, high-dose corticosteroid, and intravenous Ig[3,6]. However, the efficacy of no specific treatment regimen has not been systematically demonstrated[10]. Of note, however, a study found that the combination of acyclovir and corticosteroids effectively reduced acute neuritis in VZV myelitis patients, and the most important prognostic factor was determined to be early medical intervention[5].

Another study showed that after administration of antivirals and steroids, the interval prior to symptom improvement ranged from 3 d to 9 d, with complete recovery seen in 10 d, but some patients were left with permanent neurological deficits, such as weakness or numbness, or had even progressed to encephalitis[11]. In our case, the early application of a combination treatment involving antivirals and corticosteroids significantly relieved the patient’s symptoms.

CONCLUSION

The occurrence of TM secondary to VZV in immunocompetent patients is very rare. VZV myelitis should be suspected when a patient visits the outpatient pain clinic with HZ showing neurological symptoms. VZV myelitis must be diagnosed early, using MRI and CSF study, since delayed intervention may allow for serious complications to develop. Also, early application of a combination treatment approach using antivirals and corticosteroids may benefit patients with TM secondary to VZV.

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Duodenal ulcer caused by coil wiggle after digital subtraction angiography-guided embolization: A case report

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Abstract

BACKGROUND
Acute gastrointestinal bleeding (GIB) is a life-threatening medical emergency with high morbidity and mortality. Transcatheter embolization with endovascular coils under digital subtraction angiography guidance is a common and effective method for the treatment of GIB with high technical success rates. Duodenal ulcers caused by coils wiggled from the branch of the gastroduodenal artery, which is a rare complication, have not previously been reported in a patient with right intrathoracic stomach.

CASE SUMMARY
A 62-year-old man had undergone thoracoscopy-assisted radical resection of esophageal cancer and esophagogastric anastomosis 3 years ago, resulting in right intrathoracic stomach. He was admitted to the hospital 15 mo ago for dizziness and suffered acute GIB during his stay. Interventional surgery was urgently performed to embolize the branch of the gastroduodenal artery with endovascular coils. After 15 mo, the patient was re-admitted with a chief complaint of melena for 2 d, esophagogastrroduodenoscopy and abdominal computed tomography revealed that some endovascular coils had migrated into the duodenal bulb, leading to a deep ulcer. Bleeding was controlled after conservative treatment. Seven months later, duodenal balloon dilatation was performed to relieve the stenosis after the removal of a few coils, and the patient was safely discharged with only one coil retained in the duodenum due to difficulties in complete removal and risk of bleeding. Mild melena recurred once during the long-term follow-up.

CONCLUSION
Although rare, coil wiggle after interventional therapy requires careful attention, effective precautionary measures, and more secure alternative treatment methods.
Acute gastrointestinal bleeding (GIB) is a life-threatening medical emergency associated with a mortality rate of 8%-14%[1]. Transcatheter embolization under digital subtraction angiography (DSA) guidance has been widely considered a first-line intervention for severe GIB after failed endoscopic treatment[2]. It is a safer alternative treatment with the advantages of rapid positioning and efficiency in high-risk patients who are intolerant to surgery[3]. Endovascular coils are commonly used in DSA-guided embolization for the occlusion of targeted vessels to prevent and treat GIB due to the diversity of their size, ease of use, and better fluoroscopic visibility[4].

According to reports, the overall technical success rates of interventional transcatheter embolization in patients with active bleeding reaches 100%[5,6], whereas the clinical success rate ranges from 52% to 98%[2]. This is a widely used and mature technique in clinical practice, and the incidence and severity of complications are generally well managed. The most common complications include groin hematomas and contrast-related adverse reactions, with rates of 3%-17% and 0.04%-12.7%, respectively[7].

Coil wiggle after DSA-guided embolization has rarely been reported. Herein, we report a rare case of duodenal ulcer due to coil wiggle after digital subtraction angiography-guided embolization in a patient with acute GIB who had an intrathoracic stomach due to radical resection of esophageal cancer. This case highlights that coil displacement should be considered in patients with recurrent bleeding or new gastrointestinal ulcers after interventional treatment.

CASE PRESENTATION

Chief complaints
A 62-year-old man was admitted to the Department of Gastroenterology with melena for 2 d. Gastroscopic examination during hospitalization revealed a deep concave ulcer in the duodenal bulb with a coil-like object covered with yellow moss.

History of present illness
The patient passed a small amount of dark and tarry stools without obvious induction 2 d before presentation, without abdominal pain or hematemesis.

History of past illness
The patient underwent thoracoscopy-assisted radical resection of esophageal cancer and gastroesophageal anastomosis 3 years ago, in which the stomach and part of the duodenum were lifted to the right thorax. Approximately 15 mo before the current hospitalization for GIB, he was admitted to the oncology radiochemotherapy...
department due to dizziness. On admission, the patient had a hemoglobin level of only 37 g/L and a positive fecal occult blood test finding, which suggested the possibility of GIB. The patient underwent esophagogastroduodenoscopy, which showed that the duodenal bulb was covered with a layer of dirty yellow moss, but no signs of bleeding were found (Figure 1). With the transfusion of blood products, the patient's hemoglobin gradually recovered to 96 g/L, and his condition seemed to improve significantly. However, the patient experienced an episode of acute hematochezia and hematemesis on post-treatment day 9. After losing 2200 mL blood in just 30 min, his blood pressure dropped to 8.0/5.3 kPa and he entered a state of shock. Consultation with the gastroenterology and DSA departments indicated the possibility of acute hemorrhage in the small intestine, reaching a consensus that interventional treatment would be more likely to be beneficial. After receiving anti-shock treatment in the ward, the patient was rushed to the DSA room. Angiography showed extravasation of the contrast agent into the branch of the gastroduodenal artery (GDA) (Figure 2A). After selective probing of the bleeding artery, four embolization microcoils sized 3 mm × 3.3 mm, two embolization microcoils sized 4 mm × 3.7 mm, and two embolization microcoils sized 6 mm × 6.7 mm were selected to embolize the bleeding vessel. Complete occlusion was validated using DSA (Figure 2B). Gastroscopic examination on the following day revealed diffuse congestion and swelling of the mucosa in the gastric corpus, accompanied by diffuse erosion. Venous congestion formed a clear boundary with bloody fluid attached to the surface (Figure 3A). No active bleeding was observed after rinsing with ice-cold water. Unfortunately, due to the presence of bloody fluid and yellow mucus, pictures of the duodenal bulb were not obtained. No postoperative GIB occurred, and the patient was discharged 19 d later.

**Personal and family history**

The patient had a free personal and family history.

**Physical examination**

At admission, the patient's temperature was 36.5 °C, pulse was 78 beats/min, respiratory rate was 20 beats/min, and blood pressure was 15.7/9.4 kPa. The abdomen was flat and soft, and there was no tenderness or rebound pain in the entire abdomen. The spleen and liver were not palpable, and no blood vessel noise was observed. The borborygmus was slightly active.

**Laboratory examinations**

Hospitalization for dizziness: On admission, routine blood tests showed severe hemoglobin reduction of only 39 g/L, red blood cell (RBC) count of 1.43 × 10^{12}/L, and white blood cell (WBC) and platelet counts within the normal range. C-reactive protein level was not elevated. Blood biochemical results indicated normal transaminase, creatinine, and alkaline phosphatase levels. No abnormal coagulation indices were observed. After transfusion and fluid replacement, the hemoglobin level increased to 96 g/L and RBC count increased to 3.10 × 10^{12}/L. Seven days after severe GIB, hemoglobin level again decreased to 66 g/L, C-reactive protein level peaked at 58.3 g/L, and WBC count increased to 27.6 × 10^9/L. Fortunately, with active treatment, the patient's anemia improved significantly, inflammatory marker levels returned to normal, and the patient was discharged under acceptable conditions.

Hospitalization for melena: Blood analysis revealed that neutrophil granulocytes increased to 81.8% with hemoglobin level, blood platelet count, and RBC count in the normal range. Prothrombin level, d-dimer level, and partial thromboplastin time were normal. Further, serum C-reactive protein level increased at 17.74 mg/L (normal range, < 8 mg/L).

**Imaging examinations**

Chest computed tomography (CT) showed the right intrathoracic stomach and a small amount of effusion in both pleural cavities. After he was transferred to the operating room due to GIB, DSA was performed on the celiac artery, superior mesenteric artery, and inferior mesenteric artery. Since the stomach and part of the duodenum were in the thoracic cavity, the vessels supplying to the stomach and duodenum flowed in the direction of the diaphragm on the angiographic image, and extravasation of contrast agent was found in the branch of the GDA during the operation (Figure 2A). After selective probing of the bleeding artery, four embolization microcoils sized 3 mm × 3.3 mm, two embolization microcoils sized 4 mm × 3.7 mm, and two embolization microcoils sized 6 mm × 6.7 mm were selected to embolize the bleeding vessel.
Figure 1  Esophagogastroduodenoscopy performed seven days before the acute gastrointestinal bleeding.

Figure 2  Digital subtraction angiography images before and after arterial embolization. A: Digital subtraction angiography image showed extravasation of contrast agent at the branch of gastroduodenal artery (orange arrow); B: Digital subtraction angiography showed successful embolization of gastroduodenal artery branch.

Complete occlusion was validated using angiography (Figure 2B).

The patient was hospitalized for GIB again 15 mo later, and esophagogastroduodenoscopy revealed a deep concave ulcer in the deformed and stenotic duodenal bulb with a coil-like object covered with yellow moss (Figure 3B). It was hypothesized that the ulcer was caused by the wiggle of coils. This was confirmed by abdominal CT that revealed two radiating metallic dense shadows, one of which was located in the duodenal bulb. However, the exact number of displaced coils could not be estimated (Figure 4).

**FINAL DIAGNOSIS**

Hospitalization for dizziness: DSA imaging showed extravasation of contrast agent in the branch of the GDA, but esophagogastroduodenoscopy performed before the hemorrhage failed to identify bleeding source. The cause of the first episode of acute GIB was considered and discussed by doctors. However, based on the available
Figure 3 Esophagogastroduodenoscopy of the first hospitalization after interventional treatment and second hospitalization due to melena. A: Esophagogastroduodenoscopy revealed diffuse congestion and erosion in the gastric corpus with bloody fluid; B: Esophagogastroduodenoscopy showed a duodenal ulcer caused by coil wiggle.

Figure 4 Abdominal computed tomography revealed the displaced coils.

evidence, doctors could not draw firm conclusions. The following hypotheses were proposed: First, there was a bleeding spot covered by yellow moss that was temporarily inactive and could not be detected by examiners. Second, the presence of a bleeding spot in the distal duodenum or small intestine, which cannot be reached by esophagogastroduodenoscopy, was another hypothesis.

Hospitalization for melena: According to the patient's history of DSA-guided embolization, with the results of this esophagogastroduodenoscopy examination and CT report, the abnormally dark, tarry stool was due to the ulcer caused by the coil displacement into the duodenal bulb.

**TREATMENT**

Considering the significant bleeding risk associated with coil removal during endoscopy, we conducted a multidisciplinary discussion. The DSA surgeon indicated that they were unable to provide further treatment and recommended consultation
with the gastrointestinal surgery department, which believed that the coil could be removed by surgery. However, after careful consideration, the patient's family refused surgical treatment and chose conservative treatment. After treatment with fasting, fluid rehydration, proton pump inhibitor treatment, and gastric mucosal protectant, the patient was discharged after 9 d in the hospital.

OUTCOME AND FOLLOW-UP

The patient visited our hospital for esophagogastroduodenoscopy reexamination 7 mo later and was in good condition without GIB symptoms. After evaluation by the DSA department, the risk of bleeding was considered to be small, and endoscopic treatment was attempted. Two of the coils were removed without incident by an experienced endoscopic physician, leaving only one visible coil in the duodenal bulb due to difficulties in complete removal and risk of bleeding. Coils that could not be observed by endoscopy were not removed.

Subsequently, balloon dilation was performed to relieve duodenal bulb stenosis. The patient recovered well after coil removal and was discharged safely. At the follow-up visit, mild melena recurred, but was well controlled by medication. The patient expressed gratitude and satisfaction with treatment.

DISCUSSION

GIB is a common clinical emergency that may be fatal in severe cases with high morbidity and mortality. GIB management includes drug therapy, endoscopy, intervention, and surgery. The efficacy of drug therapy is definite. Patients can achieve cost-effective outcomes after regular medication, especially those with a likelihood of high-risk lesions, reducing the need for endoscopic therapy[6,9]. Endoscopy is the best initial method for the diagnosis and treatment of upper GIB. GIB can be diagnosed through endoscopy in 95% of cases, with a therapeutic effect achieved in 90% of cases [10]. For management of severe or refractory GIB, intervention or surgery may be required instead of repeat therapeutic endoscopy[11]. In a hemodynamically unstable state with the possibility of lower GIB, transcatheter arteriography or intervention treatment could be a safer choice.

DSA and arterial embolization techniques can provide less invasive options for patients with mass GIB, for which the primary success rate is quite high. Further, 10%-20% of patients with recurrent bleeding require repeated embolization[12]. Common complications of arterial embolization include recurrent bleeding and gastrointestinal ischemia[13]. Coil wiggle after DSA-guided embolization has rarely been reported as a complication. In a report by Kao et al[14], a 65-year-old woman developed a pseudoaneurysm after cholecystectomy with T-tube cholecystostomy, which resulted in biliary hemorrhage. The patient eventually underwent embolization. Eight years later, abdominal CT revealed a coil-like density in the hilar area with dilation of the intrahepatic bile ducts. The patient underwent percutaneous transhepatic biliary drainage due to obstructive jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) revealed five microcoils around the hepatic hilum. Endoscopic papillary balloon dilation was performed, several mixed stones were removed by the basket, and a microcoil was found in one of the stone fragments[14]. Our case reported the first case of coil displacement in a patient with right intrathoracic stomach and GIB, but similar events have been reported in patients with normal anatomical structures. In a report by Skipworth et al[15], a 55-year-old man was discharged from the hospital after receiving coil embolization for a gastroduodenal aneurysm. During outpatient follow-up, the doctor found tenderness in the patient's upper abdomen. Gastrograffin indicated a pyloric outlet and duodenal obstruction. ERCP indicated coils in the pyloric area, accompanied by ulcer formation. Unable to remove the coils endoscopically, the doctors performed sphincterotomy. The patient was safely discharged after symptom remission[15]. The patient in our case report experienced an acute attack of GIB and hemorrhagic shock, but esophagogastroduodenoscopy performed 7 d earlier failed to identify any bleeding site. Consultation of the gastroenterology and DSA department suggested the possibility of small intestinal bleeding. Hematemesis, hematochezia, and even hemorrhagic shock may also occur in severe cases with massive bleeding in the small intestine. According to the ACR Appropriateness Criteria[16], transcatheter arteriography or intervention treatment is likely more appropriate and beneficial for a hemodynamically unstable patient with small
intestinal bleeding. In this condition, intervention is considered the safest. Hemostatic measures could be initiated immediately after the bleeding site was identified using DSA, regardless of the presence of upper or lower GIB. Esophagogastroduodenoscopy was riskier because of the time lost during the procedure if the bleeding site failed to be identified in the upper digestive tract. Therefore, the patient underwent interventional treatment and had several coils embolized into the branch of the GDA. Fifteen months later, esophagogastroduodenoscopy revealed that several endovascular coils have incarcerated in the duodenum and caused ulceration. Doctors did not rule out the possibility that the coil gradually wiggled from the initial location to the position near the duodenal bulb and caused the rupture of the blood vessels. Owing to the thin wall of the duodenal bulb, the coil gradually penetrated and settled down. The phenomenon of coil displacement in this patient may be due to the fact that the esophagus surgery changed the anatomical position of the digestive tract and the normal vascular distribution structure, and the curved blood vessels were straightened, thus facilitating movement of the coil. Since the bleeding stopped after the drug treatment, there was no special treatment for the coil. Seven months later, the patient underwent endoscopic therapy after assessing the risk of bleeding, and two migrated coils in the duodenum were removed.

This case report has several limitations. First, images of the duodenal bulb on the day after interventional treatment were not obtained because of obscurity caused by the bloody fluid and yellow moss, which resulted in our inability to estimate if there was ulcer formation or ischemic change after interventional therapy. Second, the coils removed with the endoscope were not recorded or retained, so we were unable to confirm which embolized coils were penetrating the duodenum. Obviously, information regarding the migrated coils could be useful in developing effective measures.

Patients may develop imprudent arterial embolization in the long term. Therefore, its indications and surgical modalities should be clearly defined and scrutinized, and new interventions and materials such as vascular filters should be considered and expedited to cope with potential coil wiggle. The possibility of coil displacement may be greater in patients with changes in the anatomic position of blood vessels. Surgeons should carefully select the embolization site and coil size. The placement of coils of the proper size in the winding vessels could possibly reduce the risk. For recurrent bleeding or ulcers after DSA surgery, doctors should be cautious about the possibility of coil displacement.

CONCLUSION

Although coil wiggle after interventional therapy is rare, it still requires attention. For recurrent bleeding or ulcers after DSA surgery, caution should be given to the possibility of embolic displacement. The research and development of new interventional methods and materials should be accelerated to reduce the probability of such events and improve patient prognosis.

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Crab lice infestation in unilateral eyelashes and adjacent eyelids: A case report

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Abstract

BACKGROUND
Crab lice (Phthirus pubis) infestation can occur at any age, to either males or females, and across all regions of the world. However, cases involving the eyelashes and adjacent eyelids (phthiriasis palpebrarum) are rare. Usually occurring as a sexually transmitted disease, crab lice can be spread by poor hygiene or in a dirty environment through direct contact with contaminated skin (hands) or textiles (towels and clothing).

