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OPINION REVIEW

Collagen matrix scaffolds: Future perspectives for the management of chronic liver diseases

Moises Martinez-Castillo, Itzel Altamirano-Mendoza, Rafal Zielinski, Waldemar Priebe, Cristina Piña-Barba, Gabriela Gutierrez-Reyes

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Abstract

Approximately 1.5 billion chronic liver disease (CLD) cases have been estimated worldwide, encompassing a wide range of liver damage severities. Moreover, liver disease causes approximately 1.75 million deaths per year. CLD is typically characterized by the silent and progressive deterioration of liver parenchyma due to an incessant inflammatory process, cell death, over deposition of extracellular matrix proteins, and dysregulated regeneration. Overall, these processes impair the correct function of this vital organ. Cirrhosis and liver cancer are the main complications of CLD, which accounts for 3.5% of all deaths worldwide. Liver transplantation is the optimal therapeutic option for advanced liver damage. The liver is one of the most common organs transplanted; however, only 10% of liver transplants are successful. In this context, regenerative medicine has made significant progress in the design of biomaterials, such as collagen matrix scaffolds, to address the limitations of organ transplantation (*e.g.*, low donation rates and biocompatibility). Thus, it remains crucial to continue with experimental and clinical studies to validate the use of collagen matrix scaffolds in liver disease.

Key Words: Liver; Chronic liver disease; Collagen matrix scaffold; Transplant; Management

Core Tip: The relevance of this review-opinion focuses on new strategies of regenerative medicine and the use of collagen matrix scaffolds as an option in the field of chronic liver disease (fibrosis/cirrhosis and hepatocellular carcinoma). Collagen matrix scaffold can be used as a niche for native or stem cells and as a carrier for antineoplastic drugs; these strategies exhibit the potential to restore liver function and address problems associated with the scarcity of organ donors.

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INTRODUCTION

Chronic liver disease (CLD) constitutes a complex health problem, as it can be induced by various factors, including hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol abuse and nonalcoholic fatty liver disease (NAFLD), among other genetic and autoimmune conditions[1,2]. In the last 50 years, several advances have been made in the field of CLD, including the development of vaccines and antiviral regimens against viral hepatitis (HBV and HCV, respectively)[3]. Vaccination and antiviral treatment programs have reduced HBV incidence and its complications[4]. Moreover, patients with chronic HCV can be treated with direct-acting antiviral agents (DAAs)[5]. The World Health Organization (WHO) estimates that HCV will be eradicated by 2030; however, less than 10% of HCV-infected individuals have successfully completed treatment since the introduction of DAAs in 2014[6,7]. Furthermore, reactivation of HBV after treatment with DAAs has been reported, and some patients who initially showed complete elimination of HCV by DAA exhibited progressive liver damage and developed cirrhosis or liver cancer[8,9]. On the other hand, for patients with alcoholic liver cirrhosis, liver transplantation (LT) remains the only therapeutic option[10]. Stringent clinical and social criteria must be fulfilled to qualify for the transplant, which significantly impacts the life expectation[10]. NAFLD and nonalcoholic steatohepatitis (NASH) are also considered growing health problems[11]. In fact, complex NAFLD/NASH is among the top causes of hepatocellular carcinoma (HCC) in the United States, whereas NASH is the second most common indication for LT in the United States[12].

Regenerative medicine represents a promising approach in the field of tissue damage restoration and organ transplantation. Typically, tissue-engineered grafts consist mainly of three elements: scaffolds (or templates), stem cells, and growth-stimulating factors[13]. The scaffolds play a fundamental role as structural support for cell attachment, survival, and proliferation. Thus, its structure and biological and physiochemical properties must be compatible with the organ or tissue without the risk of chronic inflammation and rejection. Additionally, the ideal scaffold needs to be biodegradable and mimic the shape and function of the specific organ[14,15]. At present, several biomaterials have been reported as suitable scaffolds, including natural and synthetic polymers (*e.g.*, polylactic acid, polyglycolic acid, and polycaprolactone)[16]. Natural biomaterial that have been modeled include collagen, fibrin, laminin, and fibronectin, which are components of the extracellular matrix (ECM). Collagen is the protein of choice during the construction of synthetic and natural scaffolds, showing great biocompatibility and minimal immunogenicity. Furthermore, this protein can be degraded by the host[15,17]. It is important to mention that the generation of extracellular matrix scaffolds (EMSs) involves lyophilization and/or electrospinning methods; thus, the associated physical or chemical treatments may affect the native properties of collagen[14]. The decellularization process is another strategy for obtaining an intact EMS. This process has gained great traction; however, it needs an organ source, which requires an allogenic or xenogeneic donor[16,18,19]. After retrieval, the organ is processed by physical (*e.g.*, sonication, pressure gradient), chemical (*e.g.*, detergents, acidic or basic solutions) or biological treatments (*e.g.*, enzymes, such as trypsin and dispase) that may interfere with the compatibility and stability of the biomaterial [16]. Recently, the production of a collagen matrix scaffold (CMS) from the bone matrix after a demineralization process was described in the literature, which does not imply aggressive treatments[15,20,21]. A few studies have been conducted using ECM as a strategy to restore normal organ function in cirrhosis and HCC[18,19,22,23]. It is important to mention that the regenerative capacity of the liver can be inhibited by the excessive accumulation of ECM because it can reduce the area for liver parenchymal cell proliferation[15]. Additionally, studies in animal models have shown that stem cell transplantation promotes hepatocyte proliferation and improves liver function[24,25]. In preclinical studies, the infusion of mesenchymal stem cells (MSCs) is typically achieved by intravenous, intraarterial, intraperitoneal,

intraportal, or intrasplenic routes; consequently, the number of cells and doses required are uncertain [25]. It is possible that CMS could be used as a vehicle for the direct administration of MSCs[25,26]. Moreover, the implantation of CMS after the surgical extraction of partial tissue can function as an anchor for hepatocyte proliferation, thus improving organ function[15].

Overview of the management and LT for CLDs

Although therapeutic options largely depend on the underlying cause of liver disease, there are few proven effective treatments for advanced stages[27]. In recent years, DAAs have transformed the treatment of HCV in patients with advanced fibrosis or compensated cirrhosis. For instance, it has been shown that a long-term sustained viral response (SVR) is associated with a significant decrease in liver tissue collagen content and even regression of fibrosis in greater than 60% of patients[28]. However, the impact of such treatment in patients with decompensated cirrhosis is limited, achieving only marginal improvements[29]. The incidence of HCV-related decompensated cirrhosis and HCC are expected to decrease due to the advent of DAAs[30]. Despite these promising results, a large group of patients will still be at risk of developing HCC even after SVR has been achieved. These patients will continue to represent potential candidates for LT. Untreated HCV prior to LT results in universal recurrence of allograft infection, accelerated liver fibrosis, and subsequent graft failure[31]. The recurrence of HCV infection is universal in patients with detectable HCV RNA at the time of LT. Of the total number of recipients with post-transplantation HCV recurrence, one-third will develop cirrhosis within 5 years of LT in the absence of antiviral treatment[32]. Graft survival is lower in HCV patients compared with noninfected recipients due to various factors, such as HCV recurrences, extrahepatic manifestations of HCV infection, management issues, and complications of immunosuppression[33,34]. Complete abstinence from alcohol consumption is the cornerstone in the management of every spectrum of alcoholic liver disease (ALD)[35]. However, there are several factors that make abstinence difficult to achieve, such as lack of social support, psychiatric comorbidities, polysubstance abuse, environmental influences, and family history of alcoholism[36]. On the other hand, dietary and physical approaches are the mainstay of the management of NAFLD[37]. The amount of weight loss considered to be an effective therapeutic option is achievable in trial settings but is challenging in the clinical environment[38]. To date, several new therapeutic targets have been proposed, leading to new pharmacological therapies being tested for ALD and NAFLD; however, the majority have not been approved or evaluated in advanced liver disease[39,40].

LT is the most effective therapeutic option for patients with end-stage liver disease[41]. The procedure is typically justified in liver failure, decompensated cirrhosis (MELD ≥ 15), and/or HCC[31,35,37,41,42]. In cirrhosis, survival after LT is restricted to patients with advanced decompensation, whereas LT does not improve survival of patients with intermediate disease severity[37,43,44]. Recently, an unequivocal survival increment was demonstrated in patients with alcoholic hepatitis not responding to medical therapy compared with patients who received early transplantation[35,41,45]. However, LT is not a formal indication in all transplant centers, especially in the United States[46]. Typically, a 6-mo period of abstinence is required to identify ALD patients who will be able to refrain from alcohol consumption and not relapse after LT. However, this criterion is not mandatory in some organizations, such as the United Network for Organ Sharing, International LT Society, European Association for the Study of the Liver, and American College of Gastroenterology[35,41]. Although the requirements are changing worldwide, the number of donors is not enough to meet the demand for patients waiting for transplant. LT during end-stage liver disease related to NAFLD represents a challenge due to the high incidence of associated comorbid diseases, such as obesity, type 2 diabetes, and hypertension, with 50% of patients with BMI > 35 kg/m^2 dying within the 1st year of transplantation [47,48]. However, an upper limit of BMI that contraindicates the procedure has not been identified[49]. The post-transplant survival in NAFLD is significantly higher than that in HCV (5-year survival: NAFLD 77.81% *vs* HCV 72.15%)[50]. Although quality of life and liver function improve in patients after LT, both decrease with time[51]. For instance, in a meta-analysis, the mean 1-, 3-, and 5-year incidence rates of recurrent and de novo NAFLD after LT were 59%, 57%, and 82% as well as 67%, 40%, and 78%, respectively[52]. Nonetheless, it has been demonstrated that the prevalence of advanced fibrosis is low after LT with values of 2%–5% at 5 years, 5%–10% at 10 years, and up to 24% reported in one of the studies that followed the patients up to 15 years[53-56]. In contrast, the recurrence of alcoholic cirrhosis was responsible for approximately 90% of deaths in recipients who resumed abusive alcohol drinking [41]. Transplant recipients have a higher incidence of cardiovascular events and neoplastic diseases. The risk of de novo malignancies increases from 6% before LT to 55% by 15 years post-LT[57]. The incidence of de novo tumors as a cause of death was at least twofold higher in patients transplanted for ALD compared to other indications[58]. Additionally, tobacco use has been particularly associated with this increased risk[58]. In addition to host factors, immunosuppression is an important contributing factor for developing malignancies. NAFLD carries an increased risk of death from cardiovascular complications and sepsis[59,60]. Screening for neoplastic and cardiovascular diseases during the transplant evaluation process is crucial[35,37,41,49]. Although the number of patients waiting for LT is expected to increase, donor availability is predicted to decrease, highlighting the demand for new therapeutic options for CLD[20,60].