CASE SUMMARY
A 50-year-old woman presented to our hospital with a 2-wk history of chronic eyelid pain and itching in the right eye, which exacerbated in the evening hours and which had not resolved following a 1-wk course of antibiotics and corticosteroid ointments (for blepharitis diagnosis from another hospital). A careful ophthalmic slit-lamp and light microscope examination revealed multiple crab lice and nits on the right upper eyelashes; the right and left lower eyelashes were normal. Following the new diagnosis of phthiriasis palpebrarum, the patient was treated by removing the affected eyelashes, the crab lice, and their nits completely. Additionally, the eyelids were washed once with povidone-iodine. A follow-up examination at 2 wk later showed complete resolution of symptoms and no evidence of re-infection.

CONCLUSION
This case emphasizes the importance of correct diagnosis and complete removal of eyelashes, crab lice and nits to cure phthiriasis palpebrarum.
Key Words: Crab lice; Infestation; Unilateral eyelashes; Phthiriasis palpebrarum; Treatment; Case report

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Core Tip: Crab lice (Phthirus pubis) infestation of the eyelids and lashes (phthiriasis palpebrarum), despite manifesting eyelid pain and itching, is easy to miss, even for ophthalmologists, as the lice and nits are translucent. For the case presented here, a light microscope revealed the features of crab lice and nits in unilateral eyelashes and adjacent eyelids. Complete removal of the affected eyelashes, by trimming or plucking, followed by a single povidone-iodine rinse appears to be a simple, safe and effective method of treatment.

INTRODUCTION

Crab lice (Phthirus pubis) is a hematophagous parasite of humans[1]. Although the infection usually occurs as a sexually transmitted disease, it also can be spread by direct contact with contaminated skin (e.g., hands) or textiles (e.g., towels and clothing) [2]. Crab lice infestation involving the unilateral eyelashes and adjacent eyelids is rare among the overall spectrum of ocular surface diseases[3]. Many studies of such in the literature refer to the crab lice infection of the eyelid as phthiriasis palpebrarum[4-8]. The condition can occur in any decade of life, with case reports describing afflicted individuals ranging in age from 21 d (infant) to 75 years (elderly)[9,10]. Moreover, cases have originated from developing as well as developed countries. Here, we report a case of phthiriasis palpebrarum caused by poor hygiene or dirty environment.

CASE PRESENTATION

Chief complaints

A 50-year-old woman presented at our hospital’s ophthalmology department in October 2019, with a 2-wk history of intermittent right upper eyelid pain and itching (Figure 1), which exacerbated in the evening hours.

History of present illness

The patient reported having previously presented to another hospital with the same complaint of symptoms. There, she had been diagnosed with blepharitis and prescribed a 1-wk course of antibiotics and corticosteroid ointments. When the symptoms did not resolve with treatment, she sought assessment at our hospital.

History of past illness

No relevant information.

Personal and family history

Personal and family history-taking revealed no relevant information.

Physical examination

The patient’s best-corrected visual acuity was 20/20, in both eyes. A careful ophthalmic slit-lamp examination was conducted, and showed several parasites adherent to the right upper eyelashes of the right eye. A slight touch of the eyelashes stimulated the parasites to initiate a creeping movement in response (Video). In addition to the parasites, there were empty shells present on the eyelashes (Figure 2).
Figure 1 Slit-lamp examination of the patient’s right eyelashes and adjacent eyelids. Some macula and empty shells are seen on the eyelashes.

Figure 2 Photos of parasites and empty shells on the patient’s right eyelashes and adjacent eyelids. Empty shells are denoted by white arrow; Parasites are denoted by orange arrow.

**Imaging examinations**

A few of the parasites and empty shells were collected and examined under a light microscope (Figure 3). The gross visual characteristics of both were consistent with crab lice and nits (eggs of the crab lice)[5].

**FINAL DIAGNOSIS**

Unilateral (right eye) crab lice infection of the eyelids and eyelashes: Phthiriasis palpebrarum.

**TREATMENT**

The right upper eyelashes were trimmed to the skin surface or plucked out, to ensure complete removal of the crab lice (Figure 4A) and nits. The eyelids were subsequently washed once with povidone-iodine.
Figure 3 Photos of crab lice and nits taken from the patient's right eyelashes and adjacent eyelids, as viewed under a light microscope. Magnification 100 ×. A: Crab lice; B: Nits.

Figure 4 Some of crab lice taken from the patient and recovered eyelashes and eyelids. A: Twenty crab lice removed on cotton swabs and gauze and 6 were subjected to examination under a light microscope; B: Cleared eyelashes (regrowth) and adjacent eyelids at 2-wk after treatment.

OUTCOME AND FOLLOW-UP

A follow-up examination 2-wk later showed complete resolution of the patient's eye symptoms and no evidence of re-infection (Figure 4B).

DISCUSSION

Parasitic eye infection is a rare ocular disease, without geographic, age or sex propensity. In our clinical work, we have come across eye diseases caused by infections with demodicosis (usually inhabiting hair follicles and largely involving those on the head), cysticercosis (primarily infecting brain and muscle), and crab lice (typically as a sexually transmitted disease). The various parasitic infections feature distinctive infection and symptomological profiles. When crab lice invade eyelid skin, their nits can be observed adhering to the eyelashes. Patients afflicted with phthiriasis palpebrarum always present with eyelid pain and itching, which are unfortunately the most common symptoms of all types of eye diseases. In addition, the adult crab lice are translucent, being easy to miss by an ophthalmologist and supporting the misdiagnosis of blepharitis. The parasitic nature of crab lice includes their derivation of nutrients from human blood, via an ex vivo sucking mechanism. The symptoms of itching and pain arise from the biting of the crab lice to penetrate the skin and obtain the blood meal.

There are three transmission mechanisms for crab lice, including sexual, direct and indirect contact. Vulva infestation of crab lice is most commonly transmitted by sexual contact. Eyelid infestation is mainly transmitted by direct or indirect contact with a contaminated source. In our case, the patient had worked as a hotel cleaner for 4 years, and declared no history of sexually transmitted diseases. She could have contracted
the disease from contact with contaminated towels and clothing at her worksite. Good hygienic habits, including frequent bathing, hand washing and laundering of textiles (including personal clothing) are important ways to prevent this disease.

There are several topical drug-based treatments currently available for crab lice, namely ivermectin[11,12], pilocarpine drops[13], yellow mercuric oxide, and petrolatum ointment. However, manual removal of visible crab lice and nits remains the standard of care[14]. For our case, with visible crab lice and nits clinging to the skin and eyelashes, the right upper eyelashes were removed by trimming or plucking to ensure complete mechanical removal of the crab lice from the skin. This approach also helped to avoid immediate-future reattachment of residual crab lice and nits. Ultimately, the patient achieved complete resolution of her symptoms and showed no evidence of re-infection.

CONCLUSION

This case emphasizes the importance of correct diagnosis for crab lice infestation. The mechanical removal of crab lice and nits, in addition to complete trimming or plucking of the affected eyelashes, appears to be a simple, safe and effective method of treatment for crab lice infestation of the eyelids and eyelashes.

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Local random flaps for cervical circumferential defect or tracheoesophageal fistula reconstruction after failed gastric pull-up: Two case reports

Ye Zhang, Yang Liu, Yu Sun, Meng Xu, Xiao-Lei Wang

Abstract

BACKGROUND
Total pharyngo-laryngo-esophagectomy with a reconstruction of gastric pull-up is the most common treatment method for patients with multiple primary upper digestive tract carcinomas, such as hypopharyngeal carcinoma with thoracic esophageal carcinoma. However, neck circumferential defect and tracheoesophageal fistula after gastric necrosis are still challenging problems for surgeons and patients.

CASE SUMMARY
This case report presents 2 patients who underwent reconstructive surgeries using 4 local random flaps with a split thickness skin graft in the first case, and 6 local random flaps in the second case to close the circumferential defect and tracheoesophageal fistula after failed gastric pull-up. Both patients achieved good swallowing function and could take solid diet without dysphagia postoperatively.

CONCLUSION
For selected patients, local random flaps (with a split thickness skin graft) can be a simple and reliable solution for reconstructing tracheoesophageal fistula or cervical circumferential defect after gastric necrosis, especially when the necrosis extends below the thoracic inlet.

Key Words: Local random flap; Cervical circumferential defect reconstruction; Tracheoesophageal fistula reconstruction; Failed gastric pull-up; Total pharyngo-laryngo-esophagectomy; Case report
Core Tip: In this paper, we report 2 patients who suffered from cervical circumferential defect and tracheoesophageal fistula, reconstructed with local random flaps (with a split thickness skin graft in the first case), after failed gastric pull-up. Both patients achieved good swallowing function without dysphagia postoperatively. Local random flaps and split thickness skin graft have the advantages of easy to harvest with abundant and flexible donor sites. Herein, local random flaps (with a split thickness skin graft) can be a simple and reliable solution for reconstructing tracheoesophageal fistula or cervical circumferential defect after gastric necrosis.

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INTRODUCTION
Hypopharyngeal carcinoma is one of the most common head and neck squamous cell carcinomas. It is usually diagnosed at an advanced stage and results in substantial morbidities and mortalities. In addition, through routine esophagoscopy examination, hypopharyngeal carcinoma patients are often diagnosed with second primary esophageal squamous cell carcinoma, with the incidence rate ranging from 10% to 51.5%[1-3]. Total pharyngo-laryngo-esophagectomy is the most common treatment method for patients with multiple primary upper digestive tract carcinomas such as hypopharyngeal carcinoma with thoracic esophageal carcinoma. It is worth noting that gastric pull-up is usually used as a reconstruction method after pharyngo-laryngo-esophagectomy. However, postoperative complications associated with gastric pull-up, especially circumferential necrosis at the anastomotic site and tracheoesophageal fistula, poses a significant challenge for surgeons and patients and it may result in high mortality rates. Therefore, the reconstruction in neck and the upper mediastinum after circumferential necrosis of the gastric conduit or tracheoesophageal fistula is essential. It can help patients achieve better quality of life and prognosis. Previous studies have reported use of pedicled flaps such as the pectoralis major musculocutaneous flap, trapezius myocutaneous flap, and latissimus dorsi myocutaneous flap to reconstruct circumferential hypopharyngeal defects[4-6]. Moreover, improvement of microvascular techniques has led to widespread use of free flaps including the anterolateral thigh flap and the jejunal free flap[7,8]. Colonic interposition has also been used to deal with gastric pull-up failure[9]. In this paper, we present 2 cases of circumferential reconstruction and tracheoesophageal fistula, after failed gastric pull-up, using local random flaps (and split thickness skin graft).

CASE PRESENTATION
Chief complaints
Case 1: A 58-year-old man, presented the complaint of circumferential necrosis at the cervical part of the gastric conduit. It was 12 d after a total pharyngo-laryngo-esophagectomy with gastric pull-up for his hypopharyngeal squamous cell carcinoma with multiple primary esophageal cancer.

Case 2: A 70-year-old man, presented a pharyngeal fistula and tracheoesophageal fistula for 10 mo after a total pharyngo-laryngo-esophagectomy with gastric pull-up.

History of present illness
Case 1: The patient presented with the complaint of hoarseness for half a year and odynophagia for 3 mo. He did not complain about dysphagia and could eat solid foods without weight loss. Initial evaluation using laryngoscopy and esophagoscopy showed a lesion occupying the right pyriform sinus and extending to the inferior postcricoid, right ary-epiglottic fold, right pharyngo-epiglottic fold, both arytenoids,
the lingual surface of epiglottis, and the entrance of cervical esophagus. Several small focuses were found in the left pyriform sinus and the posterior hypopharyngeal wall. Moreover, flat lesions were found in thoracic esophagus, 36-38 cm from incisors. A biopsy confirmed all lesions to be squamous cell carcinoma. Thus, the patient underwent total pharyngo-laryngo-esophagectomy with gastric pull-up, and also bilateral neck dissection (level II-IV and VI). Furthermore, tracheostoma was made between the fourth and the fifth tracheal ring. Next, a nasogastric tube and a jejunal feeding tube were inserted for postoperative gastrointestinal decompression and enteral nutrition. On the 7th postoperative day, the patient started to drink water through his mouth but it was hard to swallow it down. He started taking a liquid diet on the 12th postoperative day. However, the cervix drainage fluid turned turbid and black. On the next day, a circumferential necrosis at the cervical part of the gastric conduit was found using video laryngoscopy. The patient presented with sepsis and toxemia symptoms.

Case 2: The patient underwent a total pharyngo-laryngo-esophagectomy with gastric pull-up and bilateral neck dissection (level II-IV and VI) 10 mo earlier in order to cure his hypopharyngeal carcinoma in another hospital. The immediate postoperative recovery was normal. On the 7th postoperative day, the drainage fluid of anastomotic stoma unexpectedly increased to 70 mL/24 h, and turned stink and black. Exploration and debridement were performed, however, no evidence of fistula or necrosis was found. So, the exploration did not enter the pharyngeal cavity. Iodoform gauze was used to pack the wound left by the exploration. Upper gastrointestinal roentgenography was performed on the 15th postoperative day. No obvious contrast medium extravasation was detected. Therefore, the patient started a liquid diet and the drainage tube was removed on the 21st postoperative day without drainage. Three days later, a fistula was found on the posterior wall of the tracheostoma, with a lot of purulent secretion. Thus, the patient underwent an emergency surgery through the original incision for a second-time exploration and debridement. Intraoperatively, extensive necrosis of the anterior wall of the gastric conduit was found which also led to a defect on the upper and posterior wall of the tracheostoma, thereby resulting in a pharyngeal fistula with tracheoesophageal fistula. The dressing was regularly changed for 9 mo in order to avoid aspiration and provide a bed of fresh granulation tissue. The patient was then sent to our center for reconstruction.

History of past illness
Cases 1 and 2: The patient had a free previous medical history.

Personal and family history
Case 1: The patient is a known alcoholic and smoker. He had no other special personal and family history.

Case 2: The patient was an alcoholic and smoker, who quit after diagnosis of hypopharyngeal carcinoma. He had no other special personal and family history.

Physical examination
Case 1: Physical examination revealed turbid and black cervix drainage with redness and swelling around the surgical site. Body temperature raised to 39 °C.

Case 2: Physical examination revealed a defect on the patient’s neck with missing anterior wall of the pharyngeal and the upper wall of the tracheostoma (Figure 1).

Laboratory examinations
Case 1: Leukocyte cell count (13.78 × 10^9/L), neutrophil count (12.16 × 10^9/L), neutrophilic granulocyte percentage (88.2%) and C-reactive protein (10.9 mg/dL) were all elevated.

Case 2: Laboratory examinations had normal results.

Imaging examinations
Case 1: Video laryngoscopy showed a circumferential necrosis at the cervical part of the gastric conduit. Bedside chest X-ray film indicated a normal pulmonary film without pleural effusion.

Case 2: Video laryngoscopy and gastroscopy showed the continuity of digestive tract was well upper and below the pharyngeal fistula and tracheoesophageal fistula. The
neck and chest computed tomography (CT) showed pharyngeal fistula communicated with cervical skin and tracheostoma, without fluid collection in the mediastinum and in the pleural cavity.

**FINAL DIAGNOSIS**

**Case 1**
The final diagnosis of the presented case was a circumferential necrosis at the cervical part of the gastric conduit after total pharyngo-laryngo-esophagectomy with gastric pull-up, leading to sepsis and toxemia.

**Case 2**
The final diagnosis of the presented case was pharyngeal fistula and tracheoesophageal fistula after total pharyngo-laryngo-esophagectomy with gastric pull-up.

**TREATMENT**

**Case 1**
The patient was taken up for emergency exploration and debridement. The exploration was performed through the original T-type incision. Intraoperatively, circumferential necrosis was found from the anastomotic line to the thoracic inlet in the anterior wall, and below the thoracic inlet in the posterior wall. Thus, debridement of necrotized tissues and extensive irrigation of the cavity with 3% hydrogen peroxide followed by sterile normal saline were performed. Then the cavity left after debridement was packed with iodoform gauze. The dressing was changed regularly for 1 mo with gauze packed in to keep the entrance to the pulled-up stomach open, and to maintain the tubular shape of the cervical cavity and a bed of fresh granulation tissue for the subsequent reconstruction.

Next, the patient was taken to the operation room for the third time. A 4 cm × 3 cm split thickness skin obtained from the right thigh, was applied to the posterior aspect and sidewall of the wound, in a tie-over fashion. In addition, a chest tube was put through the entrance of the thoracic inlet in order to avoid stricture. The tie-over dressing was removed on the 4th postoperative day and the graft was found completely successful (Figure 2A).

After another 20 d, the skin graft stably healed with the surrounding granulation and the cervical skin (Figure 2B). Therefore, a fourth operation was arranged to close the defect. The surrounding tissue including the skin was used as the anterior wall of the pharynx from three directions; the cephalic, left, and right sides (Figure 3A-C). Finally, a random flap was taken from the submandibular part and was used to cover the anterior surface defect of the neck, followed by putting a drainage under the flap (Figure 3D and E).
Case 2
An operation was arranged with the aim of closing the pharyngeal fistula and tracheoesophageal fistula. The surrounding tissue including the skin was divided into two parts, the upper part and the lower part. The lower part used as random flap was turned over to close the tracheoesophageal fistula, and became the upper and posterior walls of the tracheostoma (Figure 4A-D). Next, the side walls of the pharyngeal fistula were used as the anterior wall of the pharynx (Figure 4E). Finally, the upper part of the...
surrounding skin and subcutaneous tissue, used as another local random flap, were sewed with the reconstructed upper wall tissue of the tracheostoma in an “inverted-T” fashion in order to close the skin defect (Figure 4F).

OUTCOME AND FOLLOW-UP

Case 1
On the next day after debridement, the general condition of the patient recovered visibly. Leukocyte cell count \(7.09 \times 10^9/L\), neutrophil count \(4.89 \times 10^9/L\), neutrophilic granulocyte percentage (69%) and C-reactive protein (4.69 mg/dL) all declined. And, the body temperature returned to normal. Twelve days after the final step of the reconstruction process, the patient began to take a liquid diet. Furthermore, we performed upper gastrointestinal roentgenography, which found a small fistula. Conservative treatment was conducted with drainage and dressing change for 2 wk. And, the patient could finally take a solid diet without dysphagia.

Case 2
On the 7th postoperative day, upper gastrointestinal roentgenography was performed which indicated that there was no obvious contrast medium extravasation. Therefore, the patient was started on a liquid diet and the drainage tube was removed on the 8th postoperative day. Results indicated that the recovery was smooth. No new fistula was found and the patient could take a solid diet without dysphagia.

DISCUSSION
Gastric pull-up is one of the most common reconstruction methods for patients using total pharyngo-laryngectomy or pharyngo-laryngo-esophagectomy. The method is effective because it provides sufficient tissue for the reconstruction of circumferential defect, with only one anastomotic stoma. Moreover, the morbidity of gastric necrosis is not so high, ranging from 0% to 24%\(^{[10,11]}\). Although the circumferential necrosis rate is even less, vigilance for the necrosis is always required because necrosis can lead to...
Reconstruction after failed gastric pull-up

Zhang Y et al. There are several common risk factors for gastric necrosis, which can be divided into four parts: direct angiogenic factors, including twisting and overstretching the supplying vascular; gastric wall factors, including gastric ulcer, tight restrictive hiatus, and external beam irradiation; physical condition factors, including low perioperative cardiac output, postoperative hypotension, hypoproteinemia, and diabetic state; and finally the surgeons’ technique when creating and handling the stomach. Most risk factors can be avoided by careful preoperative preparation, delicate intraoperative manipulations, and postoperative treatment. A previous study reported that patients who have febrile and toxic symptoms for longer than 24 h or those who have coffee/dark drainage should be suspected for gastric necrosis. CT scan can help to identify the necrosis by detecting an ischemic focus or anastomotic breakdown, but the sensitivity is low. Furthermore, endoscopy can help with direct detection of the necrosis and is usually used when there is a clinical suspicion.

Reconstruction of the hypopharyngeal or esophageal circumferential defect after gastric necrosis is a challenging task that influences the postoperative quality of life. It is worth noting that reconstruction should provide an unobstructed conduit without leak and should fulfill the dead space. There are several mature techniques and flaps used in the reconstruction process. Notably, local pedicled flaps were the earliest flaps used in the reconstruction process. They have several advantages including the ease of learning this surgical technique, providing sufficient tissue, and a stable blood supply. However, the donor site can be irradiated at the same time as the primary carcinoma, thereby leading to higher leak or necrosis rate, and excessive bulkiness of the flaps can lead to tracheostoma obstruction. On the other hand, free flaps are widely used in reconstructions involving the development of microvascular surgery, especially the anterolateral thigh free flap and the free jejunal flap. They can achieve adequate donor tissue outside the radiation field, good swallowing function, and little stricture rate. In addition, their cost-effectiveness is acceptable, except for centers that do not obtain microvascular surgery techniques. Several case reports have demonstrated the use of modified free flaps including tube-in-a-tube anterolateral thigh flap, flag-shaped anterolateral thigh free flap, and inverted-omega anterolateral thigh flap. Although one study reported that a modified fasciocutaneous radial forearm free flap with two-layer closure achieved less risk of fistula and wound dehiscence, relatively high fistulation rates are usually reported when fasciocutaneous radial forearm free flaps are used in circumferential neck defects. Therefore, the flaps are not commonly used nowadays. Advanced hypopharyngeal carcinoma treatment usually involves bilateral neck dissection that results in a lack of healthy donor vessels. Studies on combining double free flaps found that it enhanced the complexity of the procedure but did not increase flap-related complications, thereby suggesting that double free flaps is a worthy choice in instances where single free flap cannot close the complex defect.

In the first presented case, gastric necrosis was diagnosed with poor general condition. The patient suffered from septic shock caused by the necrosis. Therefore, the operation time was strictly limited for safety purposes. Hence, we only performed debridement and chose exclusion therapy in order to shorten the operation time, since reconstruction with flaps needs more time. Another advantage of the exclusion therapy is that the inflammation subsides and granulation tissue turns fresh after days of dressing changes. It provides a good basement for the next-step reconstruction which reduces the fistula rate. Therefore, both patients in this case report underwent exclusion therapy to drain the necrotic material and purulent exudate in order to provide fresh granulation tissue for next step reconstruction.

The split thickness skin graft is a type of skin flap reserve that only contains the epidermis and a portion of the dermis. It is normally used to cover skin defects or is placed over muscle. It must be put on wound bed with vascularity because it has the special characteristic of no blood supply. The main advantage of split thickness skin graft is that it is easy to harvest with abundant donor sites. Another advantage is that it can be used to cover defect that is greater than the donor skin due to its good epithelialization ability. In the first presented case, necrosis of the posterior wall extended to the gastric wall below the thoracic inlet. We put the split thickness skin on the surface of the granulation tissue, which served as the side wall and posterior wall of the conduit. The epithelialization ability of the split thickness skin made it able to grow along the chest tube that we put through the thoracic inlet, thereby meeting the margin of the healthy gastric wall. In contrast, using a pedicled flap or a free flap would have required a sternotomy to suture the inferior margin with the gastric wall, thereby prolonging the operation time and causing more trauma to the patient.
For centuries, local random flap has been an important flap for performing anaplastic surgery. Its main advantage is that its blood supply does not rely on a specific vessel, which ensures that its harvest is not restricted to a certain position. Moreover, compared to pedicled flaps and free flaps, it is easier to harvest and takes less time. However, having no specific blood supply vessel is challenging to surgeons because they must design the flap well and they should carefully confirm the blood supply before and after the reconstruction procedure. In the first case, we used 4 local random flaps to accomplish the two-layer closure of the anterior wall of pharynx and the skin defect. In the second case, we used 6 local random flaps to accomplish the two-layer closure of the anterior wall of pharynx and the skin defect, as well as closure of the upper wall of the tracheostoma, which could hardly be achieved by using a single pedicled flap or a free flap. Therefore, we suggest that reconstruction using well prepared and designed local random flaps can achieve equal results as free flaps. However, it is more advantageous because it requires less operation time, causes less trauma, and requires no microsurgical technique.

**CONCLUSION**

To the best of our knowledge, this is the first case report that has reported reconstruction using local random flaps and a split thickness skin graft for cervical circumferential defects extending below the thoracic inlet. In addition, this case report provides a method for the reconstruction of tracheoesophageal fistula with a defect on the upper and posterior walls of the tracheostoma. Therefore, for selected patients, local random flaps (with a split thickness skin graft) can be used as a considerable alternative to free flaps. However, the results in this case report are limited because they must design the flap well and they should carefully confirm the blood supply before and after the reconstruction procedure. In the first case, we used 4 local random flaps to accomplish the two-layer closure of the anterior wall of pharynx and the skin defect. In the second case, we used 6 local random flaps to accomplish the two-layer closure of the anterior wall of pharynx and the skin defect, as well as closure of the upper wall of the tracheostoma, which could hardly be achieved by using a single pedicled flap or a free flap. Therefore, we suggest that reconstruction using well prepared and designed local random flaps can achieve equal results as free flaps. However, it is more advantageous because it requires less operation time, causes less trauma, and requires no microsurgical technique.

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Incurable and refractory spinal cystic echinococcosis: A case report

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CASE REPORT

Incurable and refractory spinal cystic echinococcosis: A case report

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Abstract

BACKGROUND
Although the incidence and cure rate of spinal hydatidosis are low, the recurrence rate of spinal hydatidosis is high, and the prognosis of spinal hydatidosis is poor. Therefore, we report a typical case of refractory spinal hydatidosis to increase spine surgeons’ awareness of the disease and reduce misdiagnosis and recurrence.

CASE SUMMARY
A 48-year-old man presented with back pain, significant weight loss, and paralysis of both lower limbs. The patient was misdiagnosed with spinal tuberculosis in an outside hospital. However, spinal magnetic resonance imaging (MRI) showed hyperintense cystic components on T2-weighted images and hypointensity on T1-weighted images. A lobulated, multicellular, honeycomb- appearance, septated cystic mass protruding intraspinally and compressing the spinal cord at segments T8–T9 was present. Paravertebral polycystic lobular lesions presented as a “bunch of grapes”. The ELISA test result for Echinococcus granulosus was positive. Then, a diagnosis of spinal hydatidosis and lung hydatid disease was made, and the patient underwent left transthoracic approach lobectomy, paravertebral lesion debridement, and subtotal vertebrectomy with vertebral body replacement of segments T8 and T9 by a mesh cage. The patient also underwent albendazole chemotherapy before and after surgery. One year after stopping the drug therapy, the patient developed recurrent T5 vertebral lesions and underwent a second subtotal vertebrectomy surgery. The patient is currently in good condition and is receiving long-term medication and follow-up.

CONCLUSION
The MRI feature of a “bunch of grapes” is a typical imaging indication of spinal hydatidosis. Subtotal vertebrectomy is a risk factor for postoperative recurrence. Total spondylectomy makes it possible to cure spinal hydatidosis, but antiparasitic drug therapy is also an important supplementary therapy to multimodal therapy. It is preferable for patients with spinal hydatidosis to receive life-long antiparasitic medication therapy and follow-up.
Case Report: Incurable and refractory spinal cystic echinococcosis

Zhang T, Ma LH, Liu H, Li SK. World J Clin Cases 2021; 9(33): 10337-10344

Key Words: Cystic echinococcosis; Spinal hydatidosis; Recurrence; Case report

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Core Tip: We report a rare case of typical refractory spinal hydatidosis. The magnetic resonance imaging finding of a “bunch of grapes” is a typical imaging feature of spinal hydatidosis. Subtotal vertebrectomy is a risk factor for postoperative recurrence. Total spondylectomy makes it possible to cure spinal hydatidosis, but antiparasitic drug therapy is also an important supplementary therapy to multimodal therapy. Preferably, patients with spinal hydatidosis should receive life-long antiparasitic medication therapy and follow-up.

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DOI: https://dx.doi.org/10.12998/wjcc.v9.i33.10337

INTRODUCTION

Cystic echinococcosis (hydatidosis) is caused by Echinococcus granulosus. Most cases of cystic echinococcosis are asymptomatic and are found in the liver (55%), lung (28%), spleen, kidneys, and brain[1]. The incidence of osseous cystic echinococcosis is much lower, accounting for approximately 0.5%-4% of the total reported cases[2]. The most commonly affected bone is the spine (45%), followed by the ribs[3]. In spinal cystic echinococcosis, the lesions are predominantly located in the thoracic spine (47%), followed by the thoracolumbar spine (17.7%) and the lumbosacral spine (17.7%)[4,5].

Although the prevalence of spinal cystic echinococcosis is very low, it often causes back pain or motor dysfunction in clinical practice. The imaging findings of spinal cystic echinococcosis are easily misdiagnosed as spinal tuberculosis. Primary spinal cystic echinococcosis must be considered in the differential diagnosis of atypical manifestations of vertebral lesions, especially in patients with risk factors. Early diagnosis, preferably followed by anterior radical surgery combined with antiparasitic therapy of sufficient duration, is the solution to at least prevent the progression of symptoms. Surgery and chemotherapy can improve the symptoms in most cases but may not completely cure the patient’s condition or prevent recurrences[6].

Multimodal therapy for spinal cystic echinococcosis includes drug therapy and surgical treatment. Surgery is still recognized as the “gold standard” treatment[7]. The only cure for spinal cystic echinococcosis is radical resection. However, this is rarely possible. Here, we present a case in which a patient underwent two thoracic surgical treatments but was still not completely cured.

CASE PRESENTATION

Chief complaints

In September 2012, a 48-year-old man presented with progressive back pain, weakness in the lower limbs, significant weight loss for 1 year, and paralysis of both lower limbs for 1 mo.

History of present illness

Patient’s symptoms started 1 year ago with progressive back pain, paralysis of both lower limbs for 1 mo. The patient was misdiagnosed with spinal tuberculosis in an outside hospital and underwent anti-tuberculosis treatment for 9 mo.

History of past illness

His past medical history was normal.

Grade E (Poor): 0
Grade D (Fair): 0
Grade C (Good): C
Grade B (Very good): 0
Grade A (Excellent): 0
Personal and family history
The patient was a herder living in a pastoral area for a long time.

Physical examination
Local examination of the spine revealed tenderness in the spinous process of the T8 and T9 vertebrae. There was hypoesthesia below the umbilical plane. Neurological examination revealed spastic paralysis with lower extremity motor powers of 0/5. Deep tendon flexes revealed hyperreflexia, and the Babinski sign was positive. Anal reflex, anal tonus, and voluntary anal contraction were present.

Laboratory examinations
The initial laboratory examination showed normal leukocytes (6.24 × 10^9/L), neutrophils (4.14 × 10^9/L, 66.3%), and eosinophils (0.21 × 10^9/L, 3.4%). C-reactive protein was 0.6 mg/dL, and the erythrocyte sedimentation rate was 1 mm/h. The T-SPOT test result for tuberculosis was negative, but the ELISA test result for *Echinococcus granulosus* was positive.

Imaging examinations
Radiography images revealed that the T8–9 disc space narrowed and the vertebral body height of T9 decreased (Figure 1). Axial computed tomography (CT) of the thoracic spine confirmed osteolytic destruction of the T8 and T9 vertebrae and the posterior part of the 4th, 5th, and 6th ribs on the left. Heterogeneous lesions containing hypodense cystic areas and partial calcification were also detected on the left paravertebral (Figure 1). Thoracic magnetic resonance imaging (MRI) showed hyperintense cystic components on the sagittal, coronal, and cross-sections of T2-weighted images and hypointense heterogeneous components on T1-weighted images. It showed a lobulated, multiocular, honeycomb appearance and a septated cystic mass protruding intraspinally, compressing the spinal cord at segments T8–T9. Paravertebral polycystic lobular lesions presented as a “bunch of grapes” (Figure 2). Further CT of the head, abdomen, and pelvis showed no further cystic lesions.

FINAL DIAGNOSIS
The diagnosis of spinal hydatidosis and lung hydatid disease was based on laboratory findings and typical imaging findings.

TREATMENT
An operation to achieve dorsal spine arthrodesis of segments T7–T10 was performed. Then, the patient underwent left transthoracic approach lobectomy, paravertebral lesion debridement, and subtotal vertebrectomy with vertebral body replacement of T8 and T9 by a mesh cage. Intraoperatively, the cystic lesion had a white crystal-like appearance (Figure 3). The entire vertebral body and spinal canal were infiltrated by white granular tissue, destroying the integrity of the vertebral body. The surgical wound was soaked in 10% hypertonic sodium chloride solution for 30 min. Postoperative histopathology confirmed cystic echinococcosis.

The patient underwent albendazole chemotherapy before and after surgery; the patient received two doses a day for a total of 15 mg/kg/d. Hemopoiesis and liver enzymes were monitored as recommended during treatment. Two weeks after the rehabilitation program, the muscle strength of both of the patient’s lower extremities recovered to 3/5. The senses were normal. After 6 wk, the patient was walking independently.

OUTCOME AND FOLLOW-UP
Two years later (in 2014, one year after voluntarily stopping the medication), the patient experienced increased spinal cord dysfunction, insufficient motor function, numbness, and decreased peripheral sensitivity. However, the patient did not exhibit significant sphincter dysfunction. MRI showed new lesions in the T5 vertebra and spinal canal. After continuing to take albendazole, the patient’s sensorimotor function...
gradually recovered. Therefore, it was recommended that the patient take the albendazole drug treatment for life.

During continued chemotherapy, the patient relapsed with partial paralysis of both lower extremities in 2017, and the muscle strength of both lower extremities was 2/5. Patella and Achilles reflexes were hyperactive. Thoracic MRI revealed anomalous cystic lesions with extradural expansion and invasion of the T5 vertebral body and left pedicle and transverse processes of the T5-T6 vertebrae that extended to the ribs and spinal canal and compressed the spinal cord (Figure 4). A second posterior surgical procedure was performed on the patient to remove spinal cysts. Laminectomy, costotransversectomy, and vertebrectomy were all performed at the T5 level, and the epidural cyst was removed at the same time. The patient was discharged in an independent ambulatory state 2 wk later. During the 3-year follow-up period after the second operation, the patient’s sensory and motor functions were normal. Postoperative CT showed that the intervertebral bone graft had been fused, but MRI showed that there were still hyperintense lesions in the paravertebral region (Figure 5). This patient is still undergoing long-term albendazole chemotherapy.

**DISCUSSION**

Spinal cystic echinococcosis has no characteristic signs or symptoms. Therefore, the diagnosis of such cases is difficult and is frequently delayed until signs and symptoms of spinal cord or nerve compression appear. The most common clinical manifestation is pain (59.2%–75%), followed by loss of leg strength (37%–50%)\[4,5\]. This patient was misdiagnosed with spinal tuberculosis in another hospital. Therefore, in the initial diagnosis of spinal tuberculosis or spinal pyogenic infection, according to the patient’s clinical symptoms and signs, a differential diagnosis should consider spinal hydatidosis, malignancies, giant cell tumors of bone, etc.\[8,9\]. The overall incidence of spinal hydatidosis is very low, and it is more likely to be misdiagnosed and missed. Therefore, surgeons should have sufficient knowledge about spinal hydatidosis.
Another way to reduce the misdiagnosis of spinal hydatidosis is to fully understand the imaging manifestations of hydatid disease. The most common radiologic feature of osseous lesions is a combination of multilocular cysts and reactive sclerosis[10]. When spinal hydatidosis is suspected, MRI is the first choice for evaluation. T2 images often show hyperintense cysts with clear boundaries that are rounded or oval in shape and...
flow together, while cyst septations produce “wheel-like” structures, and the presence
of daughter cysts is indicated by “rosette-like” or honeycomb-like” structures[2,10-12]. Spinal cystic echinococcosis has a characteristic appearance of images resembling a
bunch of grapes (Figure 2)[4,13]. In the typical MRI findings of this patient, would not
difficult for a physician with experience in the diagnosis and treatment of hydatid
disease to make a preliminary diagnosis of spinal hydatidosis.