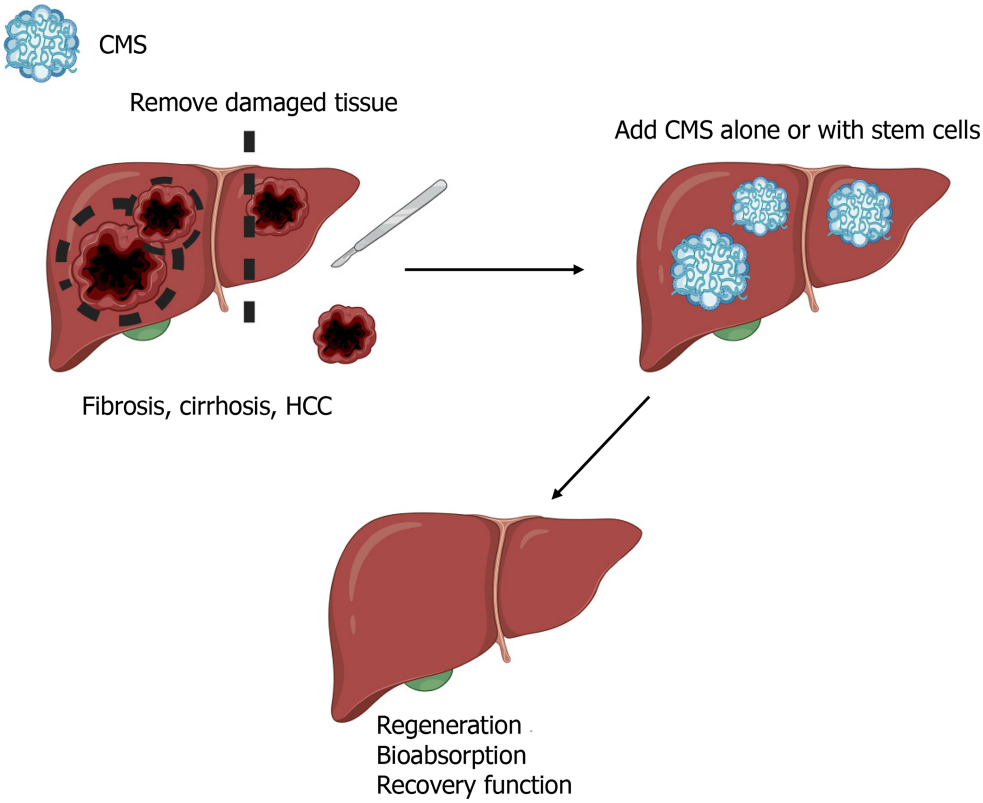

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Figure 1 Collagen matrix scaffold implantation in chronic liver disease. A: Identification and extirpation of zones with excessive damaged tissue at early or advanced stages of chronic liver disease; B: Implantation of a collagen matrix scaffold (CMS) that mimics normal liver tissue alone or in combination with mesenchymal stem cells; C: Restoration and normal function and subsequent natural elimination of CMS by the host.

CMSs and the liver

It is well understood that the main sources of fibrillar collagens in the liver are hepatic stellate cells[61]. The use of exogenous collagen during liver disease is an unconventional idea because the liver has the capability to produce and degrade its own ECM compounds[61,62]. However, it is important to highlight that dysregulation of collagen synthesis occurs in patients with liver disease and is especially marked in later stages[61-63]. For this reason, the use of CMS made with the same collagens that are present in the healthy liver could delay the progression of liver disease[15,20]. The use of CMS as a niche for liver cells was recently investigated, and positive results were revealed[15]. The authors demonstrated that CMS from bovine condyles does not cause rejection or exacerbate the inflammatory response; moreover, they demonstrated that cells like-hepatocytes, grew in the CMS. After 21 d, this biomaterial showed natural biodegradation. Nevertheless, the cellular and biological processes were not examined[15,20]. Liver regeneration has been associated with the presence of hepatic progenitor cells and a plethora of other signaling mechanisms[64,65]; however, control over regeneration is lost in CLD [65]. The allosteric effect of excessive production of ECM has been suggested as a possible mechanism that inhibits proliferation; moreover, the ratio of proliferation and apoptosis is dysregulated in advanced CLD[15,66]. The use of stem cells for tissue regeneration has been explored in several organs and tissues, but it remains an important challenge in the liver[25]. However, recent in vitro studies of human stem cells seeded in CMS have been published, showing that CMS is a good niche for this type of cells[25]. Furthermore, the use of CMS alone or in combination with MSCs can be used to restart or improve regeneration and organ function (Figure 1).

Use of CMSs to study cirrhosis

Liver cirrhosis is among the top 20 causes of disability-adjusted life years and years of life lost worldwide[67]. The incidence of liver cirrhosis is rapidly increasing worldwide, and the currently available treatment is suboptimal[68]. At present, the most effective therapeutic option is LT[41]. However, the lifelong consequences of transplantation and the scarcity of donors limits patient eligibility[69]. This leads to poor quality of life and eventually to death. Patients with cirrhosis have disease-related barriers preventing liver regeneration, but novel strategies, such as scaffolds, have driven progress toward the development of successful therapies for this condition[70,71]. In a CCl4-induced cirrhosis rat model, a comparative evaluation indicated that the group that underwent implantation of scaffolds with cultured hepatocytes displayed a better long-term recovery of liver

function than the group with direct infusion of liver cells[72]. Moreover, in the same study, the authors reported better outcomes regarding liver function in the group that underwent implantation of the scaffold cultured *in vitro* with hepatocytes compared to the cell-free scaffold group[72]. The ECM is an important regulator of liver fibrogenesis[73]. It is well known that ECM proteins have an immunomodulatory role in the liver disease microenvironment, leading to the chemotaxis of leukocytes; modulation of growth factor and cytokine functions, such as TGF-β1 and TNF-α, fibroblast migration; and some anti-inflammatory responses[62,73,74]. Recently, ECM proteins were described as prognostic biomarkers of early-stage cirrhosis[75]. Given the role of the ECM in disease progression, the incorporation of scaffolds as models *in vitro* is essential in creating the appropriate microenvironment that allows investigation of underlying pathological mechanisms and/or testing new therapies. In this context, cirrhotic human 3D liver scaffolds have been obtained through a decellularization process[76]. The cirrhotic 3D scaffold was used as a novel model to evaluate the inherent features of cirrhotic human liver and the ECM microenvironment, including the efficient homing and targeting of cells to their correct localization[19,76].

CMSs in liver cancer

HCC is among the principal causes of cancer deaths worldwide[23]. The liver parenchyma in HCC typically exhibits necrosis, inflammation, oxidative stress, and a dysregulated ECM. These events are related to genetic alterations and deregulation of multiple signaling pathways[66,77-79]. LT, resection, novel thermal and nonthermal techniques for tumor ablation and embolization are the preferred strategies to treat HCC[23]. Moreover, only a few pharmacological options (*e.g.*, bevacizumab, cabozantinib, lenvatinib, ramucirumab, regorafenib, and sorafenib), immunotherapy (*e.g.*, atezolizumab, nivolumab, and pembrolizumab), and radiation therapy (*e.g.*, conformal, stereotactic and proton beam radiation) have been used in the treatment of HCC, and these treatments are typically reserved for the advanced phase of HCC with limited success[23]. The study of HCC includes cell lines (*e.g.*, HEP-G2, HEPA 1-6, HuH7, SK-HEP-1, Hep3B)[80,81] and animal models (*e.g.*, orthotopic and xenotransplantation)[82,83]. Moreover, decellularized tumors have been proposed as a strategy of study[22]. Recently, decellularization of liver explants from human cirrhotic liver tissue (explant primary sclerosing cholangitis; cirrhotic 3D scaffolds) were used for the first time as a model for the evaluation of HCC[76]. Immunohistochemical staining showed that collagen types I, III and IV; fibronectin; and laminin were present after the decellularization process. The authors also compared the expression of different proteins after seeding Hep-G2 cells in cirrhotic 3D scaffolds[76]. Interestingly, their results showed that cell repopulation of cirrhotic scaffolds highlighted a unique upregulation in genes related to epithelial to mesenchymal transition and TGFβ signaling. Moreover, higher concentrations of TGFβ1 and fibronectin were produced by seed cells in cirrhotic scaffolds than in healthy scaffolds. This methodology allowed the authors to evaluate the microenvironment in HCC and healthy ECM from the liver with the possibility of identifying new potential therapeutic targets for drug development[76].

The ECM plays a pivotal role from the beginning of tumorigenesis to metastasis. Collagen, fibronectin and laminin can induce intracellular signaling that participates in apoptosis evasion, metastasis, angiogenesis, and proliferation[62]. Nevertheless, opposing results regarding the role of the ECM in tumor progression have been reported. Specifically, in pancreatic tumors, ECM composition inhibits tumor progression, whereas an increase in the deposition of ECM stimulates tumor progression in breast cancer. Thus, the role of ECM may depend on the cancer type[62]. Collagen synthesis increases in severe liver fibrosis (F3 and F4) compared with a healthy liver (fibrillar collagen types I, III and V)[84,85]. In fact, collagen and other ECM proteins are used as biomarkers to determine the stage of fibrosis and as predictors of cancer development[73,86,87]. It is possible that the use of CMS containing similar collagen to healthy livers from human or other mammal sources (such as ®Nukbone) improves the regeneration process. The use of CMS as support alone or in combination with HCC cell lines represents an excellent strategy for: (1) The evaluation of therapeutic drugs, including assessments of the IC_{50}, stability and the diffusion ratio[26,88,89]; (2) Implantation of CMS plus HCC cells in animals to evaluate the progression of HCC in situ and/or as a metastasis model; and (3) Tumor ablation and implantation of CMS impregnated with antineoplastic drugs to ensure elimination of all malignant cells to reduce recurrence (Figure 2)[88].

Challenges and limitations of CMSs in CLD

In a general context, the collagen used during CMS design is commonly derived from bovine, porcine, rodent, human, and marine sources, which are commercially available[90,91]. Collagen obtained from these sources exhibits differences in primary amino acid sequence, and it has been estimated that approximately 3% of the population is allergic to bovine collagen I[91-93]. Human collagen is the ideal source of collagen to eliminate certain concerns associated with xenogeneic sources, but the mass production of recombinant collagen is unsustainably expensive. Furthermore, the synthesis of hybrid collagen matrices has been proposed as a method to extract and purify collagen and modify its mechanical properties. Another important consideration is that during the creation of CMSs, the fiber arrangement/alignment is not equal to native disposition (anisotropic)[17]. However, this last concern seems to be eliminated with the incorporation of new strategies, such as CMS from Nukbone®[15,20,94]. Despite the disadvantages mentioned, collagen from bovine and porcine sources is widely and