The theoretical cure for spinal hydatidosis is radical resection, but the cure rate is
zero when surgical intervention is performed alone[4]. The main goal of spinal
hydatidosis surgery should be to remove the infected vertebrae in a craniocaudal
fashion from healthy bones to healthy bones[14] and to eradicate cysts and scolexes.
The best operation is radical resection with a safety margin of 2 cm[15], but this is
almost impossible for patients with vertebral disease. Similar to what was done for this
patient, the paravertebral lesions around the T5 and T6 vertebrae can be completely
resected, but we cannot initially expand the excision to the T5 and T6 vertebrae
because this will cause spinal instability. During this patient’s operation, we resected
the spinal and paravertebral lesions as integrally and completely as possible. The cyst
was carefully removed to avoid overflow, and hypertonic saline was used to
extinguish the scolex. However, we still could not prevent recurrence. After the first
resection of paravertebral lesions, the patient had recurrent lesions in the T5 vertebra.
Relapse of spinal hydatidosis is very common[16], and the recurrence rate reported in
the literature is as high as 89%–92.6%[4,17]. If surgery cannot prevent recurrence, then
pre- and postoperative antiparasitic drug therapy is a very important supplementary
treatment.
Subtotal vertebral resection of hydatid lesions may be the main reason for the high recurrence rate of spinal hydatidosis. Therefore, even if only a part of the vertebral body is involved, some authors still recommend total vertebrectomy to prevent recurrence. Liang et al. reported that there was no recurrence after total en bloc spondylectomy of spinal hydatidosis, and the patients were free of disease. This suggests that expanded total en bloc spondylectomy may be a better choice for this patient. However, for patients who cannot undergo total vertebrectomy, the intraoperative use of scolicidals and the use of albendazole before and after surgery are currently considered to be the standard for the treatment of spinal hydatidosis.

It is generally believed that the combination of medical treatment and surgery to prevent intraoperative cyst spillover can reduce the risk of spinal hydatidosis recurrence. Albendazole medication may not cure or prevent the recurrence of spinal hydatidosis, but it is still the only treatment option currently available for inoperable patients. Albendazole is administered to patients twice a day for a total dose of 10–15 mg/kg per day and is regarded by the World Health Organization as the first-choice mainstay drug for the treatment of hydatid disease. Praziquantel appears to have a synergistic effect by increasing plasma levels of albendazole, and there is some evidence to support the use of praziquantel in combination with albendazole during surgery. This patient has been taking albendazole for 8 years and has not been completely cured, suggesting that the combination of praziquantel and albendazole may be a better choice.

Recurrence of spinal hydatidosis may occur 20 years after initial occurrence, and albendazole withdrawal is a decisive factor in the dramatic evolution of patients. Since radical therapy for spinal hydatidosis is rarely feasible, follow-up should be performed throughout the patient’s lifetime. It may also require life-long antiparasitic drug treatment. Patients with spinal hydatidosis require long-term follow-up to understand the potential for recurrence and possible complications or sequelae associated with surgery or antiparasitic treatment. The prognosis of spinal hydatidosis is still poor, and early recognition is essential for optimal recovery.

CONCLUSION

We report a rare case of typical refractory spinal hydatidosis, and the MRI finding of a “bunch of grapes” imaging feature is typical of spinal hydatidosis. Subtotal vertebrectomy is a risk factor for postoperative recurrence. Total spondylectomy makes it possible to cure spinal hydatidosis, but antiparasitic drug therapy is also an important supplementary therapy to multimodal therapy. Preferably, patients with spinal hydatidosis should receive life-long antiparasitic medication therapy and follow-up.

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Individualized treatment of breast cancer with chronic renal failure: A case report and review of literature

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Author contributions: Cai JH and Zheng JH are the patient’s doctors, and they reviewed the literature and contributed to manuscript drafting; Lin WX, Zou J, and Li ZY reviewed the literature, analyzed and explained the results of laboratory examinations, imaging examinations and pathological examinations; Lin XQ and Chen YK collected patient information and examination data, designed and produced the figures and tables; Chen YX reviewed the literature, contributed to manuscript drafting and revised the manuscript; all authors participated in the discussion and formulation of patient chemotherapy regimens and drug dosage adjustments, and issued final approval for the version to be submitted.

Informed consent statement: Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editor.

Abstract

BACKGROUND

Studies have shown that patients with chronic renal failure (CRF) are more likely to suffer from breast cancer and other malignant tumors. To our knowledge, CRF can reduce drug excretion, thereby increase drug exposure and lead to increased toxicity, which will limit drug treatment and lead to tumor progression. Currently, there are few successful reports on the combination of docetaxel, trastuzumab, and pertuzumab (THP) as a neoadjuvant treatment regimen for HER-2 positive breast cancer patients with CRF.

CASE SUMMARY

We report a breast cancer (cT2N2M0, Her-2+/HR-) patient with CRF. It was a clinical stage IIIA tumor on the left breast. The patient had suffered from uremia for 2 years, and her heart function was normal. Based on the pathological type, molecular type, and clinical stage of breast cancer, the patient’s renal function, the clinician analyzed the pharmacological and pharmacokinetic characteristics of the antitumor drugs after consulting the relevant literature, and prescribed the neoadjuvant regimen of THP (docetaxel 80 mg/m², trastuzumab 8 mg/kg for the first dose, and 6 mg/kg for the maintenance dose with pertuzumab 840 mg for the first dose and 420 mg for the maintenance dose), once every 3 wk, for a total of 6 courses. The neoadjuvant treatment had a good effect, and the patient then underwent surgery which was uneventful.

CONCLUSION

CRF is not a contraindication for systemic treatment and surgery of breast cancer. The THP regimen without dose adjustment may be a safe and effective neoadjuvant treatment for HER-2 positive breast cancer patients with CRF.
Cai JH et al. Treatment of breast cancer with CRF

INTRODUCTION

Renal insufficiency is common in cancer patients, and the risk of impaired renal function increases with age and the appearance of comorbid diseases, such as diabetes. Breast cancer is the most common cancer in women[1-3], accounting for 30% of all newly diagnosed cancers[1]. A large number of studies have confirmed that patients with chronic renal failure (CRF) have a higher incidence of malignant tumors and mortality[4,5]. When the estimated glomerular filtration rate (GFR) drops to 10 mL/min/1.73 m², the mortality rate of cancer patients increases by 22%[6,7]. Therefore, the reduction in GFR will not only lead to serious renal complications, but also limit the treatment of tumors, thereby promoting tumor progression. Renal failure is an important factor limiting the treatment of breast cancer patients as patients with impaired renal function often experience reduced renal excretion or metabolism and changes in absorption and drug distribution, which may lead to increased treatment-related toxicity[8,9]. In hemodialysis patients, it is difficult to determine the safe and effective dosage and dosing schedule of anticancer drugs, as well as the best time for hemodialysis, which makes it difficult to develop an appropriate treatment regimen. Also, almost all clinical studies will exclude patients with CRF. Currently, apart from the case report by Modi et al[10], there are few studies on the treatment of breast cancer in patients with end-stage renal disease, and these patients rarely successfully complete a series of standard regimens of neoadjuvant therapy and surgery. This report describes the case of a breast cancer patient with CRF and the successful use of docetaxel, trastuzumab and pertuzumab (THP) as the preoperative neoadjuvant treatment regimen.

CASE PRESENTATION

Chief complaints

A 55-year-old female patient with a left breast mass attended our hospital on September 15, 2020.

History of present illness

The patient found a mass approximately 15 mm × 15 mm in size in the left breast 9 mo ago without any related symptoms. She did not undergo diagnosis and treatment; therefore, the mass has slowly increased over the past 9 mo, and it is now approximately 35 mm × 30 mm in size. This prompted her visit to our hospital.

Key Words: Breast cancer; Chronic renal failure; Neoadjuvant treatment; Dose adjustment; Pertuzumab; Case report

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History of past illness
The patient was diagnosed with uremia 2 years ago and started on regular hemodialysis treatment (hemodialysis every 48 h), and she did not produce urine.

Personal and family history
She had no history of food or drug allergies and no history of tumors or genetic diseases in her family.

Physical examination
At the time of admission, the patient’s temperature was 36.5 °C, heart rate was 85 bpm, respiratory rate was 20 breaths/min, blood pressure was 140/90 mmHg and oxygen saturation in room air was 99%. She was in an anemic state. A mass approximately 35 mm × 30 mm was palpable under the nipple of the left breast, with a hard texture, rough surface, no tenderness, poor mobility, unclear boundaries, and was not adhered to the nipple. No mass was observed on the right breast. In addition, no enlarged lymph nodes were palpable in the bilateral axillary and supraclavicular area.

Laboratory examinations
Laboratory examinations showed that the patient’s leukocyte, neutrophil, platelet, hemoglobin, creatinine, urea, cancer antigen 153 (CA153), and carcinoembryonic antigen (CEA) levels were 6.4 × 10^9/L, 4.61 × 10^9/L, 183 × 10^9/L, 96 g/L, 581.9 μmol/L, 14.27 mmol/L, 26.20 U/mL, and 6.31 μg/L, respectively.

Imaging examinations
Breast ultrasound showed a 37 mm × 31 mm × 30 mm primary lesion under the nipple of the left breast and enlargement of multiple lymph nodes in the left axillary area, the largest measuring 16 mm × 10 mm × 10 mm (Figure 1). Histopathological examination of the left breast showed infiltrating ductal carcinoma (Level II according to the WHO classification) (Figure 2). Hormone receptors (HRs), including estrogen receptor (ER) and progesterone receptor (PR), were negative, C-erbB2 was 2+, and Ki-67 was expressed in the nuclei of approximately 40% of tumor cells. The results of fluorescence in situ hybridization revealed that HER-2 was positive. Histopathological examination of the left axillary lymph nodes showed metastatic cancer, which was consistent with the breast source. Magnetic resonance imaging (MRI) showed a 37 mm × 34 mm × 31 mm mass below the left nipple and peripheral satellite lesions, which was assessed as Category 6 by the Breast Imaging-Reporting and Data System, with multiple swollen lymph nodes in the left axillary area (Figure 3).

FINAL DIAGNOSIS
The patient was diagnosed with infiltrating ductal carcinoma of the left breast and uremia. Clinical stage of her left breast cancer was cT2N2aN0, stage IIIA, and the molecular classification was HER-2 positive (HR negative).

TREATMENT
According to the patient’s age, the pathological type of breast cancer, molecular classification, clinical stage, prognostic factors, and renal function, the THP neoadjuvant treatment regimen was formulated and started on September 27, 2020. Docetaxel 80 mg/m^2, trastuzumab 8 mg/kg for the first dose, and 6 mg/kg for the maintenance dose with pertuzumab 840 mg for the first dose and 420 mg for the maintenance dose were administered. The patient received a total of six cycles of the THP regimen, and hemodialysis was performed more than 12 h after the medication. The patient tolerated the drug treatment well, and no serious drug toxicity was noted.

OUTCOME AND FOLLOW-UP
No significant neutropenia or leukopenia, and no significant cytotoxicity were observed by clinical evaluation or cardiac function examination. During subsequent treatment and follow-up, the patient’s serum creatinine and urea levels did not change.
significantly compared with those pre-chemotherapy, suggesting that dose adjustment of the THP regimen had no significant effect on renal function.

Routine blood analysis (Table 1), liver and kidney function, CEA, and CA153 levels (Table 2) were determined before each chemotherapy cycle, and breast ultrasonography and breast MRI were performed approximately every 3 mo. Prior to surgery, the left breast tumor and left axillary lymph nodes had significantly reduced in size (Figure 1). No obvious abnormalities were observed in the right breast, and no abnormal enlarged lymph nodes were observed in the right axillary and bilateral supraclavicular areas.

In September 2020, the patient had above-normal levels of CEA and normal levels of CA153, but they remained normal during both neoadjuvant chemotherapy and targeted therapy. Due to the patient’s CRF, her hemoglobin level was significantly lower than normal. Other routine tests showed no obvious abnormalities. During the follow-up period, the patient was in good condition, and no evidence of disease progression or recurrence has been found.

Figure 1 Breast ultrasound results of the patient obtained during preoperative neoadjuvant treatment. A and B: September 15, 2020. M: Left breast mass (37 mm × 31 mm × 30 mm) (A) and LN: Left axillary lymph node (the largest node was 16 mm × 10 mm × 10 mm) (B); C and D: December 21, 2020. M-LBR: Left breast mass (16 mm × 13 mm ×12 mm) (C) and LN: Left axillary lymph node (the largest node was 13 mm × 8 mm × 6 mm) (D); E and F: January 26, 2021. MLBR: Left breast mass (12 mm × 9 mm × 8 mm) (E) and LN: Left axillary lymph node (the largest node was 10 mm × 6 mm × 5 mm) (F).


Table 1 Peripheral blood analysis results

<table>
<thead>
<tr>
<th>Date</th>
<th>Leukocytes (10⁹/L)</th>
<th>Neutrophils (10⁹/L)</th>
<th>Platelets (10⁹/L)</th>
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<td>October 17, 2020</td>
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<td>November 8, 2020</td>
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<td>65</td>
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<td>72</td>
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</table>

Table 2 Renal function and serum tumor markers

<table>
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<th>Urea (mmol/L)</th>
<th>CA153 (U/mL)</th>
<th>CEA (μg/L)</th>
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<td>28.6</td>
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<td>8.43</td>
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</table>

CA153: Cancer antigen 153; CEA: Carcinoembryonic antigen.

DISCUSSION

The National Comprehensive Cancer Network and the Chinese Anti-Cancer Association Clinical Oncology Cooperative Professional Committee guidelines indicate that for cT2N2aM0 stage IIIA and HER-2+/ER-/PR- invasive breast cancer patients, the preoperative neoadjuvant treatment regimen of taxanes + trastuzumab + pertuzumab is recommended [11]. After six cycles of neoadjuvant therapy, the clinical stage of left breast cancer in this patient was cT1N1aM0, stage IIa, and she underwent modified radical mastectomy for left breast cancer and left axillary lymph node dissection with clear surgical margins.

Based on the patient’s renal function, the pharmacokinetics, pharmacodynamics, and safety of various drugs, we chose the neoadjuvant treatment regimen of THP for this patient.

Docetaxel and paclitaxel are commonly used taxane chemotherapeutics. Both are rarely excreted by the kidneys, but the renal excretion rate of paclitaxel is higher than that of docetaxel. It has been reported that paclitaxel causes mild nephrotoxicity, while docetaxel does not cause nephrotoxicity [12]; and the incidence and severity of allergic reactions to docetaxel are lower than those of paclitaxel [13]. Docetaxel is a new anti-microtubule agent, which can promote the polymerization of tubulin and stabilize the microtubules by preventing their disintegration [14]. Docetaxel enters the liver through the blood and binds to proteins under the action of the cytochrome P450 subtype enzyme type 3A4 enzyme (CYP3A4) in the liver. More than 70% of the drugs are transformed into inactive metabolites, which are then excreted in feces through transport by P-glycoprotein in the intestine and bile. Another 10% of the drugs are excreted in the urine, and only a few drugs are excreted as prototypes [15]. Studies have shown that the pharmacokinetic parameters of docetaxel in hemodialysis patients are not affected, and its exposure is slightly increased, but no toxic effects have been observed in patients [16]. Docetaxel was selected as a chemotherapeutic drug for this patient by comprehensive evaluation. Liu et al. [17] administered docetaxel in a patient with the same disease, and no obvious side effects were observed.

Trastuzumab is a recombinant humanized monoclonal antibody directed against HER-2 [18]. After trastuzumab binds to HER-2 on the surface of tumor cells, it can induce antibody-dependent cell-mediated cytotoxicity and has a killing effect on tumor cells overexpressing HER-2. It has been approved for the treatment of early [19, 20] and metastatic [20, 21] breast cancer. In the third phase of the study, the addition of
Figure 2 Pathological results of left breast tumor and left axillary lymph node biopsies. A: Hematoxylin and eosin-stained sections revealed that the tumor cells grew in a solid and patchy infiltrating manner (original magnification: 200 ×); B: Hematoxylin and eosin-stained sections revealed that the left axillary lymph node was metastatic carcinoma, which was consistent with the breast source (original magnification: 200 ×); C: C-erbB2 (2+) was uncertain in neoplastic cells by immunohistochemical analysis (original magnification: 200 ×); D and E: Estrogen receptor and progesterone receptor were negative in neoplastic cells by immunohistochemical analysis (original magnification: 200 ×); F: Ki-67 was expressed in the nuclei of approximately 40% of tumor cells (original magnification: 200 ×); G: HER-2 was amplified by fluorescence in situ hybridization (original magnification: 200 ×).

Trastuzumab to standard chemotherapy was associated with disease progression time (7.4 mo vs 4.6 mo), effective time (9.1 mo vs 6.1 mo), and overall survival (25.1 mo vs 20.3 mo). The renal excretion of trastuzumab is very low[22,23], and its main toxicity is cardiotoxicity[24], while renal toxicity is low. In a pivotal trial conducted by Slamon et al[19], 0.3% of patients receiving trastuzumab combined with chemotherapy developed severe (grades 3 and 4) renal damage. Micallef et al[25] treated breast cancer in two hemodialysis patients using trastuzumab and achieved good clinical results.

Pertuzumab is a recombinant humanized monoclonal antibody directed against the extracellular dimerization domain (subregion II) of HER-2, thereby blocking the ligand-dependent heterodimerization reaction between HER-2 and other HER-2 family members, including epidermal growth factor receptor, HER-3, and HER-4[26]. Pertuzumab has been approved for the neoadjuvant treatment of patients with HER-2-positive, locally advanced, inflammatory or high-risk early breast cancer[27], or for the first-line treatment in patients with advanced breast cancer overexpressing HER-2 in the European Union[28]. The NEOSPHERE study confirmed that adding pertuzumab to TH can further increase the pathological complete response rate of HER-2 positive patients[29]. The PEONY study verified the effectiveness and safety of the THP regimen in an Asian population[30]. Studies on the potential effects of trastuzumab or docetaxel on the pharmacokinetics of pertuzumab have been carried out. An analysis showed that there was no evidence that trastuzumab or the combination of docetaxel and trastuzumab had an effect on the metabolism of pertuzumab[31].
To the best of our knowledge, a pharmacokinetic study of pertuzumab has not been conducted in patients with renal impairment, and there are few reports on the application of pertuzumab in breast cancer patients with CRF. However, nephrotoxicity of pertuzumab is uncommon, and the clinical trials CLEOPATRA, NEOSPHERE, TRYPHAENA, and APHINITY have not found any obvious renal adverse reactions. In addition, the monoclonal antibody is mainly cleared through a large-volume, non-specific Fc receptor-mediated immunoglobulin G (IgG) clearance mechanism and a specific targeted-mediated drug disposal pathway. The intact monoclonal antibody cannot be filtered by the glomerulus to be excreted through the kidney due to its large molecular weight. Monoclonal antibodies can be excreted by the kidneys after being broken down into peptide fragments and amino acids by the lysosomal pathway in the corresponding effector cells. At the same time, the peptide fragments and amino acids generated by decomposition can also participate in the body’s energy supply and in the synthesis of new proteins[32]. The metabolism of endogenous IgG occurs in various tissues and plasma in the body. Using a physiologically based pharmacokinetic model, it is estimated that the contribution of skin, muscle, liver, and intestinal tissues to the clearance of endogenous IgG are 33%, 24%, 16%, and 12%, respectively[33]. This shows that the kidney’s contribution to the elimination of endogenous IgG is low. In addition, based on a population pharmacokinetic analysis, renal impairment is not expected to affect exposure to pertuzumab. Based on limited clinical studies and reports, we conclude that renal excretion of pertuzumab is very low. The product description also does not regard renal damage as a contraindication to pertuzumab. Therefore, we preferred to use trastuzumab and pertuzumab dual target therapy. It is worth noting that there are few reports on pertuzumab in breast cancer patients with CRF, which may be a unique feature of this case.

In breast cancer patients with CRF, drug metabolism and dosage selection are issues that must be considered in order to avoid aggravation of systemic toxicity caused by renal failure. Considering the clearance of drugs during dialysis, appropriate timing of medication should be selected for hemodialysis patients. Docetaxel is rarely excreted by the kidneys. Limited data have shown that docetaxel can be safely used in patients with renal insufficiency without the need for dose adjustment[34]. Docetaxel can be safely used in chronic peritoneal or hemodialysis patients at standard doses[35].
Trastuzumab does not cause nephrotoxicity as a single agent, and relevant data indicate that treatment with trastuzumab is not affected by age or renal function. The product feature summary does not recommend adjusting the dose of trastuzumab in patients with mild to moderate chronic kidney disease. No information is provided on the dose adjustment of trastuzumab due to hemodialysis in the United States. Docetaxel and trastuzumab were used in this breast cancer patient with renal failure without dose adjustment, which is similar to the case report by Liu et al.[17]. There are similar considerations for these two drugs. There are no data on the use of pertuzumab for treating dialysis patients. The product feature summary recommends that in patients with mild or moderate renal insufficiency, the dose need not be adjusted, and there is no recommended dosage for patients with severe renal insufficiency. In the population pharmacokinetic analysis, renal damage did not affect drug disposal. There are few reports on pertuzumab nephrotoxicity, and population pharmacokinetic studies have found that covariates, such as renal function (serum creatinine), do not have a statistically significant effect on the pharmacokinetic parameters of pertuzumab [36].

Our patient was clinically diagnosed with CRF stage 5. Considering the rare renal toxicity of trastuzumab and pertuzumab, we did not adjust the drug dosage which consisted of docetaxel 80 mg/m², trastuzumab 8 mg/kg for the first dose, and 6 mg/kg for the maintenance dose with pertuzumab 840 mg for the first dose and 420 mg for the maintenance dose, every 3 wk. Hemodialysis was performed more than 12 h after chemotherapy.

CONCLUSION

The THP regimen has a minimal effect on renal failure, and as a neoadjuvant therapy for breast cancer patients with positive HER-2, it has a good effect in downstaging breast cancer. In this case, the drug dose was not adjusted, and the patient had no obvious nephrotoxicity or cardiotoxicity. Therefore, the THP regimen without dose adjustment may be a safe and effective neoadjuvant therapy for HER-2 positive breast cancer patients with CRF. CRF is not a contraindication for systemic treatment and surgery for breast cancer. Individualized treatment of these patients can be achieved by multidisciplinary collaboration and close monitoring of renal function.

ACKNOWLEDGEMENTS

The authors are very grateful to the data providers in the study.

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Persistent fibrinogen deficiency after snake bite: A case report

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Author contributions: Xu MH and Chen C designed the research study; Xu MH, Li J and Han L performed the research; Xu MH, Li J and Chen C analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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

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Specialty type: Medicine, research and experimental

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Peer-review report’s scientific quality classification

Abstract

BACKGROUND
Venom-induced consumption coagulopathy (VICC) is characterized by coagulation dysfunction accompanied by decreased coagulation factor activity and fibrinogen (FBG) concentrations. We report a patient with VICC caused by snake bite who manifested persistent FBG deficiency without abnormal coagulation factor activity. This information may be helpful in diagnosing and treating VICC.

CASE SUMMARY
A 49-year-old man who had been bitten by a snake 13 h previously was admitted to the Emergency Department of our hospital with visible swelling of a finger and a bleeding puncture site. The provisional diagnosis was VICC, this being made based on persistent bleeding from the puncture site and subcutaneous hemorrhage. Laboratory evidence of coagulation abnormalities, including fibrinolysis, and findings on thromboelastography confirmed VICC. He had persistent afibrinogenemia requiring intravenous infusions of cryoprecipitate and fresh frozen plasma, together with continuous large doses of human FBG. After this treatment, the patient’s right upper limb swelling improved significantly and his subcutaneous hemorrhage resolved. All of his abnormal laboratory findings returned to normal by day 25. During 6 months’ of follow-up, the patient had no further hemorrhagic events.
CONCLUSION
Hemorrhagic snake venom can result in coagulation dysfunction characterized by persistent FBG deficiency without abnormal coagulation factor activity.

Key Words: Snake bite; Coagulation disorders; Venom-induced consumption coagulopathy; Fibrinogen deficiency; Fibrinogen infusion therapy; Case report

Core Tip: Venom-induced consumption coagulopathy (VICC) is characterized by decreased coagulation factor activity and fibrinogen (FBG) deficiency. Hemorrhage-inducing snake venom contains several ingredients that directly or indirectly consume fibrinogen through multiple mechanisms. We report a rare case with persistent afibrinogenemia without abnormal coagulation factor activity after snake bite. Our report may assist the diagnosis and treatment of FBG deficiency in patients with VICC.

INTRODUCTION
Snake bite is a major and often neglected public health problem. An estimated 1.8 million people are bitten by snakes annually worldwide and more than 125000 of them die as a result[1]. In China, there are approximately 50 species of poisonous snakes and 10 venomous snakes and the death rate from snake bite is 5%-10%. Coagulation dysfunction is the most common consequence of snake bite, venom-induced consumption coagulopathy (VICC) being the most important form of such coagulation dysfunction. Coagulants in venom can cause significant declines in coagulation factors, platelet counts, and fibrinogen (FBG) concentrations, resulting in failure of blood to coagulate and severe bleeding[2,3]. Here, we report an uncommon case of snake-bite-induced VICC that was characterized by persistent FBG deficiency without abnormal coagulation factor activity. Treatment centered around continuous infusions of FBG was successful. Our findings may assist diagnosis and treatment of FBG deficiency in patients with VICC. To the best of our knowledge, no similar case has been reported. Because this is only a case report, the need for ethical approval was waived by the Ethics Committee of Tongji Hospital, which complies with the relevant institutional and national policies.

CASE PRESENTATION
Chief complaints
A 49-year-old man was bitten by a snake, with his chief complaint being bleeding for 13 h after that bite.

History of present illness
The patient was bitten on his right index finger by a snake (species unknown) while working on a construction site. The bite caused local swelling, pain, numbness, and bleeding, without dizziness, fever, diarrhea, consciousness disorders, or other symptoms. He was rushed to a local hospital for treatment, where he underwent puncture site drainage and antivenin injection, administration of coagulation factor supplements and other treatments. He was transferred to our hospital 13 h after the snake bite.

History of past illness
The patient was in good health, with no history of chronic or infectious diseases.
Table 1 Results of coagulation and fibrinolysis test

<table>
<thead>
<tr>
<th>Days after bite</th>
<th>PT</th>
<th>INR</th>
<th>FBG</th>
<th>APTT</th>
<th>TT</th>
<th>D-D</th>
<th>FDPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt; 120</td>
<td>&gt; 10</td>
<td>&lt; 0.5</td>
<td>&gt; 180</td>
<td>&gt; 240</td>
<td>&gt; 60</td>
<td>&gt; 150</td>
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<td>&gt; 10</td>
<td>&lt; 0.5</td>
<td>&gt; 180</td>
<td>&gt; 240</td>
<td>&gt; 60</td>
<td>&gt; 150</td>
</tr>
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<td>&gt; 120</td>
<td>&gt; 10</td>
<td>&lt; 0.5</td>
<td>&gt; 180</td>
<td>&gt; 240</td>
<td>&gt; 60</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 120</td>
<td>&gt; 10</td>
<td>&lt; 0.5</td>
<td>&gt; 180</td>
<td>&gt; 240</td>
<td>&gt; 60</td>
<td>&gt; 150</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 120</td>
<td>&gt; 10</td>
<td>&lt; 0.5</td>
<td>&gt; 180</td>
<td>&gt; 240</td>
<td>&gt; 60</td>
<td>110.5</td>
</tr>
<tr>
<td>5</td>
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<td>&lt; 0.5</td>
<td>&gt; 180</td>
<td>&gt; 240</td>
<td>&gt; 60</td>
<td>83.7</td>
</tr>
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<td>&gt; 10</td>
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</tr>
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<td>16</td>
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<td>1.19</td>
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<td>2.35</td>
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<td>1.05</td>
<td>1.51</td>
<td>31.4</td>
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<td>&lt; 4.0</td>
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<td>25</td>
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<td>1.04</td>
<td>2.66</td>
<td>32.5</td>
<td>15.5</td>
<td>&lt; 0.22</td>
<td>&lt; 4.0</td>
</tr>
</tbody>
</table>

Day 0: day when the patient was bitten; INR: International normalized ratio; PT: prothrombin time; FBG: fibrinogen; APTT: activated partial thromboplastin time; D-D: D-dimer; FDPs: fibrinogen degradation products; TT: thrombin time.

Table 2 Results of coagulation factor activity level

<table>
<thead>
<tr>
<th>Days after bite</th>
<th>II 70%-120%</th>
<th>V 70%-120%</th>
<th>VIII 60%-150%</th>
<th>X 70%-120%</th>
<th>XI 60%-150%</th>
<th>XII 50%-150%</th>
</tr>
</thead>
<tbody>
<tr>
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<td>41</td>
<td>246</td>
<td>59</td>
<td>85</td>
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<tr>
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<td>86</td>
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<td>79</td>
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<td>95</td>
<td>107</td>
<td>127</td>
<td>89</td>
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</tr>
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<td>89</td>
<td>101</td>
<td>112</td>
<td>99</td>
<td>83</td>
<td>72</td>
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<td>113</td>
<td>94</td>
<td>129</td>
<td>105</td>
<td>95</td>
<td>103</td>
</tr>
</tbody>
</table>

Day 0: day when the patient was bitten.

**Personal and family history**

The patient had no history of smoking, drinking, or familial cancers.

**Physical examination**

On admission, the patient’s temperature was 36.9°C, heart rate 107 bpm, respiratory rate 25 breaths/min, blood pressure 91/63 mmHg and oxygen saturation in room air 98%. There was visible swelling of the right index finger and the puncture site was still oozing blood. The patient’s right upper limb had been coated with jidesheng sheyao (a local herbal medicine, specific ingredients unknown).

**Laboratory examinations**

Laboratory tests for coagulation and fibrinolysis on admission showed a prothrombin time (PT) of > 120 s, international normalized ratio (INR) > 10, FBG < 0.5 g/L, activated partial thromboplastin time > 180 s, thrombin time (TT) > 240 s, D-dimer > 60 μg/mL FBG equivalent units, and FBG degradation products > 150 mg/mL. The timing and results of coagulation and fibrinolysis tests are shown in Table 1. Multiple markers were beyond the limits of detection for the first 7 d after the bite. Coagulation factor activity levels are shown in Table 2. Coagulation factor activity decreased slightly after the bite, normalizing within 4 d (Figure 1).
Figure 1 The result of changes in prothrombin time (PT) and activated partial thromboplastin time (APTT), fibrinogen (FBG) and FBG degradation products (FDPs) with days during treatment. A: PT and APTT; B: FBG and FBG degradation products. Indicators above the upper limit are assigned as a maximum value, whereas those below the lower limit are assigned as a minimum value.

**Imaging examinations**
Vascular ultrasonography revealed intermuscular vein thrombosis in the left upper extremity and superficial vein thrombosis in the left lower extremity.

**Further diagnostic work-up**
Five days after the bite, thromboelastography (TEG) showed R time, 35.3 min, and no coagulation curve was formed (Figure 2A). After addition of 2 g/L FBG preparation to whole blood samples in vitro, the coagulation curve pattern was close to normal (Figure 2B): R time, 9.7 min; K time, 1.9 min; α angle, 72.1, maximum amplitude, 72.0; coagulation index (CI), 0.5; and amplitude at 30 min, 0.0.

**FINAL DIAGNOSIS**
The final diagnosis of the presented case was snake-bite-related VICC characterized by
persistent afibrinogenemia without abnormal coagulation factor activity.

TREATMENT

The following treatment was administered. Cryoprecipitate (CRYO) 6 U, fresh frozen plasma (FFP) 600 mL, and human FBG 0.5 g were first injected intravenously 13 h after the bite. For 5 d thereafter, FFP, CRYO and FBG were administered daily as replacement therapy. Timing and specific doses are shown in Table 3.

OUTCOME AND FOLLOW-UP

During treatment, the swelling in the patient’s right upper limb improved significantly and his subcutaneous hemorrhage resolved by day 11. Twenty days after the bite, the results of TEG returned to normal. The patient’s afibrinogenemia lasted for 11 d, after which it began to improve, resolving completely by day 25 (Figure 1). All coagulation-related laboratory results returned to normal by 25 d after the bite. The patient was discharged 26 d after the bite and followed up for 12 mo after discharge. No further hemorrhagic events occurred.

DISCUSSION

Hemorrhagic snake venom can cause consumption of various coagulation factors and FBG through multiple mechanisms, leading to VICC[4,5]. VICC is often characterized by undetectable PT prolongation[6], increased INR, and decreased FBG, usually accompanied by a significant increase in D-dimer concentration. Decreases in FBG concentrations occur in all types of VICC[4].

There are three main protease families in hemorrhagic snake venom: Snake venom metalloproteinases (SVMPs), serine proteinases (SVSPs), and phospholipase A2. SVMPs promote conversion of prothrombin (II) into thrombin (IIa) and activate the fibrinolytic system, resulting in rapid consumption of FBG and various coagulation factors[1]. SVSPs commonly exhibit thrombin-like fibrinolytic functional activity. However, unlike thrombin, SVSPs are highly selective, acting directly on the α-chain of FBG and promoting polymerization of the resulting fibrin monomers[7]. The polymerization products are unstable and easily soluble by plasmin. Therefore, SVSPs only consume FBG and do not activate the coagulation pathway, leading to FBG deficiency only and a less severe type of VICC, in which other coagulation factors are generally unaffected.

One case report described a woman who was bitten by a rattlesnake and had an FBG deficiency and low platelet count[2]. In an Australian survey, 112 of 138 patients with complete VICC lacked FBG and factors V and VIII[3]. Our patient had persistent FBG deficiency without detectable changes in coagulation factor activity. To the best of our knowledge, this combination has not previously been reported. TEG showed that the coagulation curve was close to normal after addition of FBG preparation[8]. Given that our patient’s coagulation factors and platelet counts were normal, we believe that
he had the type of coagulation dysfunction that is mediated via the above-mentioned SVSPs pathway. This type of dysfunction is characterized by FBG deficiency without abnormal coagulation factor activity. Thus, SVSPs were likely the main active components of the snake venom and responsible for the subsequent development of VICC. Our patient’s persistent afibrinogenemia may have been attributable to deposition into and subsequent slow release of some active components of snake venom from his hand, resulting in long-term toxicity. The specific mechanism of underlying persistent afibrinogenemia requires further elucidation.

The mainstays of treatment for VICC are antivenin and replacement therapy. The main replacement therapies are infusions of CRYO, FFP and FBG, and thus, directly supplementing these coagulation factors. In our case, early infusion of coagulation factors/plasma/FBG did not result in complete recovery of coagulation function, and TEG indicated that there was a serious deficiency of FBG. Therefore, continuous large doses of FBG were infused as follow-up treatment, achieving restoration of normal coagulation with FBG concentrations to 0.5–1.0 g/L and return of PT and INR to near normal range[4]. Thus, FBG infusion at an early stage has a positive effect, despite its concentration recovering slowly[9].

CONCLUSION

Hemorrhagic snake venom can result in coagulation dysfunction characterized by persistent FBG deficiency without abnormal coagulation factor activity. In patients with VICC, replacement therapy centered around FBG infusion can achieve restoration of coagulation function.

ACKNOWLEDGMENTS

We thank Dr. Reynolds T, MBBS, FRACP, for editing the English text of a draft of this manuscript.