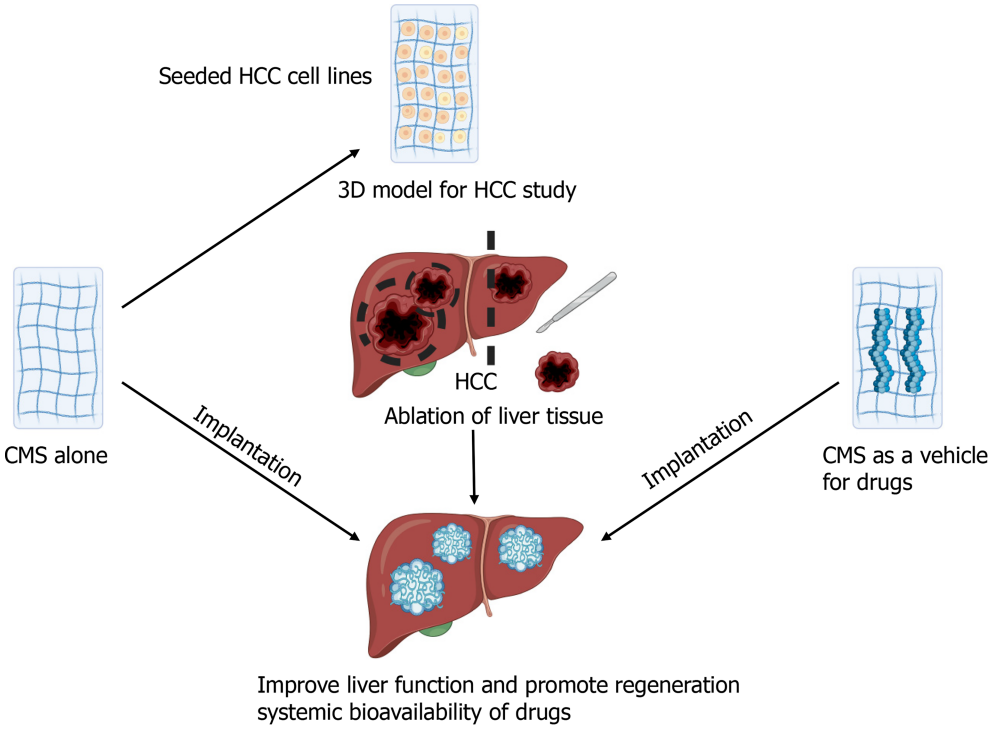

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Figure 2 Collagen matrix scaffold implantation in hepatocellular carcinoma. Collagen matrix scaffold (CMS) can be used alone or in combination with hepatocellular carcinoma cell lines (*e.g.*, HEP-G2 and/or HuH7) as a 3D model. Resection of tumor- or liver-damaged tissue and subsequent implantation of CMS alone or impregnated with antineoplastic drugs can be used to evaluate drug bioavailability and improve liver function.

successfully used in clinical settings[95,96] (Figure 3).

It is important to mention that the predominant type of collagen in healthy liver is collagen I, III and V, whereas the dysregulation of several collagens has been reported during liver disease progression induced by different factors[86]. In this sense, it was reported that patients with ALD displayed higher levels of type III collagen in the cirrhosis stage than healthy controls[97]. Moreover, collagen III formation progressively supersedes the degradation of this type of collagen. However, increased collagen VI degradation compared with synthesis (PRO-C3) was noted in the same stages[97]. In a similar manner, PRO-C3 (marker of synthesis) allowed discrimination of F3 and F4 in NAFLD, and the results revealed superior ROCs at this stage compared with the aspartate aminotransferase to platelet ratio index, FIB-4, and NAFLD fibrosis score[98]. In addition, collagens III, IV, V, and VI showed significant increases from early to late fibrosis (F4 or cirrhosis) in hepatitis C. Collagen IV was the most useful discriminator between early and late stages, whereas collagen V and VI showed the strongest expression in early fibrosis stages[99]. Taken together, these studies provide evidence that the synthesis and degradation of collagens is not a static process. The extirpation of liver zones with excessive deposition of atypical collagens followed by the implantation of CMS that mimics normal liver tissue collagen, such as CMS from Nukbone®, could improve and restore normal liver function[15]. However, it is important to research the implications of the use of different types of collagen in the context of CLD and CMS during fibrosis, cirrhosis, and HCC induced by the different etiologies.

CONCLUSION

The use of CMS in CLD is a promising tissue engineering strategy to recover liver function. It avoids the use of organs from donors and, thus, also sidesteps the transplant waiting list, compatibility issues, pre- and postoperative care (immunosuppression), and other ethical considerations. The use of CMS also represents an exciting and important, novel tool for the development and evaluation of pharmacological options for cirrhosis and HCC. Furthermore, CMS could even be developed in the future as a treatment targeting the early stages of liver disease, including fibrosis.

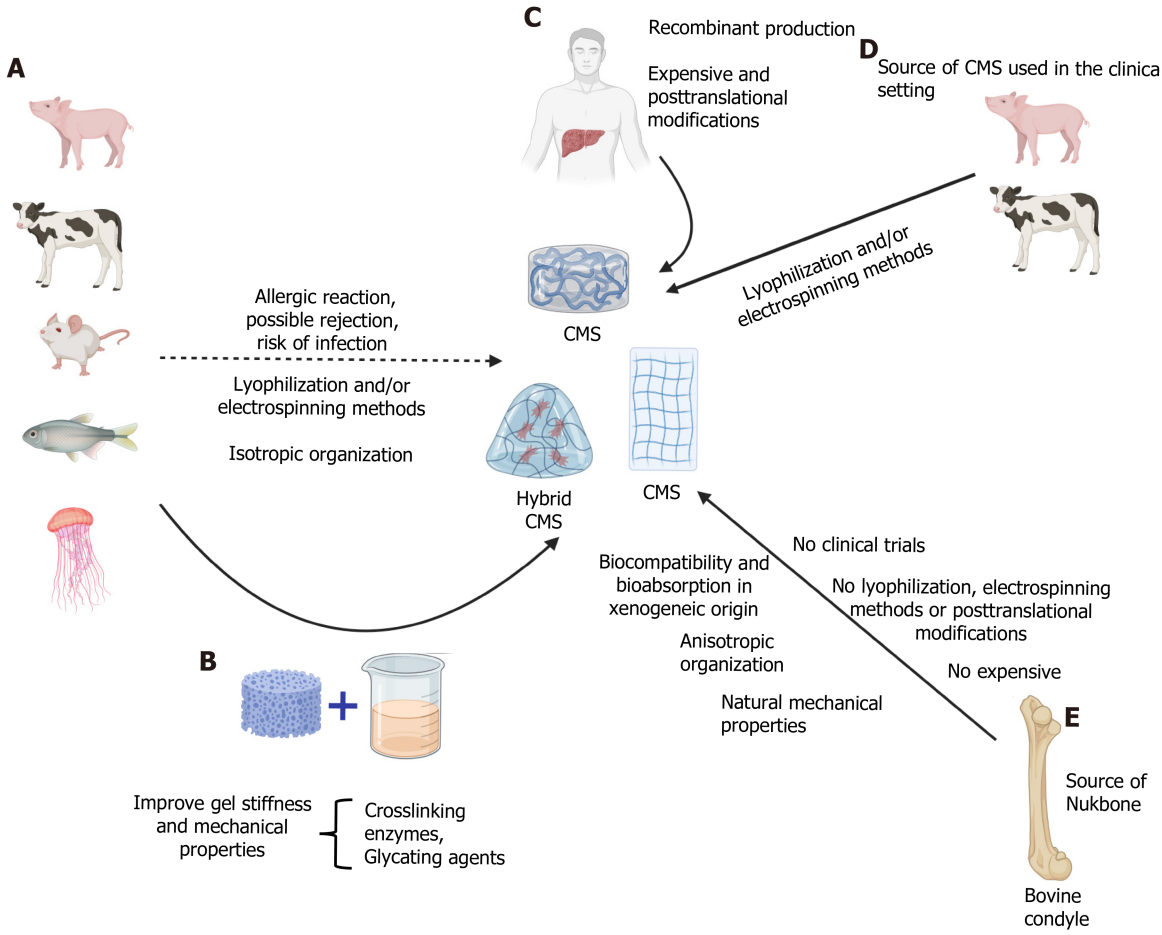

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Figure 3 Challenges and limitations of collagen matrix scaffolds. A: Xenogeneic sources of collagen promote allergic reactions, rejection or risk of infections (*e.g.*, bovine spongiform encephalopathy). Lyophilization and/or electrospinning methods are used to obtain collagen matrix scaffold (CMS), which alter their natural properties, including isotropic organization; B: Hybrid collagen matrices using crosslinking enzymes (*e.g.*, lysyl oxidase and transglutaminase) and glycating agents (high concentrations of ribose) to improve mechanical properties and stiffness; C: The production of human recombinant collagen is expensive, and current recombinant systems lack native prolyl 4-hydroxylase activity; D: The available sources of CMS are obtained from bovines and pigs using lyophilization and/or electrospinning methods; E: Nukbone obtained from bovine condyles as a CMS source showed great advantages; however, it is important to validate its use in clinical trials. The next step of CMS is explored in the context of the different stages of chronic liver disease induced by distinct liver insults.

FOOTNOTES

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MINIREVIEWS

Sex dimorphism and metabolic profiles in management of metabolic-associated fatty liver disease

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Abstract

Metabolic-associated fatty liver disease (MAFLD) refers to the build-up of fat in the liver associated with metabolic dysfunction and has been estimated to affect a quarter of the population worldwide. Although metabolism is highly influenced by the effects of sex hormones, studies of sex differences in the incidence and progression of MAFLD are scarce. Metabolomics represents a powerful approach to studying these differences and identifying potential biomarkers and putative mechanisms. First, metabolomics makes it possible to obtain the molecular phenotype of the individual at a given time. Second, metabolomics may be a helpful tool for classifying patients according to the severity of the disease and obtaining diagnostic biomarkers. Some studies demonstrate associations between circulating metabolites and early and established MAFLD, but little is known about how metabolites relate to and encompass sex differences in disease progression and risk management. In this review, we will discuss the epidemiological metabolomic studies for sex differences in the development and progression of MAFLD, the role of metabolic profiles in understanding mechanisms and identifying sex-dependent biomarkers, and how this evidence may help in the future management of the disease.

Key Words: MAFLD; Sex differences; Metabolic profiles; Metabolism

Core Tip: Metabolic-associated fatty liver disease (MAFLD) refers to the build-up of fat in the liver associated with metabolic dysfunction and has been estimated to affect a quarter of the population worldwide. Metabolomics represents a powerful approach to studying metabolic disease, including MAFLD, and to identify potential biomarkers and putative mechanisms. Some studies demonstrate associations between circulating metabolites and early and established MAFLD, but little is known about how metabolites relate to and encompass sex differences in disease progression and risk management. In this review, we will discuss the role of metabolic profiles in understanding mechanisms and identifying sex-dependent biomarkers, and how this evidence may help in the future management of the disease.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver diseases that occurs with different stages ranging from steatosis to cirrhosis or hepatocellular carcinoma. In 2020, the classical conception of NAFLD was revised and consequently, a new entity called metabolic-associated fatty liver disease (MAFLD) was defined. Unlike NAFLD, MAFLD does not exclude patients who consume alcohol or those who have other liver diseases. MAFLD prioritizes and values the metabolic involvement of the liver and the consequences of liver metabolism impairment on the progression of the disease[1]. At the clinical level, MAFLD seems more useful for the study of the advanced stages of the disease, since, by focusing on the metabolic dysfunction, MAFLD allows to include a greater number of patients and individuals at risk than the classic definition of NAFLD[2]. However, as expected for recently proposed definitions, the criteria for the use of MAFLD as a clinical entity is not unanimous and NAFLD is still the most used term[3]. Currently, the prevalence of NAFLD and MAFLD is continuously increasing in both adult and child populations due to the epidemics of obesity and type 2 diabetes mellitus. Although MAFLD and NAFLD share a large part of their clinical profile and produce similar long-term outcomes, the actual trend for increase mortality for both of them reflect different situations. Increased liver-related mortality among NAFLD patients seems driven by NAFLD-related liver complications and extra-hepatic diseases such as cardiovascular disease, extra-hepatic cancers, or kidney diseases[4]. MAFLD patients show greater risk for all-cause mortality and an equal risk for cause-specific mortality comparing to NAFLD patients[5].