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Table 3 Dates and specific doses of replacement therapy

<table>
<thead>
<tr>
<th>Days after bite</th>
<th>CRYO (u)</th>
<th>FFP (mL)</th>
<th>FBG (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>600</td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>1600</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>30.5</td>
<td>3450</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>1900</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>600</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
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</tr>
<tr>
<td>7</td>
<td>—</td>
<td>—</td>
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</tr>
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<td>9</td>
<td>—</td>
<td>—</td>
<td>2.0</td>
</tr>
<tr>
<td>12</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Day 0: day when the patient was bitten; CRYO: cryoprecipitation; FFP: fresh frozen plasma; FBG: fibrinogen.


Successful prolonged cardiopulmonary resuscitation after intraoperative cardiac arrest due to povidone-iodine allergy: A case report

Bing-Bing Xiang, Yu-Ting Yao, Shu-Lan Jiao

Abstract

BACKGROUND
Iodophor (povidone-iodine) is widely used clinically because of its broad-spectrum antibacterial effects. Although extremely rare, it may cause anaphylactic shock, which itself carries the life-threatening risk of cardiac arrest.

CASE SUMMARY
We present a case in which a patient with postoperative infection went into anaphylactic shock and cardiac arrest caused by povidone-iodine during secondary surgery. The patient was successfully resuscitated by 2 h of cardiopulmonary resuscitation.

CONCLUSION
This is the first known case of cardiac arrest caused by povidone-iodine allergy.

Key Words: Povidone-iodine; Allergy; Anaphylactic shock; Cardiac arrest; Cardio-pulmonary resuscitation; Case report

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Core Tip: We report a rare case of cardiac arrest caused by povidone-iodine allergy.
representing a life-threatening complication never reported before. The patient was successfully resuscitated by 2 h of cardiopulmonary resuscitation, which suggests that a favorable outcome of prolonged cardiopulmonary resuscitation is possible.

**INTRODUCTION**

Iodophor (povidone-iodine) is an iodine complex formed by molecular iodine and polyvinylpyrrolidone (also called "povidone") in combination with surfactants[1]. Povidone-iodine is widely used clinically because of its broad-spectrum antibacterial effect[2]. Several cases of skin allergies caused by povidone-iodine have been reported, but cases of the drug-induced anaphylactic shock are extremely rare. Here, we present the first case of cardiac arrest caused by a povidone-iodine allergy. The American Heart Association recommends stopping resuscitation for patients who do not respond to at least 20 min of advanced cardiovascular life support[3]. Our pediatric patient had a postoperative infection and went into anaphylactic shock with cardiac arrest due to povidone-iodine administration during secondary surgery. She was successfully resuscitated after 2 h of cardiopulmonary resuscitation (CPR).

**CASE PRESENTATION**

**Chief complaints**

A 9-year-old girl was admitted to our hospital for treatment of postoperative infection after orthopedic surgery for a spinal deformity.

**History of present illness**

The patient was found to have spinal malformation four years ago, and then she underwent spinal orthopaedic surgery in our hospital one year ago. The patient developed wound infection a week ago and came to our hospital for further treatment.

**History of past illness**

The patient had no history of hypertension, coronary disease, or diabetes mellitus. The patient was allergic to penicillin and cephalosporins.

**Personal and family history**

Personal and family history of the patient was normal.

**Physical examination**

Findings from physical examination on admission were normal, except for presence of a slight scoliosis.

**Laboratory examinations**

Routine preoperative evaluations did not show any pre-existing abnormalities.

**Imaging examinations**

Routine preoperative evaluations did not show any pre-existing abnormalities.

**FINAL DIAGNOSIS**

We conducted a skin sensitivity test on the patient during the postoperative follow-up and found that she was indeed allergic to povidone-iodine. By reviewing the
experience of the previous surgery and anesthesia, we ruled out the possibility that this patient was allergic to the anesthetic and ancillary drugs (i.e., sevoflurane, dexmedetomidine, propofol, remifentanil, sufentanil, rocuronium, crystal liquid, hydroxyethyl starch solution, succinyl gelatin solution). In addition, when the patient underwent re-operation 1 year later, we avoided the use of povidone-iodine and the patient did not develop allergies during operation.

**TREATMENT**

**Anesthesia induction**
Postoperative infection debridement and unilateral internal fixation removal were performed under general anesthesia with tracheal intubation on March 29, 2019. After entering the operating room at 08:00, pulse oxygen saturation (SpO$_2$), electrocardiogram (ECG) and body temperature were monitored. Before general anesthesia, the patient’s blood pressure was 84/54 mmHg, heart rate was 98 beats/min, oxygen saturation was 100%, and body temperature was 36.5 °C. Anesthesia induction was performed at 08:30, with intravenous injection of sufentanil (15 µg), propofol (50 mg), and rocuronium (20 mg), followed by tracheal intubation and end-tidal CO$_2$ (ETCO$_2$) monitoring. At that time, the ETCO$_2$ was 38 mmHg and the airway peak pressure was 14 cm H$_2$O. Then, radial artery puncture and deep vein catheterization were performed for continuous invasive arterial intra-arterial blood pressure and central venous pressure (CVP) monitoring. Continuously-pumped remifentanil (at 10 µg/kg/h), dexmedetomidine (at 0.4 µg/kg/h), and sevoflurane (2%) were administered to maintain anesthesia.

**Intraoperative management**
At 09:40 during the initial operation, the surgeon disinfected the skin with dilute povidone-iodine (Batch No. 20200703S; Shanghai Likang Disinfection High-tech Co., Ltd., Shanghai, China), during which transient hypotension occurred at 56/37 mmHg and then the blood pressure returned to normal at 86/53 mmHg after treatment with 3 mg ephedrine. Subsequently, the operation was started and the blood pressure was stable. At 11:15, the surgical wound was rinsed with dilute povidone-iodine, during which the blood pressure dropped to 65/37 mmHg and the heart rate rose to 112 beats/min. The blood pressure returned to normal at 81/47 mmHg after intravenous administration of 3 mg ephedrine. At 11:42, the surgical wound was irrigated with a large amount of povidone-iodine. Suddenly, the blood pressure waveform became low and flat and the arterial pulsation became weak, with the airway pressure soaring to 30 cm H$_2$O. Suspecting anaphylactic shock caused by povidone-iodine, which would have infiltrated the blood system through the surgical wound, antiallergic treatment was given immediately by injecting 100 µg epinephrine and 40 mg methylprednisolone intravenously. Due to the non-exclusivity of anesthetic allergies, the anesthesia maintenance medications (i.e., dexmedetomidine, intravenous remifentanil and sevoflurane) were discontinued immediately, and then 2 mg midazolam was given intravenously. Even so, the patient’s condition worsened. The ECG waveform and blood pressure waveform disappeared, and the carotid pulse could not be felt. The surgeon immediately stopped the operation and closed the incision with a sterile surgical towel. CPR was performed after the patient was turned over and an injection of 1 mg epinephrine was given intravenously six times. Spontaneous circulation returned at 11:49, but cardiac arrest occurred again at 11:58. Immediately, CPR was performed again and intravenous injection of 1 mg epinephrine was given a total of 30 times. The epinephrine was pumped at 0.1-0.2 µg/kg/min, norepinephrine was pumped at 0.1-0.3 µg/kg/min and dopamine was pumped at 5-10 µg/kg/min continuously. At 12:30, the depth of anesthesia was enhanced by administering sufentanil (10 µg), midazolam (2 mg), and vecuronium (4 mg). At 13:42, spontaneous circulation returned, but was followed by cardiac arrest reoccurrence; at 13:47, spontaneous circulation returned. At that time, the patient’s blood pressure was 136/87 mmHg, heart rate was 121 beats/min, and ETCO$_2$ was 42 mmHg. After observation for about 1 h, the patient’s vital signs were stable under the maintenance of vasoactive drugs. At 14:45, the patient was turned over into the lateral position and the operation was continued, with intravenous injection of midazolam (5 mg), continuous remifentanil pumping (at 10 µg/kg/h) and inhalation of sevoflurane (2%). The surgical incision was sutured at 17:00, and the operation was completed. At 17:20, the patient was sent to the intensive care unit under endotracheal intubation for
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Table 1 Clinical features of immunoglobulin E-mediated allergy to povidone-iodine from published case reports

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Site</th>
<th>Onset delay</th>
<th>Clinical features</th>
<th>Skin testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>López Sáez et al[9], 1998</td>
<td>27</td>
<td>M</td>
<td>Skin wound</td>
<td>Immediately</td>
<td>Pruritus of the soles, generalized urticaria, facial angioedema</td>
<td>+</td>
</tr>
<tr>
<td>Adachi et al[10], 2003</td>
<td>59</td>
<td>F</td>
<td>Mucosa</td>
<td>10 min</td>
<td>Pruritus in the genital area, erythema, generalized urticaria, SAP: 40 mmHg, dyspnea</td>
<td>+</td>
</tr>
<tr>
<td>Le Pabic et al[11], 2003</td>
<td>32</td>
<td>M</td>
<td>Surgical wound</td>
<td>A few minutes</td>
<td>Anaphylactic shock and acute respiratory distress syndrome</td>
<td>+</td>
</tr>
<tr>
<td>Pedrosa et al[12], 2005</td>
<td>9</td>
<td>M</td>
<td>Skin</td>
<td>10 min</td>
<td>Urticaria, facial angioedema, dyspnea</td>
<td>+</td>
</tr>
<tr>
<td>Komericki et al[13], 2014</td>
<td>42</td>
<td>M</td>
<td>Surgical wound</td>
<td>15 min</td>
<td>Generalized urticaria, tongue swelling, SAP: 94 mmHg, moderate bronchospasm</td>
<td>+</td>
</tr>
<tr>
<td>Gray et al[14], 2013</td>
<td>12</td>
<td>F</td>
<td>Skin wound</td>
<td>Not mentioned</td>
<td>Not detailed, one previous allergy include generalized urticaria, facial angioedema and shortness of breath</td>
<td>+</td>
</tr>
<tr>
<td>Castelain et al[15], 2016</td>
<td>56</td>
<td>M</td>
<td>Knee wound</td>
<td>Immediately</td>
<td>Pruritus on the knee spreading to the whole body, generalized erythema, sweating, SAP: 70 mmHg</td>
<td>+</td>
</tr>
<tr>
<td>Moreno-Escobosa [16], 2017</td>
<td>4</td>
<td>M</td>
<td>Skin wound</td>
<td>20 min</td>
<td>Eyelids angioedema, generalized urticaria, SAP: 80 mmHg</td>
<td>+</td>
</tr>
</tbody>
</table>

*+*: Positive; *−*: Negative; F: Female; M: Male; SAP: Systolic arterial pressure.

postoperative intensive care, with continuous norepinephrine pumping (at 0.3 µg/kg/min) and epinephrine (at 0.15 µg/kg/min) intravenously. When she left the operating room, her blood pressure was 106/62 mmHg, heart rate was 98 beats/min, SpO₂ was 97%, CVP was 12 mmHg, and body temperature was 35 °C. Both pupils were equally large and round, with a diameter of approximately 3 mm. Figure 1 demonstrates the intraoperative vital signs.

OUTCOME AND FOLLOW-UP

The patient’s vital signs and general condition were stable after 4 h follow-up. The tracheal tube was removed on March 31, 2019 and the patient was discharged from the hospital on May 16, 2019. No related neurological complications were found during the 1 year of follow-up.

DISCUSSION

Povidone-iodine is an unshaped binding compound composed of iodine, povidone and surfactant that is widely used in the clinic due to its broad-spectrum antibacterial effect[2]. So far, there have been no reports on the resistance of bacteria to povidone-iodine. Rinsing or soaking with dilute povidone-iodine solution in spinal surgery is routinely used for debridement of patients with postoperative infection or trauma. Since 1998, approximately 8 cases of immunoglobulin E-mediated allergy to povidone-iodine after disinfecting skin or mucosa have been reported (Table 1). Hypersensitivity reactions to povidone are immediate[1,4]. Since the early 1980s, however, approximately 40 cases of delayed allergic reaction to povidone-iodine have been reported, for an estimated incidence of 0.4%. Nonoxynol, a surfactant, is the allergen of povidone-iodine implicated as the cause of delayed hypersensitivity reactions. Since 2010, unlike povidone-iodine (Mylan), povidone-iodine (Betadine) no longer contains nonoxynol. Delayed hypersensitivity to povidone-iodine usually manifests as contact dermatitis, and does not lead to anaphylactic shock.

From a pathophysiological point of view, anaphylactic shock is an extreme manifestation of immediate hypersensitivity. In our case, the patient suffered from anaphylactic shock due to povidone-iodine, which is considered to be an immediate allergic reaction caused by povidone. Dewachter et al[1] have shown that iodine never participates in the allergic reaction of povidone-iodine, which contrasts with our previous impression of an “iodine allergy”. Krohne et al[5] also observed this
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Figure 1. Intraoperative vital signs. DBP: Diastolic blood pressure; ETCO₂: End-tidal CO₂; HR: Heart rate; SBP: Systolic blood pressure; SpO₂: Pulse oxygen saturation.

phenomenon, and confirmed that there is no cross-reaction between different classes of iodine-containing drugs. Therefore, people allergic to iodized contrast agents are not prohibited from using povidone-iodine, and there is no evidence supporting the avoidance of iodized drugs in patients allergic to seafood. Therefore, pre-existing allergic diseases should be carefully considered during preoperative evaluation. If a patient is identified as allergic to povidone-iodine, then if povidone-iodine is necessary to irrigate the wound to avoid or treat surgical site infection, it may be replaced with vancomycin powder.

The "2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care"[6] pointed out that when ETCO₂ is less than 10 mmHg after 20 min of CPR that is, when the patient does not respond to at least 20 min of advanced life support termination of resuscitation should be considered. However, in recent years, many cases of successful CPR exceeding the traditional 20 min have been reported. Although the majority have had a poor outcome, certain successful cases with complete neurological recovery have been reported. Relevant studies have confirmed that when CPR lasts more than 20 min, the resuscitation success rate falls to 25.5% and the survival rate falls to 5.6%[7]. Considering that the patient in this case was relatively young with no underlying diseases, and the cause of cardiac arrest, anaphylactic shock, was clear and reversible, the whole rescue team chose to continue the rescue even though the CPR had lasted more than 20 min, which involved timely communication with the patient's family and their signing of an informed consent form. The patient was finally resuscitated after continuing CPR for 2 h. This case proves that the duration of CPR can be extended under appropriate circumstances.
Cardiac arrest due to complications related to surgery or anesthesia has been found to be inversely correlated with intraoperative immediate death and postoperative 3-mo mortality[5]. High-quality CPR is also considered to be one of the important factors influencing whether to prolong the duration[6]. Continuous invasive blood pressure and ETCO₂ monitoring can better guide CPR, so as to ensure the quality of CPR. During CPR in this case, ETCO₂ was mostly maintained above 20 mmHg and mean blood pressure was above 70 mmHg. In addition, blood gas analysis provides important objective evidence, and prompted our team to continue with the CPR, which can often provide a basis for predicting the outcome of patients with cardiac arrest.

CONCLUSION

In general, anaphylactic shock caused by povidone-iodine is extremely rare. Obviously, early detection of povidone-iodine allergy is very important. For patients allergic to povidone-iodine, the drug should be avoided and switched to another disinfectant agent. Constant vigilance is needed when using large amounts of povidone-iodine to irrigate a wound during operation. In this case, the ultimate disinfectant agent. Nevertheless, frequent use of large amounts of povidone-iodine may increase the risk of allergic reactions. Therefore, it is important to consider the allergy risk when choosing a disinfectant agent.

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CASE REPORT

Clinical algorithm for preventing missed diagnoses of occult cervical spine instability after acute trauma: A case report

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Author contributions: Zhu C and Yang HL conceived the study design, carried out the study, and drafted the manuscript; Im GH and Liu LM carried out the initial analyses and reviewed and revised the manuscript; Zhou CG and Song YM coordinated and supervised data collection and critically reviewed and revised the manuscript for important intellectual content; all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work; Im GH is a native English speaker and refined the language of the manuscript; Zhu C and Yang HL contributed equally to this work.

Informed consent statement: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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

CARE Checklist (2016) statement:

Abstract

BACKGROUND

Missed or delayed diagnosis of cervical spine instability after acute trauma can have catastrophic consequences for the patient, resulting in severe neurological impairment. Currently, however, there is no consensus on the optimal strategy for diagnosing occult cervical spine instability. Thus, we present a case of occult cervical spine instability and provide a clinical algorithm to aid physicians in diagnosing occult instability of the cervical spine.

CASE SUMMARY

A 57-year-old man presented with cervical spine pain and inability to stand following a severe fall from a height of 2 m. No obvious vertebral fracture or dislocation was found at the time on standard lateral X-ray, computed tomography, and magnetic resonance imaging (MRI). Subsequently, the initial surgical plan was unilateral open-door laminoplasty (C3-7) with alternative levels of centerpiece mini-plate fixation (C3, 5, and 7). However, the intraoperative C-arm fluoroscopic X-rays revealed significantly increased intervertebral space at C5-6, indicating instability at this level that was previously unrecognized on preoperative imaging. We finally performed lateral mass fixation and fusion at the C5-6 level. Looking back at the preoperative images, we found that the preoperative T2 MRI showed non-obvious high signal intensity at the C5-6 intervertebral disc and posterior interspinous ligament.