The prevalence of MAFLD is very high worldwide with numbers rapidly increasing in low- and mid—income countries. In adulthood, the average prevalence of MAFLD worldwide in 2015 was 25%, being higher in South America (31%) and the Middle East (32%)[6]. More recent studies show even higher rates of MAFLD with an estimated prevalence in adults as high as 30%, being even higher in the Middle East and North Africa (approximately 43%) followed by South America and Asia (approximately 33%)[7]. The numbers at a young age are especially worrisome. In childhood, one of the greatest risk factors that contribute to the initiation and development of MAFLD is obesity. In overweight and obese children, the prevalence of MAFLD can reach up to 36%. Nevertheless, the worldwide prevalence of MAFLD among the general pediatric population is 8% with the highest rate in Central America and the Middle East[8,9].

The prevalence of MAFLD seems to differ among men and women even at young ages. The prevalence of MAFLD in the juvenile population is higher in men than in women both before and after puberty[8,10]. In the adult population, the prevalence of MAFLD is also higher in men than in pre-menopausal women. However, the incidence in post-menopausal women increases markedly suggesting a potential role for sex hormones in the mechanisms of the disease[7,11].

The burden of the disease in the national health systems and the population is increasingly higher. Due to the increase in cases in children, the disease becomes chronic at a younger age. It is estimated that, in the coming decades, the incidence will continue increasing and so will the costs in health systems worldwide[7,9]. We herein review the influence of sex hormones on hepatic and mitochondrial metabolism and how sex hormones contribute to the development of MAFLD. It seems critical to identify new risk and early disease biomarkers, which include relevant biological factors like sex in the risk estimation, for a future better management of the disease. ´Therefore, we specifically focus on if the sex variable is currently considered when stratifying patients in metabolomics studies and if it is used to search new biomarkers based on metabolomics in the development of MAFLD.

SEX AND LIVER METABOLISM

The liver is an organ with a key role in the homeostasis of human metabolism. Due to the architecture of the hepatic lobules and the arrangement of the portal triad with respect to the hepatic vein, there is a metabolic zonation in the liver, which leads to a liver metabolism not exactly uniform within the hepatic lobule[12]. The liver is an organ with a high metabolic rate and, among other functions, is responsible for regulating lipid and carbohydrate metabolism in the body. Regarding lipid metabolism, circulating lipids enter the hepatocyte and can: (1) Be oxidized for energy, (2) be esterified and form very-low-density lipoprotein (VLDL) particles, and (3) stored and stay in the hepatocyte. In addition, the hepatocyte can synthesize new lipids by de novo lipogenesis (DNL). Regarding carbohydrate metabolism, the liver can store sugars in the form of glycogen or synthesize de novo carbohydrates depending on the needs of the body. Both lipid and carbohydrate metabolism are coupled and highly regulated. When the homeostasis of metabolism is altered, lipids can accumulate pathologically in the organ causing stress and cell damage and sugars can remain circulating in the blood aggravating insulin resistance[13].

Sex hormones are steroid hormones derived from the cholesterol molecule. All sex hormones can bind to receptors in the liver cells. Based on their chemical structure, they are classified into three large groups: estrogens, androgens, and progestogens[14]. The liver is actively involved in the metabolism and interconversion of these sex hormones[15]. Estrogens, the main female sex hormone, are divided into estrone (E1), 17β-estradiol (E2) and estriol (E3), being E2 the main one. Like any steroid hormone, 95% of estrogens travel through the bloodstream binding to steroid hormone-binding globulin. The remaining 5% circulates freely. Estrogens bind to its receptors, estrogen receptors (ERs), present in the cell nucleus. There are two types, ERα and ERβ, which are differentially expressed depending on tissue [16,17]. In addition, there is a third type of receptor called the G-protein-coupled estrogen receptor, which is located on the plasma membrane and is also important in estrogen signaling and cell function [18]. Androgens, the main male sex hormone, belong to a group of sex hormones that includes among others, testosterone, and dihydrotestosterone. These hormones bind to androgen receptors, located in the cell nucleus[14]. Finally, progesterone is a hormone released by the corpus luteum into the ovary. It is mainly responsible for the stimulation of the mammary glands, and the preparation and maintenance of pregnancy. Progesterone can bind to two nuclear progesterone receptors (PR), PR-A and PR-B, expressed primarily in areas of the brain. Other receptors for progesterone located on the plasma membrane have also been described[19]. In women, the ovaries are responsible for producing estrogens, progestogens and androgens, which can be aromatized and converted into estrogen. In men, Leydig cells present in the testicles produce testosterone, which can aromatize and become estrogen[17].

Hepatic metabolism is highly regulated and sex hormones have been shown to contribute significantly to this regulation. Up to 72% of the genes related to liver metabolism can be expressed differentially based on sex[20]. The effects of sex hormones on liver metabolism are summarized in Figure 1. Estrogens are directly related to a protective mechanism against liver fat accumulation by promoting lipolysis and inhibiting DNL. In addition, estrogens contribute to maintaining a hepatic cholesterol balance by promoting lipoprotein synthesis, the secretion of VLDL particles, increasing high-density lipoprotein production and eliminating oxidized low-density lipoprotein. They also improve mitochondrial function, increase free fatty acid (FFA) oxidation, improve glucose tolerance as well as insulin sensitivity and decrease inflammatory processes in the liver[14,17,20,21]. Androgens also have some protective role against the development of hepatic steatosis. They can promote VLDL exocytosis, DNL inhibition, homeostasis of carbohydrate metabolism and mitochondrial beta-oxidation of FFA[14, 20]. The role of progesterone in fat liver metabolism and accumulation seems more diluted. Although this hormone is metabolized in the liver, the impact on woman liver health may be partially detrimental. High levels of progesterone in women are related to the development of insulin resistance and some liver damage[22]. Not only are the mechanisms explaining these effects unclear, but also, more investigations are needed to confirm these observations.

There are certain situations in which the levels of sex hormones decrease both in men and women. This condition is known as hypogonadism and has been related to the development of MAFLD[21]. Menopause or estrogen hypogonadism, physiological conditions in which estrogen levels abruptly decrease, have a notable impact on women. Decreased estrogen levels in women can lead to increased hepatic steatosis by decreasing VLDL secretion and increasing DNL[14,20,23]. Decreased estrogen levels also encompass a decrease in the body's metabolic rate which contributes to weight gain and the development of obesity[16], factors that contribute to the incidence of insulin resistance and an increased risk of developing liver fibrosis[14,20]. Healthy women have higher levels of estrogen than androgens. However, this situation is reversed in polycystic ovary syndrome (PCOS). PCOS is one of the most common endocrinopathies associated with young women that is characterized by high levels of androgens, lack of ovulation and the presence of polycystic ovaries. Hyperandrogenism associated with PCOS doubles the risk of developing MAFLD, and increases the incidence of obesity, insulin resistance and metabolic syndrome, all related to MAFLD, compared to female controls[24-26]. In men, hypogonadism is a syndrome that is defined by decreased testosterone levels. Hypogonadism due to testosterone deficiency has also been shown to increase the risk of developing hepatic steatosis, obesity, and insulin resistance[24,27]. A recent meta-analysis revealed that total serum testosterone was

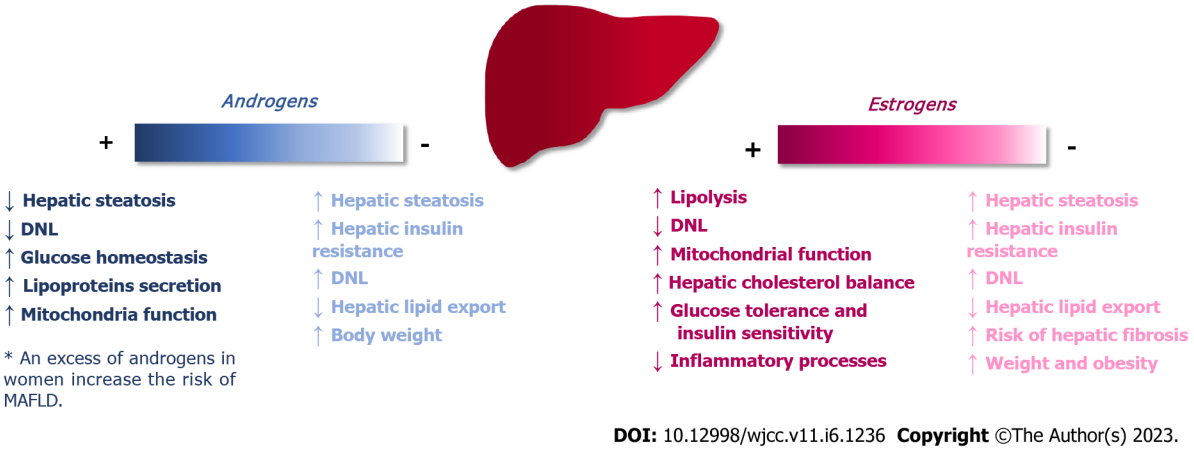

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Figure 1 Effects of androgens and estrogens in liver metabolism. (+) means higher concentration and (–) less concentrations of specific sex hormone. (↑) means an increase and (↓) a decrease in a specific hepatic function. DNL: *De novo* lipogenesis.

decreased in men with MAFLD *vs* men without MAFLD[28]. Decreased androgen levels in men leads to an increase in circulating triglycerides[23], a decrease in VLDL secretion, an increase in DNL, insulin resistance, and increased body weight[14,20], all of them related to MAFLD.

MITOCHONDRIAL METABOLISM, THE LIVER, AND SEX HORMONES

Mitochondria represent approximately 20% of the hepatocyte volume[29]. They carry out critical metabolic functions related to lipids, carbohydrates, and amino acids. The conversion of pyruvate to acetyl-CoA and its oxidation occurs through the tricarboxylic acid (TCA) cycle at the mitochondrial matrix. This cycle generates adenosine triphosphate (ATP), nicotinamide adenine dinucleotide, flavin adenine dinucleotide and other important metabolites such as citrate, succinate, malate, and oxaloacetate. Citrate, a precursor molecule of lipogenesis, is synthesized in the mitochondrial matrix and exported to the cytosol for the initiation of DNL. Succinate is transformed into fumarate by the electron transport chain (ETC) for cellular respiration and ATP production. Malate and oxaloacetate may initiate the process of gluconeogenesis for glucose synthesis. In turn, acetyl-CoA can be used for the synthesis of ketone bodies in a process known as ketogenesis. The beta-oxidation of fatty acids, which generates a large amount of acetyl-CoA, also takes place in the mitochondrial matrix. The acetyl-CoA produced during beta-oxidation of fatty acids can also enter the TCA cycle or alternatively initiate ketogenesis[29,30]. On the other hand, the ETC is not perfect and during respiration free radicals can be produced. As a consequence, the mitochondria are the place in the cell where more reactive oxygen species (ROS) are produced. Under physiological conditions, antioxidant systems cope with the accumulation of ROS and decrease the number of toxic molecules. However, under pathological conditions, the accumulation of ROS can affect the integrity of DNA, both mitochondrial and nuclear. In addition, mitochondria are related to the production of S-adenosylmethionine, a methyl group donor molecule. This molecule can modulate gene expression by producing epigenetic changes in DNA. Finally, the mitochondria act as a sensor of cell viability, being related to processes of apoptosis and necrosis[30]. All these events and processes taking place at the mitochondria combined with the predominant role of mitochondria in liver metabolism places this organelle at the center of many mechanistic hypotheses about MAFLD pathogenesis[29].