CONCLUSION

MRI of cervical spine trauma patients should be carefully reviewed to detect disco-ligamentous injury, which will lead to further cervical spine instability. In patients with highly suspected cervical spine instability indicated on MRI, lateral...
INTRODUCTION

Cervical spine instability can result from injury to vertebral bone, intervertebral disc or ligament, or other soft tissue. Investigating cervical spine instability after acute trauma is important. Missed or delayed diagnosis can have catastrophic consequences for the patient, resulting in severe neurological impairment[1,2]. Multiple radiological techniques are used to evaluate the stability of the cervical spine, such as X-ray, computed tomography (CT), and magnetic resonance imaging (MRI). Currently, however, there is no consensus on the optimal strategy for diagnosis of occult cervical spine instability. Only a few cases have been reported in the literature regarding the diagnosis and treatment of unrecognized cervical spine instability[3-5]. Here, we present a case of occult cervical spine instability and provide a clinical algorithm to aid physicians with diagnosis of occult instability of the cervical spine.

CASE PRESENTATION

Chief complaints

A 57-year-old man presented with cervical spine pain and inability to stand following a serious fall from a height of 2 m.

History of present illness

The patient had no prior history with regard to the lesion.

History of past illness

The patient had no specific history of past illness.

Personal and family history

The patient had no known personal or family medical history.

Physical examination

Physical examination revealed cervical spine tenderness and neurological deficits. He had grade 2/5 muscle strength in his right upper extremity and grade 0/5 muscle strength in his other extremities. He also had dysesthesia below bilateral C5 dermatomes.
Laboratory examinations
All ordered laboratory tests (complete blood count, basic metabolic panel, lipid panel, liver panel, coagulation tests, urinalysis, and stool analysis) were normal.

Imaging examinations
No obvious vertebral fracture or dislocation was found at the time on standard lateral X-ray, CT, and MRI (Figure 1A and B). No other injuries or comorbidities were found.

FINAL DIAGNOSIS
The patient was diagnosed with hyperextension injury of the cervical spinal cord and cervical spinal canal stenosis.

TREATMENT
The initial surgical plan was unilateral open-door laminoplasty (C3-7) with alternative levels of centerpiece mini-plate fixation (C3, 5, and 7). However, after the above procedures were completed, intraoperative C-arm fluoroscopic X-rays revealed significantly increased intervertebral space at C5-6, indicating instability at this level (Figure 1C) that was previously unrecognized on preoperative imaging. Therefore, after obtaining consent from the patient’s family, we removed the centerpiece mini-plate on C5 and then performed lateral mass fixation and fusion at the C5-6 level.

OUTCOME AND FOLLOW-UP
There were no neurological or other major surgical complications. When the patient was discharged from the hospital, he had regained some motor function in his upper extremities: grade 3/5 muscle strength in the right upper extremity and grade 2/5 muscle strength in the left upper extremity. He continued to have grade 0/5 muscle strength in his lower extremities and dysesthesia below bilateral C5 dermatomes.
Looking back at the preoperative images, we found that the MRI at the time of admission showed non-obvious high signal intensity at the C5-6 intervertebral disc and posterior interspinous ligament on T2 MRI (Figure 1B). This, in conjunction with a preoperative lateral X-ray, either under traction at the bedside or in the operating room after anesthesia and muscle relaxation prior to surgery, could have identified the occult cervical spine instability earlier rather than intraoperatively.

**DISCUSSION**

Medical history, physical examination, and multiple radiological techniques are used to diagnose instability of the cervical spine after acute traumatic injury. For patients with cervical spine tenderness and/or neurological deficit, static lateral X-ray is the first-line imaging modality for assessing obvious fractures or dislocation of the cervical spine. CT is the gold standard for detecting occult cervical spine fractures but is unable to detect instability in the cervical spine caused by injury to the intervertebral disc, ligament, or other soft tissue\[6,7\]. MRI provides detailed soft-tissue imaging but has a sensitivity of only 75% in detecting ligamentous injury\[7,8\]. Therefore, a more accurate and efficient protocol needs to be developed in order to prevent missed diagnoses of occult cervical spine instability.

Preoperative lateral X-ray under traction or after anesthesia and muscle relaxation should be used to evaluate occult instability of the cervical spine. Unlike in a standard lateral X-ray, lateral X-ray under axial traction provides the benefit of elongating the soft tissue of the neck, thus reducing muscle spasms that may obscure cervical spine instability on a standard lateral X-ray\[9\]. For patients who require concomitant trauma surgery, lateral X-ray can be obtained after anesthesia and muscle relaxation prior to surgery to assess the stability of the cervical spine. Some physicians may recommend getting flexion/extension lateral X-rays, which unlike static lateral X-rays, may detect instability of the cervical spine from a subtle disc or ligamentous injury\[10,11\]. However, the use of flexion/extension X-rays after acute cervical spine trauma is debated since this movement of the neck may aggravate the injury\[12\]. Generally, however, it is not advisable to use flexion/extension X-rays for patients with neurological deficits after acute trauma or for patients who have limited ability to flex or extend the cervical spine due to pain or muscle spasm. Therefore, we recommend a lateral X-ray under traction or after anesthesia and muscle relaxation as a safe and effective method for identifying occult cervical spine instability.

To help prevent missed diagnoses, we created a clinical algorithm to assist physicians with diagnosis of occult cervical spine instability (Figure 2). Upon patient presentation, medical history should be obtained, careful physical examination should be performed, and static lateral cervical spine X-ray, CT, and MRI should be performed to assess cervical spine instability. If lateral X-ray and CT do not show signs of cervical spine instability, but MRI suggests possible instability caused by soft-tissue

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**Figure 2** Clinical algorithm for diagnosing occult cervical spine instability. CT: Computed tomography; MRI: Magnetic resonance imaging.
injury, bedside lateral X-ray under traction needs to be performed to determine whether there is indeed instability. If the patient requires concomitant trauma surgery, lateral X-ray after anesthesia and muscle relaxation should be obtained prior to surgical incision to evaluate stability of the cervical spine. To avoid missed diagnosis, careful review of preoperative MRI and lateral X-ray under traction or after anesthesia and muscle relaxation is necessary.

CONCLUSION

MRI of cervical spine trauma should be carefully reviewed to detect disco-ligamentous injury, which leads to further cervical spine instability. In patients with highly suspected cervical spine instability indicated on MRI, lateral X-ray needs to be performed under traction or after anesthesia and muscle relaxation to avoid missed diagnosis of occult cervical instability.

REFERENCES

Carbon ion radiotherapy for synchronous choroidal melanoma and lung cancer: A case report

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Author contributions: Zhang YS and Hu TC designed the experiment; Ye YC drafted the manuscript; Han JH, Li XJ and Zhang YH collected the data; Chen WZ and Chai HY analyzed and interpreted the data; Pan X, Wang X and Yang YL wrote the article.

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Abstract

BACKGROUND
Despite being the most common intraocular malignancy among adults, choroidal melanoma is a rare cancer type, even more so when accompanied by lung cancer. We report a patient with synchronous choroid melanoma and lung cancer treated with carbon ion radiotherapy (CIRT).

CASE SUMMARY
A 41-year-old woman was transferred to our center with a diagnosis of choroidal melanoma in her right eye. During the examination, we found a right lung tumor that was histologically diagnosed as lung cancer. The patient was treated with CIRT for both malignant neoplasms. The CIRT dose was 70 photon equivalent doses (GyE) in five fractions for the right eye choroidal melanoma and 72 GyE in 16 fractions for the right lung cancer. At 3 mo after CIRT, the choroidal melanoma completely disappeared, as did the right lung cancer 7 mo after; the patient was in complete remission.

CONCLUSION
CIRT may be an effective treatment for double primary lung cancer and choroid melanoma.

Key Words: Melanoma; Lung neoplasms; Heavy ion radiotherapy; Neoplasms; Choroid neoplasms; Case report

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Uveal melanoma is the most common primary ocular malignancy among adults[1] and is treated with conventional surgery or various radiotherapy techniques[2,3]. The most common radiotherapy modalities are plaque brachytherapy and proton radiotherapy (PRT)[4-6]. However, carbon ion beams conform to the prescribed dose better than proton beams because of a sharper lateral falloff. Carbon ion beams are also biologically advantageous over PRT in treating relatively resistant tumors. Therefore, carbon ion radiotherapy (CIRT) was hypothesized to have similar or better clinical outcomes than PRT for choroidal melanoma. The National Institute of Radiological Sciences (NIRS) in Japan started using CIRT for uveal melanoma in 2001, and, as anticipated, CIRT was safe and effective[7]. CIRT is also effective with acceptable toxicity for early-stage and locally advanced non-small cell lung cancer. Moreover, it is equally safe and effective for elderly patients or patients with severe comorbidities who cannot receive surgery or chemoradiotherapy[8-10].

We present a case of concurrent choroidal melanoma and lung cancer that was successfully treated with CIRT. This report follows the CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development[11].

### CASE PRESENTATION

#### Chief complaints

A 41-year-old woman was referred to the Wuwei Heavy Ion Center in June 2020 with choroidal melanoma of her right eye.

#### History of present illness

The right eye melanoma was histologically confirmed via fine-needle aspiration biopsy at an eye hospital. Written informed consent was obtained from the patient for publication.

#### Laboratory examinations

The immunohistochemical profile was C-erbB-2 (-), CK7 (+), Ki-67 (index = 25 %), Napsin A (+), P63 (-), and TTF-1 (+).

#### Imaging examinations

Computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated that the tumor was located on the cranial side of the right eye. The patient presented with right eye malaise with gradual diminution of vision in the right eye over a period of 2 mo. After being transferred to our center, the patient's vision rapidly worsened, and she became completely blind in 15 d.

The patient underwent MRI at our hospital (3.0T; Siemens), which identified a lesion behind the right eye bulb from abnormal T1- and T2-weighted signals and high intensity on diffusion-weighted images (Figure 1). Ophthalmoscopy of the right eye showed a solid dark-gray mass in the posterior segment of the choroid with intense brown pigmentation occupying the posterior third of the vitreous chamber and mild retinal detachment at the peripheral choroidal mass rim. The mass was dome-shaped, 11.1 mm × 12.1 mm in size, and occupied a third of the posterior segment of the right eye.

#### Core Tip: Simultaneous choroidal melanoma and lung cancer are extremely rare. This report details a case of a 41-year-old woman with right-side choroidal melanoma and lung cancer treated with carbon ion radiotherapy. Seven months after treatment, the patient was in complete remission.

### INTRODUCTION

Uveal melanoma is the most common primary ocular malignancy among adults[1] and is treated with conventional surgery or various radiotherapy techniques[2,3]. The most common radiotherapy modalities are plaque brachytherapy and proton radiotherapy (PRT)[4-6]. However, carbon ion beams conform to the prescribed dose better than proton beams because of a sharper lateral falloff. Carbon ion beams are also biologically advantageous over PRT in treating relatively resistant tumors. Therefore, carbon ion radiotherapy (CIRT) was hypothesized to have similar or better clinical outcomes than PRT for choroidal melanoma. The National Institute of Radiological Sciences (NIRS) in Japan started using CIRT for uveal melanoma in 2001, and, as anticipated, CIRT was safe and effective[7]. CIRT is also effective with acceptable toxicity for early-stage and locally advanced non-small cell lung cancer. Moreover, it is equally safe and effective for elderly patients or patients with severe comorbidities who cannot receive surgery or chemoradiotherapy[8-10].

We present a case of concurrent choroidal melanoma and lung cancer that was successfully treated with CIRT. This report follows the CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development[11].
Figure 1 Magnetic resonance imaging of the right eye showed an abnormal signal shadow behind the right eye bulb, short T1 and T2 signals, and high diffusion-weighted imaging signals.

During the examination, a tumor in the lower lobe of the right lung was also observed. A multidisciplinary team discussion concluded that double primary neoplasms, ocular metastasis of lung cancer, and ocular melanoma with lung metastasis were possibilities. Subsequently, the patient underwent a lung biopsy, which indicated infiltrating acinar adenocarcinoma.

**FINAL DIAGNOSIS**

The final histologically confirmed diagnoses were: (1) choroidal melanoma of the right eye, cT2N0M0 [per the American Joint Committee on Cancer (AJCC) 8th edition]; and (2) right-sided lung cancer, infiltrating acinar adenocarcinoma, cT3N0M0, IIb (per the AJCC 8th edition), KPS: 90. CIRT for lung and eye cancer was planned after discussion with the patient and family.

**TREATMENT**

First, we treated the right eye tumor. The patient was immobilized in a supine position with a bite block device (trUpoint ARCH; CIVCO, Orange City, IA, United States) (Figure 3). A set of 1-mm thick CT images was obtained using a CT simulator. Gross tumor volume (GTV) was determined using CT images and referencing the ophthalmoscopy and MRI findings. Clinical target volume (CTV) was defined as GTV plus 1 mm, and planning target volume (PTV) was the CTV plus a 1.0-mm margin. CIRT was performed with the anterior and right lateral portals. The total prescribed dose was 70.0 photon equivalent doses (GyE) in 5 fractions (Fx; 2 Fxs from the anterior portal and 3 Fxs from the right lateral portal) once daily, five times per week (Monday to Friday). Carbon ion doses were expressed in GyE, defined as the physical dose multiplied by the relative biological effectiveness (RBE) of the carbon ions, which was assumed to be 3.0[12].

After completing CIRT for choroidal melanoma, we continued with treating the right-sided lung cancer. The patient was immobilized in the prone position using a customized vacuum cushion and chest thermoplastic mask. CT images were obtained using four-dimensional CT (4DCT) with 3-mm thick images. GTV was delineated based on the 4DCT images, CTV was defined as GTV plus 5 mm, ITV was defined as
Figure 2 Ophthalmoscopy of the right eye. A, B: Solid dark gray mass in the posterior segment (choroid) with intense brown pigmentation, occupying posterior third of the vitreous chamber along with mild retinal detachment observed at the peripheral rim of the nodular choroidal mass. The mass size of 11.11 mm × 12.1 mm.

Figure 3 Head immobilization with trUpoint.

CTV plus the tumor motion on the 4DCT images, and PTV was expanded by 5 mm based on ITV. The CIRT plan delivered 72 GyE to the target volume in 16 Fx using the broad-beam method once daily, five times per week (Monday to Friday).

CIRT was planned using the carbon ion plan (ciPlan, version 1.0; IMP, Lanzhou, China). Treatment planning included a biologic treatment plan optimization procedure using the carbon ion Treat Plan (ciTreat) (version 1.0, IMP) treatment planning software system that considers local RBE values calculated by the ciPlan software based on the mixed beam model.

Efficacy evaluation was performed based on the Response Evaluation Criteria in Solid Tumours version 1.1 guidelines. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 guidelines were used to evaluate adverse events. The Radiation Therapy Oncology Group (RTOG) acute radiation injury classification criteria were used to evaluate radiation damage. During and after CIRT, there were only grade 1 adverse events and no grade ≥ 2 RTOG acute effects.

OUTCOME AND FOLLOW-UP

Ophthalmic examination before CIRT revealed complete loss of vision in the right eye. One month after CIRT, the patient’s right eye began to perceive light and continued to gradually improve. Table 1 presents findings of the ophthalmic examination. After 3 CIRT Fxs, mild right eye edema occurred. Upon CIRT completion, MRI demonstrated that the melanoma increased, with obvious retinal detachment (Figure 4A). One month after CIRT, the choroid tumor was smaller, and the retinal detachment was resolved (Figure 4B). Three months after CIRT, the right eye choroid tumor disappeared completely, achieving complete remission (CR) (Figure 5). The patient’s right eye vision slowly returned (Table 1).
Table 1: Ophthalmic examination

<table>
<thead>
<tr>
<th>Time after CIRT</th>
<th>Right VOD</th>
<th>Right IOP, mmHg</th>
<th>Left VOD</th>
<th>Left IOP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before CIRT</td>
<td>HM/30 cm</td>
<td>9.8</td>
<td>1.0</td>
<td>16.4</td>
</tr>
<tr>
<td>1 mo after CIRT</td>
<td>Light perception</td>
<td>13.9</td>
<td>1.0</td>
<td>18.8</td>
</tr>
<tr>
<td>2 mo after CIRT</td>
<td>Hand motions</td>
<td>11.0</td>
<td>0.8</td>
<td>18.2</td>
</tr>
<tr>
<td>4 mo after CIRT</td>
<td>0.02</td>
<td>14.0</td>
<td>1.0</td>
<td>15.2</td>
</tr>
<tr>
<td>6 mo after CIRT</td>
<td>0.04</td>
<td>13.0</td>
<td>1.0</td>
<td>16.0</td>
</tr>
</tbody>
</table>

CIRT: Carbon ion radiotherapy; VOD: Vision right eye; VOS: Vision left eye; IOP: Intraocular pressure.

DISCUSSION

A middle vascular pigmented layer, including the iris, ciliary body, and choroid, comprises the uvea of the eye\(^{[13]}\), and uveal tract melanomas are anterior or posterior tract lesions. Anterior tract melanomas involve the iris, and posterior tract melanomas involve the ciliary body and the choroid layer. Malignant uveal melanomas are more common in the choroid and ciliary body than in the iris. Melanomas are highly malignant cancers\(^{[14]}\). There are several histological subgroups with various degrees of aggressive behavior and systemic metastases risk. Cytogenetic features, such as chromosome 3 monosomy and the mutations in the GNAQ and BAP1 genes, are also related to higher aggressiveness and systemic spread.
Recently, PA62 and MLH1 germline mutations were associated with a hereditary predisposition to the risk of uveal melanoma, and several other genes also have potential associations with uveal melanomas[15]. The clinical presentation of uveal melanoma relies on the mass location within the uveal tissue, size, pigmentation, associated bleeding, retinal detachment, inflammation, and extrascleral extension.
Most patients experience decreased visual acuity and blurred vision[1]. Although there are many cutting-edge treatment techniques, visual prognosis is usually poor, and many patients develop functional blindness in the affected eye. Further, metastasis to the liver and other organs is a primary cause of death despite recent advances in medical therapy[16].