Mitochondria are also regulated by sex hormones. Estrogens stimulate the expression of mitochondrial proteins encoded in nuclear DNA as ATP synthase-related proteins or ETC proteins. Estrogens offer protection against the degenerative effects of age by increasing antioxidant defenses, increasing ATP levels, decreasing lipoperoxidation, and decreasing levels of ROS. In addition, estrogens co-regulate the processes of mitochondrial fusion and fission, enhancing mitochondrial biogenesis and inhibiting mitophagy and apoptosis. Estrogens also promote mitochondrial DNA transcription and stimulate oxygen consumption[31-33]. Androgens, on the other hand, stimulate mitochondrial biogenesis by increasing mitochondrial content (mitochondrial DNA and mitochondrial proteins), inhibiting mitophagy, maintaining the integrity of ETC and protecting these organelles from the degenerative effects of age[32,34]. The impact of MAFLD in the interaction between sex hormones and mitochondria can be two-fold. First, MAFLD can alter sex hormone levels and consequently decrease the protective effect on the mitochondria (Figure 1). Second, the accumulation of FFA and sugars inside the hepatocyte can impact the metabolic functions in the mitochondrial matrix. The most dramatic consequences include alterations in the cell respiration pattern, with decreased ATP production and an overproduction of ROS. Beta-oxidation can also be hampered with FFA to be consumed by alternative

pathways in peroxisomes (beta-oxidation) or microsomes (omega-oxidation), which in turn can increase ROS and toxic intermediates (dicarboxylic acids) production. All these alterations produce ultra-structural mitochondrial changes at different levels. Different studies report increased permeability of the outer and inner membranes, abnormal mitochondria shapes or deletion of mitochondrial DNA[35,36]. All these facts suggest that the study of mitochondrial metabolism both in the cell and also by studying mitochondrial metabolism products in available biofluids (such as blood) may help in further investigating fatty liver disease mechanisms. The identification of early mitochondrial dysfunction, combined with other risk factors, like body mass index, sex, and age, may provide the basis for early detection and risk stratification in MAFLD management.

METABOLIC PROFILES TO CHARACTERIZE SEX DIMORPHISM IN MAFLD

Each molecule involved in the chemical reactions that take place in a living organism is called a metabolite. The set of metabolites involved in all the chemical reactions in a living organism is called the metabolome. Omics are a set of analytical sciences that are responsible for the study of a specific biological set. Currently, there are many types of omics, however, the big four omics are genomics, transcriptomics, proteomics, and metabolomics[37,38]. There are mainly two analytical techniques that allow detecting (qualitative analysis) and quantifying (quantitative analysis) metabolites in biological samples. These are Nuclear Magnetic Resonance (NMR) and Mass Spectroscopy (MS)[39,40]. With NMR and MS, the metabolites existing in a biological sample (serum, plasma, urine, faeces, cells, or tissue) at the time of measurement can be determined. Because the metabolome is at the end of the -omics cascade, metabolomics reflects changes that occur at the proteomic, transcriptomic, or genomic level. Consequently, interpretation of metabolite levels and metabolomic profile is highly complex. Subsequently metabolomics is more used for identifying relevant biomarkers and signatures and less used for providing mechanistic hints. Nevertheless, metabolomics can be a helpful tool in the study of diseases in which metabolic dysfunction is at the center of the pathogenesis, such as MAFLD[41,42].

The metabolome is sex-dependent since very early stages of life. In general, biological sex differences can be included into one of 3 groups: (1) Sex dimorphisms, in which some biological trait is only expressed in men or women; (2) Sex differences, in which a biological trait has a range of possibilities but is predominant in one sex with respect the other; and (3) Conditions in which there is no obvious difference between sexes for some biological trait but differences can show up under some conditions like stress, disease or some pharmacological treatments[43,44]. The extension of these three groups to metabolites as biological traits is straightforward. Metabolites, which are different between men and women only in MAFLD patients would fall within the third group and would represent ideal candidates for a stratified MAFLD risk model.

There are sex dimorphisms and sex differences in many metabolic processes of the organism, specifically of the liver, which are intrinsically related to many other differences detailed in the sections above, including sex hormones, and mitochondria function. Most metabolic pathologies, as MAFLD, affect differently men and women, with different risk factors, different disease progression and even difference prevalence under similar conditions[45]. The alteration of sex hormones, due to age or due to some pathological processes, and the development of MAFLD are strongly associated. Figure 2 shows a simplified summary of these links (Figure 2). Although most, if not all, epidemiological studies have information about the sex of the participants, only in the last decades -omics studies have analyzed their data adjusting or stratifying by sex, and many suggested biomarkers are released with unisex models. Our knowledge about the influence of sex and sex hormones in metabolism strongly suggest that these analyses need to be stratified by sex (not just adjusted) for identifying sex-specific biomarkers and building sex-dependent risk models. Table 1 shows different studies which analyzed the metabolome and the metabolic changes happening in established NAFLD accounting for the metabolic differences between men and women. A recent study suggests that cardiovascular risk in NAFLD patients could be stratified according to levels of Trimethylamine-N-oxide (TMAO), which is a gut microbiota-derived metabolite associated to cardiovascular risk[46]. In another study, women exhibited lower levels of TMAO than men. In addition, obese patients at higher risk of NAFLD also showed higher levels of TMAO. However, the authors did not stratify women by pre- or post-menopause and estrogen influence in these levels and associated risk[47]. In a different research, serum metabolomic profiles were measured in a young cohort at two time-points, at approximately 10 years old (T1) and 16 years old (T2). There were metabolites significantly different between MAFLD and controls at both time points and different between boys and girls. All the metabolites were related to lipid, amino acid, and carbohydrate metabolism[48]. Branched-chain amino acids (BCCA) are critical switches between health and disease[49]. A recent study analyzed these metabolites in obese patients with different NAFLD severity. They concluded that there was a correlation between BCCA levels, sex, and the degree of MAFLD severity. In women, the concentration of BCCAs in plasma was lower than in men. However, the levels of BCCA in women sharply increase with disease progression from control to non-alcoholic steatohepatitis (NASH)-fibrosis, whereas in men a parallel decrease was observed. Interestingly, there was a strong association between circulating BCAA and liver fibrosis only present in women[50].

Table 1 Studies related to "fatty liver disease", "metabolomics" and "sex"

Ref.	Cohort origin	No. of patients	Sex variable	Platform used	Different metabolites between sexes
Barrea *et al*[47], 2018	Naples, Italy	137	59 men (43.1%) and 78 women (56.9%)	HPLC-MS	Serum TMAO
Perng *et al*[48], 2020	Exploring Perinatal Outcomes among Children (EPOCH), USA	395	199 boys (50.7%) and 196 girls (49.3%)	MS	Lipid, amino acid, nucleotide and carbohydrates metabolism pathways
Grzych *et al*[50], 2020	Antwerp University Hospital (Belgium)	112	53 men (47.3%) and 59 women (52.7%)	MS	Leucine, valine and isoleucine (BCAA)
Ioannou *et al*[51], 2020	USA	57	51 men (89.5%) and 6 women (10.5%)	LC-MS and NMR	Mainly BCAA, lactate, TMAO, choline and creatinine
McGlinchey *et al*[52], 2022	UK, France, Germany, Brazil and Italy	627	339 men (54%) and 287 women (45%)	UHPLC coupled to QTOFMS, and GC coupled to QTOFMS	Serum lipids and polar metabolites (lactate, citrate, isoleucine, lysine, alanine, *etc.*)

BCAA: Branched chain amino acid; GC: Gas chromatography; HPLC-MS: High-performance liquid chromatography – mass spectroscopy; LC-MS: Liquid chromatography – mass spectrometry; MS: Mass spectroscopy; NMR: Nuclear magnetic resonance; QTOFMS: Quadrupole-time-of-flight mass spectrometry; TMAO: Trimethylamine-N-oxide; UHPLC: Ultrahigh-performance liquid chromatography.

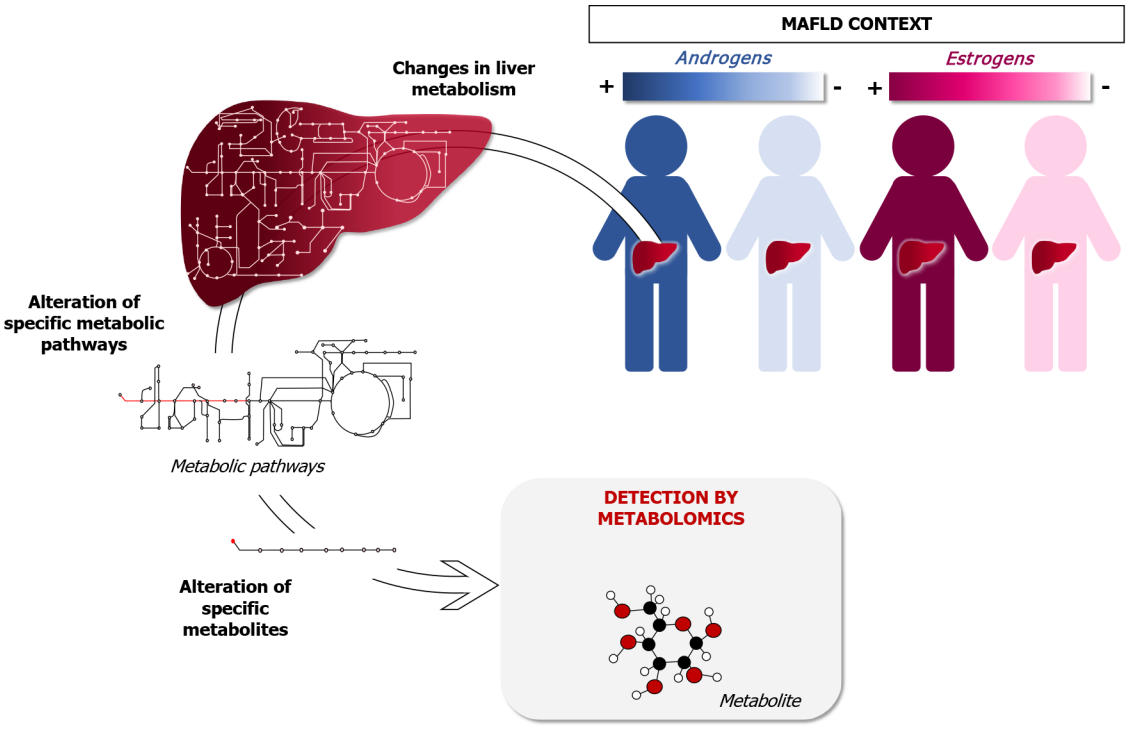

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Figure 2 The use of metabolomics in the context of metabolic-associated fatty liver disease and sex hormones. Liver metabolism is affected by sex hormone levels. It has been seen that, in metabolic-associated fatty liver disease (MAFLD) disease, there is a decrease in androgens and estrogens which influences liver metabolism. Metabolomics allows the measurement and study of metabolites in a biological sample (liver tissue, blood, urine, faeces, *etc.*). The application of metabolomics to men and women at different stages of the disease would provide great information for the search of biomarkers and the study of MAFLD.