Most patients with uveal melanoma undergo enucleation. Globally, a relatively small population of patients receive some form of radiotherapy. The most common radiotherapy modalities for uveal melanoma are plaque brachytherapy and PRT. Brachytherapy is effective for small-to-medium-sized uveal melanomas with thicknesses of less than 7 mm, whereas PRT is used when the uveal melanoma is larger or closer to the optic disc or fovea, taking advantage of the Bragg peak and biological profile. Neurer techniques, such as stereotactic radiosurgery with CyberKnife, achieve similar local control rates with eye retention to PRT but have a poorer post-treatment visual prognosis[17]. Carbon ion beams have unique physical and biological properties that make high-precision, high linear energy transfer (LET) radiotherapy [12]. For choroidal melanoma, high-dose radiation with excellent dose conformity is necessary for optimal results, similar to PRT and plaque brachytherapy. Therefore, we expected that CIRT was suitable for treating this tumor. Moreover, the high LET characteristics of carbon ions make it an effective treatment that is likely to achieve comparable tumor control with a lower dose than PRT. NIRS results have demonstrated that for choroidal melanoma, CIRT is at least comparable to PRT[18,19].

Multiple primary malignant neoplasms indicate the simultaneous presence of two or more primary malignancies of different histological types in the same patient, which can affect multiple tissues and organs[20]. Currently, the most accepted criteria for diagnosing primary malignant tumors are that each tumor should be histologically confirmed as malignant, occur in different parts or organs, differ regarding the histological, cytological, and morphological features and immunohistochemical phenotypes, and the possibility that one tumor is the metastasis of another must be completely excluded clinically, radiologically, and pathologically[21].

CONCLUSION

We report a case of synchronous lung cancer and choroid melanoma. Both lesions were treated with CIRT, resulting in their complete resolution. The patient is currently experiencing relapse-free survival 7 mo after completing CIRT. The treatment outcome suggests that CIRT is an effective option for synchronous double primary lung cancer and choroid melanoma, and favorable results are likely.

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734-741 [PMID: 30467928 DOI: 10.1111/cas.13890]


Heart failure as an adverse effect of infliximab for Crohn's disease: A case report and review of the literature

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Abstract

BACKGROUND
Anti-tumor necrosis factor agents were the first biologic therapy approved for the management of Crohn's disease (CD). Heart failure (HF) is a rare but potential adverse effect of these medications. The objective of this report is to describe a patient with CD who developed HF after the use of infliximab.

CASE SUMMARY
A 50-year-old woman with a history of hypertension and diabetes presented with abdominal pain, diarrhea, and weight loss. Colonoscopy and enterotomography showed ulcerations, areas of stenosis and dilation in the terminal ileum, and thickening of the intestinal wall. The patient underwent ileocolonectomy and the surgical specimen confirmed the diagnosis of stenosing CD. The patient started infliximab and azathioprine treatment to prevent post-surgical recurrence. At 6 mo after initiating infliximab therapy, the patient complained of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea that gradually worsened. Echocardiography revealed biventricular dysfunction, moderate cardiac insufficiency, an ejection fraction of 36%, and moderate pericardial effusion, consistent with HF. The cardiac disease was considered an infliximab adverse effect and the drug was discontinued. The patient received treatment with diuretics for HF and showed improvement of symptoms and cardiac function. Currently, the patient is using...
A 50-year-old woman with previous resection of the small intestine due to a stenosing CD disease, receiving treatment with infliximab, presented in the Emergency Room complaining of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea.

Chief complaints

CONCLUSION

This reported case supports the need to investigate risk factors for HF in inflammatory bowel disease patients and to consider the risk-benefit of introducing infliximab therapy in such patients presenting with HF risk factors.

Key Words: Heart failure; Infliximab; Anti-tumor necrosis factor therapy; Crohn's disease; Inflammatory bowel disease; Case report

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Core Tip: Anti-tumor necrosis factor agents were the first biologic therapy approved for the management of Crohn's disease (CD). While rare, heart failure (HF) is a potential adverse effect of these medications. In this report we describe a patient with CD who developed HF after treatment with infliximab. The clinical, diagnosis, imaging, and treatment details are all provided and discussed in this case report. This reported case supports the need to investigate risk factors for HF in inflammatory bowel disease patients and to consider the risk-benefit of introducing infliximab therapy in such patients presenting with HF risk factors.


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INTRODUCTION

Infliximab is a monoclonal antibody against tumor necrosis factor (TNF) and has revolutionized the treatment of Crohn's disease (CD)[1]. Despite its effectiveness in promoting clinical and endoscopic responses[2], the medication is not free from adverse events, such as anaphylactic reactions, increased risk of infections and neoplasms such as lymphomas, appearance of autoimmune diseases such as psoriasis and systemic lupus erythematosus, and more rarely, heart failure (HF)[3,4].

HF is a clinical syndrome resulting from structural and functional cardiac abnormalities, resulting in insufficient supply of oxygen and nutrients to tissues[5]. The prevalence of HF worldwide is 23 million people[5]. The role of TNF in the pathophysiology of HF is controversial. However, Levine et al[6] demonstrated increased serum levels of TNF in patients with advanced HF and Torre-Amione et al[7] showed that TNF levels correlate with disease severity. Furthermore, clinical studies of agents that promote TNF blockade were initially promising[8-10]. However, large-scale randomized studies were discontinued as the results showed no improvement in HF or mortality[11]. Moreover, the use of infliximab is associated with worse outcomes in some HF patients, showing that TNF blockers may exacerbate or even trigger HF[12]. The current case report describes a patient with CD who manifested HF after treatment with infliximab. In addition, the current relevant literature is reviewed.

CASE PRESENTATION

Chief complaints

A 50-year-old woman with previous resection of the small intestine due to a stenosing CD disease, receiving treatment with infliximab, presented in the Emergency Room complaining of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea.
History of present illness

In 2016, the patient presented with diarrhea with 10 liquid bowel movements/day associated with abdominal pain, nausea, vomiting, and weight loss of 25 kg over 6 mo. Physical examination revealed a 10-cm mass in the mesogastric region. Colonoscopy showed ulcerated stenosis of the ileocolic regions and the anatomopathological examination was consistent with nonspecific colitis with mild inflammatory activity. Abdominal ultrasound showed a segmental inflammatory process in the small intestine. Small bowel follow-through (Figure 1) and computed tomography enterography (Figure 2) showed irregularities in the mucosa consistent with ulcerations in the small intestine, stenosis and dilation in the terminal ileum, and thickening of the intestinal wall with hypertrophy and subserous lymphoid accumulations, suggesting chronic inflammation and consistent with fibro-stenosing CD. Due to extensive resection of the small intestine and presence of residual lesions, combined treatment with infliximab (5 mg/kg) and azathioprine (2 mg/kg/d) was chosen. Colonoscopy performed 6 mo after initiation of the treatment showed four erosions in the ileocolonic anastomosis and one ulcer in the neo-terminal ileum (Rutgeerts score i2). Due to the endoscopic observed activity, the dose of infliximab was increased to 10 mg/kg. Infliximab and anti-infliximab antibody trough levels were not available. Thirty days after infliximab dose optimization, the patient complained of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. She reported the onset of mild symptoms with progressive worsening since the introduction of infliximab.

History of past illness

The patient presented a medical history of diabetes and arterial hypertension was treated with glibenclamide, losartan, and hydrochlorothiazide.

Personal and family history

There was no family history.

Physical examination

On physical examination, the patient presented with tachypnea (26 rpm), tachycardia (116 bpm), jugular venous distension, right hypochondrial pain, hepatomegaly (3 cm), and lower limb edema.

Imaging examinations

Chest radiography showed an increase in the cardiac area. Electrocardiogram findings included sinus rhythm, signs of left atrial overload, and alteration of diffuse repolarization with strain pattern of V4-V6. Echocardiography revealed biventricular dysfunction, moderate HF, and an ejection fraction of 36%. Coronary angiography was performed, and coronary artery disease was ruled out.

FINAL DIAGNOSIS

The final diagnosis was HF as an adverse effect of infliximab therapy.

TREATMENT

The infliximab was withdrawal and furosemide was prescribed. Significant improvement in symptoms was noted after 5 d of modified treatment. The patient started treatment for HF with enalapril, carvedilol, spironolactone, and amlodipine and remained asymptomatic. A new echocardiography examination showed an ejection fraction of 42%, moderate systolic dysfunction with diffuse hypokinesia, eccentric hypertrophy, significant increase of left atrium, restrictive diastolic dysfunction, mild insufficiency of aortic and tricuspid valves, and mild pulmonary arterial hypertension (42 mmHg).
Figure 1 Small bowel follow-through showing accelerated intestinal transit. Areas of stenosis in portions of the ileum, and the ileocecal valve with filiform aspect interspersed with areas of intestinal dilation. Presence of mucous relief irregularity with "cobblestone" images due to filiform ulcerations.

OUTCOME AND FOLLOW-UP

After discontinuation of the anti-TNF therapy, the patient started exhibiting symptoms of CD activity, such as diarrhea, abdominal pain, fatigue, and weight loss. The patient then started treatment for CD with anti-IL-23 (investigational product) with significant improvement of symptoms. Currently, she has three evacuations per day with no bleeding or abdominal pain. Colonoscopy showed more than five aphthous ulcers < 5 mm each in the neo-terminal ileum without lesions in the anastomosis (Rutgeerts score i2). The patient will undergo a new colonoscopy after one year of therapy.

DISCUSSION

Treatment of CD aims for clinical and endoscopic remission and includes the use of antibiotics, steroids, immunosuppressants, and biological therapies including anti-TNF, anti-integrin, and anti-interleukin agents[13,14]. Anti-TNF agents include infliximab, adalimumab, and certolizumab[2] and are indicated in patients refractory or intolerant to corticosteroids, thiopurines, and methotrexate.

The choice of the drug should take into account the location, activity, and severity of the disease, response to previous therapies, presence of complications, medication efficacy, and development of side effects, in addition to the presence of extra-intestinal manifestations[13,15]. Individual patient characteristics, such as preference for route of administration, costs, and risk benefit of the drugs, should also be assessed[13,15]. In the current reported case, infliximab combined with azathioprine was chosen as the
Figure 2 Computed tomography enterography. Mucosal irregularities consistent with ulcerations in the small intestine, stenosis and dilation in the terminal ileum, and thickening of the intestinal wall with hypervascularity of the mesentery and vascular dilatation (comb sign).

Figure 3 Surgical specimen measuring 70 cm showing severe disease with thickening of the ileum associated with ulcerations, stenosis, and dilation and mesenteric infiltration.

A therapeutic option, taking into account access to medication and the patient's preference for intravenous administration. These drugs were provided by the state's high-cost drug dispensing program[16].
Anti-TNF agents have good long-term safety profiles[17]. Contraindications for their use include the presence of active infection, demyelinating disease, cancer, and HF [absolute in the New York Heart Association (NYHA) Functional Classification NYHA III-IV and relative in NYHA II][18,19]. The patient in the current report had risk factors for the development of cardiovascular disease, such as hypertension and diabetes, but had no previous diagnosis or symptoms suggesting HF at the time that infliximab was prescribed. The patient had no previous echocardiogram. The consensus regarding the treatment of inflammatory bowel disease (IBD)[14,20] does not recommend screening or assessment of cardiac function before initiating anti-TNF therapy. According to the American Heart Failure guidelines[21], there is evidence supporting the use of brain natriuretic peptides (BNP) to aid in the diagnosis or exclusion of HF as a cause of symptoms. These biomarkers are increasingly being used in population screening to detect incident HF, despite not having a formal recommendation[21] or being available for use in clinical practice.

The ATTACH (Anti-TNF Therapy Against Congestive Heart failure) trial[3] evaluated the efficacy and safety of infliximab in patients with moderate to severe HF (NYHA classes III and IV). The study found that symptoms worsened and concluded that short-term TNF-α antagonism did not demonstrate a benefit and was associated with greater occurrence of adverse events and mortality. Therefore, their use is not indicated under these conditions. Kwon et al.[22] followed patients with rheumatoid arthritis, psoriatic arthritis, and CD that were treated with anti-TNF (etanercept or infliximab) and observed 47 patients who developed HF, of which 81% had no previous symptoms and 19% had worsening of preexisting symptoms. Among those who developed HF, 50% did not have risk factors, such as myocardial infarction, coronary disease, hypertension, or diabetes[22]. The average interval between the first anti-TNF infusion and diagnosis of HF was 3.5 mo (24 h to 24 mo)[22]. The mean age of the patients was 62 years[22], demonstrating that HF can manifest at any time during the use of the medication, even in patients without a diagnosis or previous symptoms. In our current case, we observed clinical and echocardiographic manifestations of HF 8 mo after the first infusion of infliximab, despite reports of symptoms beginning since the first infusion. However, the symptoms were mild and not considered by the patient after the first infusion. She only reported symptoms when they became disabling after the dose of the medication was increased.

Studies have sought to clarify the precise role of TNF-α in the regulation of cardiac function in patients with IBD, especially in the progression of HF[23]. The biological activity of TNF-α seems to be related to its serum concentration. At low levels, it induces local inflammation with the expression of adhesion molecules and stimulates the production of IL-1. At an increased level, systemic effects can be observed, such as fever, increases in acute phase reagents, cachexia, hypotension, and cardiovascular collapse[18]. Its intracellular effects occur by binding to two membrane receptors, TNF receptors 1 and 2 (TNFR1 and TNFR2)[24]. TNFR1 is expressed in most cells of the immune system and other systems, such as the heart, and mediates pro-inflammatory and pro-apoptotic signals[18]. In contrast, TNFR2 is found in hematopoietic and endothelial cells and is related to survival pathways[18]. There is also induction of complement-dependent and antibody-dependent cytotoxicity through the binding to
Reverse signaling is another mechanism responsible for the cardiotoxic effects of TNF-α. Transmembrane TNF produced by cardiac cells functions as a receptor for anti-TNF agents, which serves as a signal for the production of more TNF-α in the tissue and thereby increases cardiotoxicity[28,29]. Therefore, drug-induced HF should be suspected in patients who develop HF after receiving any anti-TNF therapy and discontinuation of medication is recommended in these cases[26]. In a meta-analysis conducted by Kwon et al.[22], ten patients under 50 years of age who developed HF after the use of anti-TNF were evaluated. Of these patients, nine discontinued the medication, three presented complete HF resolution, six presented partial improvement, and one died. In the current case, infliximab was discontinued, and diuretic therapy was initiated for HF treatment. The patient showed improvement of symptoms and echocardiographic parameters after discontinuation of the anti-TNF; however, complete recovery of cardiac function was not achieved.

The mechanism by which infliximab causes HF in patients with CD remains uncertain. As such adverse events in populations using these medications are under-reported, it is difficult to infer a causal relationship. Attention should be paid to the recent development or exacerbation of HF in patients who have started anti-TNF therapy. Should this occur, biological therapy with another mechanism of action should be considered.

We believe that the reported patient probably had previous asymptomatic cardiac structural damage, related to presented risk factors such as diabetes mellitus and arterial hypertension, characterizing stage B of AHA/ACC classification[30]. With exposure to infliximab, especially after dose optimization to 10 mg/kg, HF decompensation could be observed. Thus, we could assume that exposure to infliximab was the main causal factor related to the onset of acute HF in this patient, who probably had previous structural heart disease.

Patients with symptomatic HF are classified as having AHA/ACC C or D stage, and their symptoms are qualified according to a symptomatic score, with NYHA being the most used score of them[30]. In patients with severe symptomatic HF NYHA III and IV, the recommendation is to avoid use of infliximab[18,19]. In patients with HF and mild symptoms (NYHA I and II), who worsen after using infliximab, it is recommended to discontinue the medication to assess cardiac function and to start the adequate treatment for the cardiac condition. However, there are no recommendations for asymptomatic patients, in AHA/ACC stages A or B. Stage A of the AHA/ACC classification includes patients at increased risk of developing HF but without cardiac damage or any cardiac symptoms. Stage B comprises patients with structural or functional cardiac damage, but asymptomatic[30].

We recommend for patients in AHA/ACC stage A who are indicated to use infliximab: (1) Pre-treatment basal BNP dosage; (2) Strict control of associated comorbidities such as diabetes mellitus, arterial hypertension, and coronary artery disease; (3) Close monitoring of signs and symptoms of HF after starting treatment with infliximab; and (4) Infliximab concentration monitoring and dose correction according to the therapeutic target.

The recommendations for patients in stage B of the AHA/ACC are: (1) Pretreatment echocardiography in patients with baseline BNP levels above the reference value for outpatients; (2) If echocardiography (current or previous < 5 years) is normal or with minimal change, the recommendations are the same for patients in stage A of the AHA/ACC, as detailed above; and (3) If echocardiography (current or previous) shows signs of structural and/or functional heart disease, it is recommended to start infliximab after adequate control of comorbidities, and introduction and dose adjustment of beta-blockers and angiotensin converting enzyme inhibitors or angiotensin receptor blockers. In addition, it is recommended to avoid other medications that potentially cause HF decompensation, use dose of 5 mg/kg for infliximab, other specialties medical monitoring, and strictly monitor signs and symptoms of HF. We also emphasize the need for further studies on this topic.

In the present case, other possible causal factors of HF have been ruled out. Chagasic myocarditis, an endemic disease in Latin America caused by infection by Trypanosoma cruzi, was ruled out by Chagas negative serology and the absence of
electrocardiographic findings of the disease such as conduction disorders, low QRS voltage, arrhythmias, and changes in the QT interval[31]. Viral myocarditis is an important differential diagnosis in the face of acute HF in an immunosuppressed patient. However, the patient did not present infectious symptoms, common in this type of infection, and there was an improvement with the suspension of anti-TNF.

Conomyocardial biopsy, indicated for confirmation of viral myocarditis, was not performed due to the absence of criteria for the procedure, such as the presence of ventricular arrhythmias or atrioventricular block, hemodynamic instability, or lack of therapeutic response[32]. The acute coronary syndrome was excluded through cardiac catheterization.

**CONCLUSION**

The reported case supports the need to investigate risk factors for HF in IBD patients and to consider the risk-benefit of introducing anti-TNF therapy in such patients presenting HF risk factors.

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