Although liver disease can be diagnosed by noninvasive measurements, the gold standard still remains the liver biopsy. Biopsy-confirmed MAFLD classified by degree of severity in simple steatosis, early NASH, and advanced NASH was used to obtain metabolomic profiles of liver disease progression in another metabolomic study. Although the sample size was low and the power of the study was limited, the authors identify some differences between different degrees of severity which did not correlate with differences between sexes[51]. Finally, a larger study also analyzed serum metabolomics in 627 patients to classify them based on the degree of severity of the disease stratified by sex. The authors identified a set of common metabolic traits associated to liver disease severity regardless of sex and a different set of

metabolites that changed specifically in men or in women. In the fibrosis stage, men presented 5 sex-specific metabolic differences whereas women show 17 sex-specific metabolic differences[52].

CONCLUSION

Metabolism is highly influenced by the effects of sex hormones. Specifically, hepatic metabolism and mitochondrial metabolism change depending on sex hormone levels. Recent studies show that individuals with altered estrogen or androgens levels have higher risk of developing fatty liver disease or progressing to more severe stages than those with normal levels. MAFLD is associated to metabolic alterations in liver and mitochondria. Among these, the identification of early mitochondrial dysfunction, combined with other risk factors, like body mass index, sex, and age, may provide the basis for early detection and risk stratification in MAFLD management. Because the metabolome is at the end of the -omics cascade, metabolomics reflects changes that occur at the proteomic, transcriptomic, or genomic level. Metabolomics is a helpful tool in the study of diseases in which metabolic dysfunction is at the center of the pathogenesis, such as MAFLD. In this review, we briefly explained the role of different metabolic compartments in the development of MAFLD and critically review current state-of-the-art evidence from metabolomic studies on sex dependency of fatty liver disease. Not only are more studies needed to clarify the role of metabolites and their use as biomarkers, but also, it is vital that future research includes the sex variable.

FOOTNOTES

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MINIREVIEWS

Epidemiology and etiology of chemical ocular injury: A brief review

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Abstract

Chemical ocular injury is one of the common ophthalmologic emergencies that can cause vision loss and serious complications. Despite all protective measures, it continues to be a serious public health problem, especially in young male patients. Although it is known that injuries occur most frequently in the workplace and in young male patients, there is a variable frequency and distribution in different regions around the world. In addition, with the coronavirus disease 2019 pandemic, there are changing trends in ocular chemical injuries. This review aims to specify an update on the epidemiological and etiological features of ocular chemical injuries.

Key Words: Chemical ocular injury; Alkaline; Acid COVID-19; Epidemiology; Etiology

Core Tip: Epidemiological and demographic characteristics are important to prevent ocular chemical injuries, one of the most important ocular emergencies.

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INTRODUCTION

Ocular surface chemical injuries are ophthalmological emergencies that can cause prompt destruction, serious anterior segment complications, and permanent visual loss[1] (Figure 1). Chemical eye injuries have accounted for a significant proportion of ocular traumas over the years. Studies in the 80s-90s report that chemical injuries

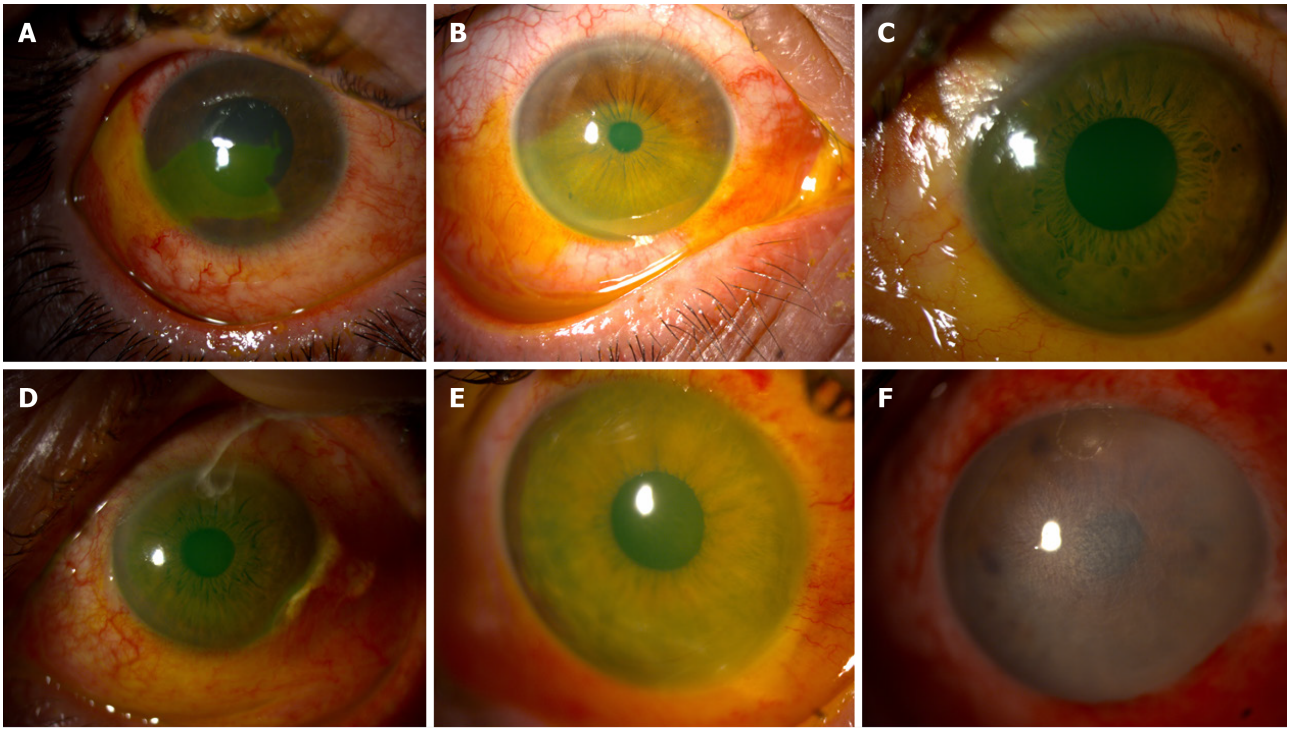

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Figure 1 Various grade chemical ocular injury cases. A-F: Grade 1 to 6.

accounted for 7.7%-18.0% of all ocular injuries. In 2018, Sharma *et al*[2] reported that chemical injuries are responsible for approximately 11.5%-22.1% of ocular injuries[3]. Effective and rapid intervention, clinical evaluation of the injury severity, and prompt treatment are essential. Injury grade depends on the causative agent type, pH, and exposure time. Appropriate and sufficient management of the chronic process of the disease results in better visual outcomes and lower complication rates. The visual prognosis of a severe ocular chemical injury is generally poor[4]. However, current developments in treatment strategies are encouraging for both visual and clinical outcomes. Evaluation of the epidemiological and etiological factors of ocular chemical injuries benefits to prevent injuries. Ocular chemical injuries can be classified in accordance with various factors such as agent type, type of injury, gender, and age. It is known that most injuries occur at work in the young male population. However, it varies according to the socioeconomic and educational status of the countries, and the rate of use of protective equipment[5]. Ocular chemical injuries may occur due to assault and assault injuries are frequently associated with more serious injuries[6,7]. Consequently, ocular chemical injuries and their sequelae create a serious social, economic, and psychological burden. This brief review aims to present a current approach to the epidemiology, etiology, and predisposition of ocular chemical injuries.

SEVERITY AND PREVALENCE

Ocular chemical injuries account for 10.7%–34.7% of all chemical burn injuries. Also, 0.1%–15.5% of all ocular traumas among hospitalized adults are secondary to ocular chemical injury, and this rate has increased over the years[8,9]. For example, a study from Serbia reported that ocular surface chemical injuries accounted for 2.7% of hospitalized ocular injuries in 1999 and 15.5% in 2008[10]. In 2021, in a meta-analysis of 88 studies, Ahmed *et al*[5] reported that ocular chemical injuries have an incidence ranging from 5.1 to 50 per 100000 population per year in different countries. The incidence of chemical injury was reported as 5.11/100000/year in the United States in 2015 and 5.6/100000/year in the United Kingdom in 2019. Likewise, in 2015, it was reported as 50/100000/year for the working population in Switzerland. In economically underdeveloped countries, the rate of chemical ocular injuries was lower (2.2%-8%) among emergency ocular traumas, and it was 11-13% in developing countries such as Turkey [11,12]. Considering the seasonal distribution of chemical injuries, it has been reported that they occur more frequently in Serbia and the United States in summer and in Turkey in winter[13].

The severity of injury varies considerably between studies, with the frequency of mild injuries ranging from 57% to 70%. The prevalence of severe injury in the United Kingdom was reported as 0.02/100000/year in 2009 and 0.29/100000/year in 2019. Similarly, it was reported as 1.58/100000/year in China in 2010[14,15]. The distribution of chemical injury severity may vary in accordance with

socioeconomic conditions. In the literature, in developed countries, low-grade chemical injuries (grades 1-3) account for approximately 83%-90% of all chemical injuries. In contrast, severe injuries occur more frequently in developing and underdeveloped countries[15,16]. Bizrah *et al*[17] reported that of all ocular chemical injuries, 83% were low-grade injuries and 17% were serious injuries in the United Kingdom. In contrast, a similar study from India reported that 51% of eyes had low-grade injuries, but 35.9% had serious injuries[18]. While only alkaline agents were evaluated, Merle *et al*[19] reported that 50% of injuries were grade I, 31% were grade II, and 19% were grades III-IV according to the Roper-hall classification, in Martinique. Similarly, Moon *et al*[20] found that 75% of all alkali ocular surface injuries were grade I injuries in Australia. Nevertheless, the hospitalization rate was not related to economic development. Assault-related ocular chemical injuries are not unique to developing countries with similar frequency worldwide. Moreover, there has been a global increasing trend recently[21]. Assault-related cases were noted to result in more serious injuries globally. Studies from India and Martinique reported that 50% and 32.7% of assault-related eye injuries are high-grade injuries, respectively[22].

CAUSATIVE AGENTS

Alkaline injuries are more common than acidic injuries due to their extensive industrial and domestic use[23]. Alkaline agents pose a therapeutic challenge in the management of chemical injuries. Alkaline agents have a higher penetration rate than acids[24]. The most important factor determining the potency of an alkaline agent is pH, and severe corneal damage occurs if the pH is 11.5 or more[25]. Alkaline agents cause saponification of cell membranes due to their lipophilic nature. The hydroxyl ions in alkali cause saponification of the cell membrane, leading to cell membrane lysis. They can promptly penetrate the anterior segment of the eye, such as the iris, ciliary body, trabecular meshwork, and crystalline lens. The inflammatory response progresses quickly due to the release of proteolytic enzymes from the injured tissue. In addition, associated vascular damage leads to ischemia. In contrast, acids fix and coagulate the superficial tissues which prevent deep penetration of the agent[26]. Alkaline injuries account for 19–73% of all cases of ocular chemical injury. The rate of ocular chemical injuries caused by alkaline agents was reported to be 66.7%-67.9%[27,28]. Acids account for approximately 5%–47.6% of cases, with sulfuric, hydrochloric, and nitric acids being common[13,29]. High-grade injuries mostly occur with alkaline agents. Kılıç Müftüoğlu *et al*[30] reported that 80.9% of chemical injuries were due to alkaline agents, and 48.1% of patients with alkali damage were severe. Sodium hydroxide and lime were the most common causative agents, causing 26% and 65% of alkaline ocular surface injuries, respectively [31]. Among alkaline substances, ammonia has the highest destructive potential, and lime is relatively less toxic[32]. The most common cause of ocular surface injuries by acidic agents is sulfuric acid, which rarely causes high-grade ocular injuries. Injuries with these agents have often occurred in the industry (construction, manufacturing, chemical, petroleum, *etc*.) and at home (household cleaning and personal care products)[33]. However, distinct from other acids, hydrofluoric acid has a strong liquifying effect on cell membranes and has an analogous effect to alkaline agents[34]. In spite of being a weak acid, hydrofluoric acid easily penetrates the corneal epithelium. In deeper tissues, hydrofluoric acid dissolves, and the free fluoride ions released cause irreversible damage[35].

The workplace was a common site of ocular surface injury, where 43%–86% of all cases in adults occurred. Ocular chemical injuries were responsible for 6%-45% of occupational ocular injuries and 2.8% of occupational burns. Characteristically, young males working in the industry are the most common patient group[36]. In the literature, it is reported that almost two-thirds of ocular injuries occur in the workplace among people of working age and male gender (ratio 3-8:1). In a study conducted in Germany, a total of 131 severe ocular injuries were recorded, with 84% being chemical injuries and 72% being work-related[16]. In a study from Turkey, Akgun *et al*[37] reported that the most common cause of injury (45.1%) was occupational accidents and it was more common in men (male/female: 86/18) in the last 10 years. There is a variability of protective equipment used in the workplace, depending on the development status of the country. From Nigeria, Adepoju *et al*[38] reported that protective equipment was not used in any of the work-related chemical ocular injuries. Moreover, even in developed countries, the use of protective equipment may still be inadequate. Domestic and hobby injuries accounted for 7%-33% of ocular chemical injuries. In the United States, domestic injuries were more common in children (13.8%) and patients over 65 (16.4%) compared to the 18-64 age group (8.72%)[39].

AGE AND GENDER

While ocular chemical injuries can occur in all age groups, it is known that the group most at risk is young adult men. It has been reported in studies that 54.4%-97.5% of the cases were men. However, the rate of injuries caused by domestic products is higher in women. It is known that patients between the ages of 15-35 account for more than half of all cases[18,40,41]. However, several studies in the United States, Serbia, and China noted that 41-50 years old had the highest injury frequency of all age groups [13,42]. Furthermore, children are at risk for ocular chemical injuries. The rate of ocular trauma

secondary to chemical injury in children was similar to that in adults. Haring *et al*[39] reported that 19.9% of patients with ocular chemical injuries admitted to the emergency department in the United States were children. A study from India reported that chemical injuries were responsible for 3.9% of ocular traumas in children under 14 years of age. Some studies have suggested a higher incidence of serious injury in children[43]. Vajpayee *et al*[40] reported that 85% of ocular chemical injuries in children required surgical intervention and 70.1% of patients had severe sequelae such as limbal stem cell deficiency. In contrast to adults, chemical injuries in the pediatric population are generally associated with domestic accidents, and the most common source of injury varies between diverse studies[44]. The most reported causative agents were domestic chemicals such as detergent capsules, lye, sodium hydroxide, household cleaning products, deodorants, and perfumes in many studies[45]. Haring *et al* [39] reported that the rate of acid-related chemical burns in children was higher than that with alkaline agents. In a study from Turkey, Korkmaz *et al*[46] reported that the causes of the majority (51.6%) of ocular surface injuries in children are unknown or neutral substances.

The incidence of such accidents differs in special age groups depending on the developmental stages of children. Haring *et al*[39] reported that the risk of chemical ocular injury was highest between 1 and 2 years of age and that the rate of alkaline burns was higher in children 3 years of age and younger, in their study involving 143985 patients. A study from the United Kingdom reported that 92.5% of ocular face injuries with detergent capsules occurred in children under 5 years of age[47]. As in adults, the incidence of ocular chemical injuries tends to be higher in boys. Korkmaz *et al*[46] evaluated pediatric chemical eye injuries in the last 10 years and reported that the mean age was 10.4 ± 5.5 years, 27.2% were younger than 5 years old, and 63.6% were boys. Pollard *et al*[48] reported that children aged 4 years and younger experienced eye injuries at a rate of 32% more than other age groups. The profile of causative agents for the geriatric population is similar to that for children, probably due to retirement and spending most of the day at home. Similar to the pediatric population, common agents of ocular surface injuries in elderly patients are bleach, chlorine, detergent, gasoline, glue, lens cleaner, oil, and paint[49].

Due to the coronavirus disease 2019 (COVID-19) pandemic, a changing trend is detected in the etiology of ocular chemical injury, as in many situations. Contrary to the pre-pandemic data, neutral causes have become more common due to the increased use of alcohol-based hand sanitizers, which is a neutral chemical agent, during the pandemic period[50]. The yearly average of patients with ocular surface burns decreased to 316 patients during the COVID-19 phase as compared to 445 patients during the pre-COVID-19 phase[51]. In a recent meta-analysis, 3 of 5 studies that compared the incidence of chemical eye injuries during the pandemic and control periods, reported a decreased incidence of chemical eye injury during the pandemic period. However, the rate of chemical eye injuries increased among all ocular traumas[52]. Martin *et al*[53] reported that although there was no significant difference in the rate of chemical injuries in children during the pandemic compared to the control period (4% and 5% in 2019 and 2020, respectively), chemical eye injuries due to alcohol-based disinfectants increased from 1 case to 16 cases. Wasser *et al*[54] reported that the incidence of pediatric chemical injury was 36 in 2019, increasing to 72 cases during the pandemic. Furthermore, a significant increase in chemical injuries due to alcohol-based disinfectants was observed. Finally, compared to the pre-pandemic period, ocular trauma remained stable but the proportion of chemical injuries increased by 13.7%[55].

ETHNICITY

Although it has been reported in various studies that ocular chemical injuries are more common in Afro-Caribbean, Caucasian, and non-Hispanic ethnicities, a clear relationship between ethnicity and the prevalence of ocular chemical injury has not been identified[56].

CONCLUSION

Ocular chemical injuries are one of the most important ocular emergencies, constituting a significant proportion of all traumas. To minimize sequelae, prompt and accurate treatment in the early period and successful management of complications in the long term are essential. Chemical ocular injuries have significant psychological, physical, and economic effects, especially since serious injuries can cause permanent blindness. The distribution and severity of ocular chemical injuries worldwide vary according to socio-economic conditions, as in all other traumas. In order to prevent further damage due to ocular chemical injury, it is important to understand the epidemiological and demographic characteristics of the injury and take precautions accordingly.

FOOTNOTES

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MINIREVIEWS

Review of the prevalence, diagnostics, and containment measures of the current mpox outbreak

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Abstract

Monkeypox (mpox), is a disease from the *Poxviridae* family that can cause several serious medical issues. This mini-review sought to analyze the existing literature regarding the current mpox outbreak with a focus on the prevalence, diagnostics, and containment measures. Mpox cases have been reported to World Health Organization (WHO) from 85 Member States in all six WHO regions during the period of January 1, 2022, through August 3, 2022. Standardized or optimized guidelines for the clinical care of patients with mpox are limited, particularly in low-resource settings. In an effort to achieve guidance and meet standards, special attention should be paid to this outbreak in order to eradicate such a rare infectious disease by analyzing prevention and control measures. Patient outcomes may also be poor, and their illnesses may last for a long time. The spectrum of clinical symptoms, including complications and sequelae, as well as

aspects of the illness may be indicators of sickness severity and complications; therefore, its clinical presentation must be better understood to improve containment measures. In addition, it is important to create and evaluate a standard of care that takes a variety of parameters into account, including antiviral, immune therapies, and clinical metrics that are particular to mpox. The global emergence of mpox has presented new challenges for public health and has called for further investigation into its epidemiological profile across international contexts.

Key Words: Monkeypox virus; Outbreak; Prevalence; Containment; Epidemiology; Orthopoxvirus

Core Tip: Monkeypox (mpox) cases have been reported to WHO from 85 Member States in all six World Health Organization (WHO) regions from January 1, 2022, through August 3, 2022. Over 25000 laboratory-confirmed cases and 122 suspected cases, including 11 fatalities, had been reported to WHO as of August 3, 2022. Most of these cases since May 13, 2022, have come from nations lacking evidence of mpox transmission. Standardized or optimized guidelines are limited for the clinical care of patients with mpox, especially in low-resource settings. This paper aims to review the prevalence, diagnostics, and containment of mpox.

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INTRODUCTION

The illness known as monkeypox (mpox) is brought on by a mpox virus infection. The mpox virus is a DNA virus of the *Orthopoxvirus* genus in the *Poxviridae* family, of which smallpox is also a member[1]. As a result of smallpox eradication in 1980 and the ceasing of smallpox vaccination, mpox is presently the major *Orthopoxvirus* to affect public health[2]. Mpox, which primarily affects Central and Western Africa regions, has recently started to spread globally[2]. Microscopically, the mpox virus presents as a brick-like virion in its structure. Two distinct strains of mpox have been found in various regions of Africa. Clade 1 has been responsible for spreading illness in the Congo Basin, whereas Clade 2 was isolated in West Africa[3]. The 2022 European/North American outbreak may have revealed a third strain that is related to Clade 2 and has been labeled Clade 3[3] and is comprised of the hMPXV-1A clade, as well as the following lineages: A1, A1.1, A.2, and B.1[4]. Initial sequence data from 15 isolates show that the DNA genome has more mutations than expected, suggesting that the circulating virus may be rapidly adapting to humans[3]. It needs to be considered that the orthopoxviral genome is plastic and that it has experience with the deletion of large regions which may allow the virus to spread faster and become more virulent[5].

The majority of mpox patients during the global outbreak in 2022 were symptomatic. Infections without symptoms seem to be uncommon. Traditional cases of mpox have a systemic sickness that includes fevers, chills, myalgias, and lymphadenopathy, a key differentiating sign, as well as a distinctive rash that must be distinguished from other vesicular eruptions (*e.g.*, herpes simplex, varicella, and smallpox)[3]. However, some individuals have presented with vaginal, rectal, and/or oral lesions without the initial prodrome during the mpox epidemic outbreak that began in May 2022[3].

Several studies of mpox have reported complications, including secondary infections, bronchopneumonia, sepsis, encephalitis, and corneal infections with subsequent vision loss[3]. Transmission can occur from animal-to-human, human-to-human, and even human-to-animal as evidenced in a human-to dog-transmission reported by Seang *et al*[6]. The possibility of human-to-animal transmission is of current concern since domestic animals and new wild animals may become animal reservoirs of the mpox virus. Zoonotic viruses can transfer from one or more non-human animal species to humans, such as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[7]. It is believed that non-human primates, such as monkeys and African rodents, served as the virus's hosts before progressively spreading to humans and making them contagious[8].

In endemic countries of Africa, only wild animals including rodents and primates have been identified as animal reservoirs[6,8]. Nonetheless, prairie dogs in the USA and captive primates in Europe have been identified as new animal reservoirs[6]. The virus that causes mpox is primarily spread through a bite, scratch, or contact with the bodily fluids of an infected animal[3]. Additionally, it

can be obtained by preparing bush meat[3]. Mpox virus transmission from person-to-person can happen in several ways: direct contact with infectious sores, scabs, or bodily fluids; indirect contact through objects that have picked up the infection, such as clothing or linens that have come into touch with contaminated body fluids or sores[3]. Though prolonged face-to-face contact might be necessary for transmission to occur *via* this method, the mpox virus is also thought to be spread by respiratory secretions[3]. Because the mpox virus can pass *via* the placenta from the mother to the fetus, it is also believed to be transmitted through vertical transmission[3]. This paper aims to review the prevalence, diagnostics, and containment of mpox.

METHODOLOGY

A mini-review was conducted to narrate the epidemiological aspects associated with the current monkeypox outbreak. An electronic literature review was carried out primarily using Med Line Plus, Google Scholar, and PubMed. For the compiled data, the search was not only restricted to peer-reviewed articles released between January 1, 2014, and August 4, 2022. Grey literature sources were also visited to learn more about monkeypox cases. Keywords like the monkeypox virus, its prevalence globally, diagnostic approaches, and containment, respectively were taken into consideration when choosing articles or manuscripts. The topic's relevance was then considered while deciding which articles to include (Figure 1).

PREVALENCE AND INCIDENCE

The mpox epidemiological prevalence as reported to the World Health Organization (WHO) on August 3, 2022, is analyzed in this paper[9]. The study's focus is depicted from laboratory-confirmed cases[7]. These data points are from patients who had both confirmed and probable cases that were reported to the WHO European region[9]. Furthermore, mpox cases have been reported to WHO from 85 Member States in all six WHO regions from January 1, 2022, through August 3, 2022[9]. Over 25000 Laboratory-confirmed cases and 122 suspected cases, including 11 fatalities, had been reported to WHO as of August 3, 2022[9]. Most of these cases since May 13, 2022, have come from nations where there has never been evidence of mpox transmission[9]. Alternatively put, this is the first time that sustained chains of transmission and cases have occurred in countries without any immediate or direct epidemiological connections to West or Central Africa[9].

As depicted in Figure 2, the United States of America (USA) leads with 5825 or 23.2% of the confirmed cases of mpox, followed by Spain which accounted for 18.3% (4577), and the United Kingdom (UK) with 11.0% (2759)[9]. Additionally, 88.9% of all cases recorded globally are from the top ten impacted nations which also include France with 8.2% (2054), Brazil with 5.9% (1474), the Netherlands with 3.7% (927), Canada with 3.2% (803), Portugal with 2.5% (633), and Italy with 2.0% (505)[9]. Twenty nations have noted an increase in the weekly number of cases over the last week of July, with the USA reporting the largest increase[9]. As of August 3, 2022, 14 countries have reported no new cases in the past 21 d. In contrast, seven new nations (*e.g.*, the Philippines, Uruguay, Montenegro, Sudan, Liberia, Cyprus, and Bolivia) have reported their first case within the last week[9].

DIAGNOSTIC APPROACHES WITH SIGNALING PATHWAYS, VIRAL GENOMICS, AND LABORATORY TESTING

The signaling pathway is a series of chemical processes in which a collection of components in a cell cooperate to regulate a cell's function. Host protection against mpox depends on type I and type II interferon signaling, natural killer cell activity, and serologic immunity[10]. Mpox can suppress interferon signaling and elude host viral detection, which can result in case fatality rates of up to 11.0% [10]. Intriguingly, analytical findings also showed that the mpox-infected rhesus monkey (*Macaca mulatta*) kidney epithelial (MK2) cell line model was primarily regulated by a cluster of differentiation 40 (CD40), plasmin, and histamine, whereas the mpox-infected human HeLa cell line model was primarily regulated by interferons, macrophages, and neutrophil-related signaling pathways[11]. It was also seen to have several highly significant expressed genes that were essential for the development of mpox infection in both monkey and human models, including CXCL1, TNFAIP3, BIRC3, IL6, CCL2, ZC3H12A, IL11, CSF2, LIF, PTX3, IER3, ADORA2A, and DUOX1[11]. These genes include several epigenetic regulators, including members of the histone cluster family, HIST1H3D, and HIST1H[11].

Comprehensive diagnostic approaches for mpox may help to reduce the outbreak[12-14]. Each lesion is assumed to be clonal in generalized rashes brought on by *Orthopoxvirus* species[15]. As a result, a genome sequence obtained from a single lesion may not accurately represent the patient's population, albeit this is not always the case for lesions that are the main sites of infection[15]. It is speculated that

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Figure 1 Article selection.

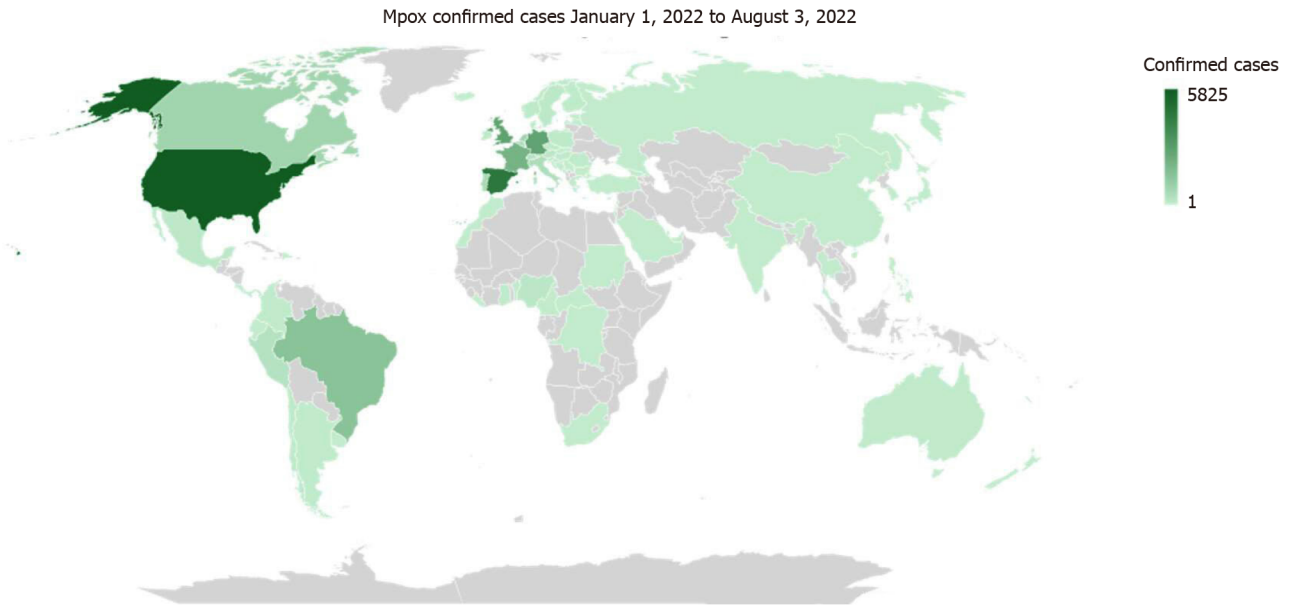

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Figure 2 Monkeypox cases confirmed globally (January 1, 2022 to August 3, 2022). The darker-shaded countries depict a greater population infected with confirmed cases of monkeypox, whereas lighter shades indicate fewer cases. This figure replicates cases of infection throughout the period of early January 2022 to August 2022 and enables insight into the spread of future outbreaks with the depiction that the darker green shading had more reported cases.

finding more of these parental sequences will be recovered from secondary rash lesions and a larger proportion of adaptive changes in genomes recovered from initial rash lesions of viruses closer to the zoonotic parent are more suited for disseminated infection[15]. Sequencing genomes from several lesions from both the primary and secondary rash of specific individuals is necessary to fully understand the evolution and adaptation of the mpox virus in this global outbreak[15]. By amplifying DNA fragments, a polymerase chain reaction (PCR) test of skin lesions or fluid can verify a diagnosis [16]. A patient's mpox virus status can be determined by a positive *Orthopoxvirus* PCR in the case of an individual who is suspected of having mpox[16]. Additionally, seminal fluid, upper respiratory fluid, blood, and urine may contain the virus nucleic acid[17-19]. Table 1 further depicts the possible diagnostic tests for identifying mpox or the *Orthopoxvirus* from clinical samples[20].

CONTAINMENT THROUGH MEDICATIONS AND VACCINATIONS

Comprehensive measures to combat the mpox virus, including increasing vaccine production and distribution, development and testing of new antiviral drugs, making testing more accessible and convenient, and collaborating with local health departments and trusted messengers in communities may mitigate the spread of the virus[12-14]. To alleviate symptoms, manage complications, and prevent long-term sequelae, clinical care for mpox should be fully optimized[2,21]. Treatment mostly focuses on reducing the effects because there are no specific drugs available for the management of mpox[22,23]. Although there are presently no therapies specifically approved against human mpox, two orally bioavailable medications, brincidofovir, and tecovirimat, have been shown to be relatively effective against *Orthopoxviruses* (including mpox) in animal models[17]. These two antivirals are currently recommended therapeutics in humans and may be beneficial against mpox[21]. The European Medical Association has authorized the antiviral tecovirimat, marketed under the name TPOXX, which was initially created for smallpox treatment in both children and adults[22]. Tecovirimat interacts with the

Table 1 Various diagnostic tests are used in identifying *Orthopoxvirus*

Test	Definition	Pros	Cons
RT-PCR	Checks for the existence of DNA markers unique to mpox	Can provide a diagnosis of an active case utilizing a patient's lesion material. Viral DNA is used in the procedure and can remain stable if the material is stored in a cold, dark environment. Specifically made to target the mpox virus	Extremely sensitive tests where contamination risks are considered high. The tools and materials needed for these tests are costly. Must be carried out by trained professionals at a reputable laboratory
Viral culture/isolation	Live virus is grown from a patient specimen	Can produce a pure, live viral culture that will allow for accurate species categorization. Since viremia is not always present during sickness, patient samples from lesions are the most accurate for this approach	It takes many days to finish the test. Attempts to cultivate patient specimens may be hampered by the presence of bacteria. For viral identification, more classification is required. Must be carried out by trained professionals at a reputable laboratory
Tetracore Orthopox BioThreat Alert	Tests to see whether O*rthopoxvirus* antigens are present	A point-of-care diagnostic tool that may quickly diagnose an active case utilizing patient-provided lesion material. Can be done with minimal experience at room temperature	The mpox virus cannot be detected with this technique. Tests must be conducted in endemic areas. Less accurate than PCR
Electron microscopy	A distinct picture of a brick-shaped particle is produced by negative staining, enabling visual identification of a poxvirus and other particles	Can be used to locate viral components in a biopsy specimen, scab material, vesicular fluid, or viral culture. Can distinguish between a herpesvirus and an *Orthopoxvirus*	*Orthopoxviruses* have morphological similarities to one another. Must be carried out in a reputable laboratory with qualified personnel and an electron microscope
Immunohisto - chemistry	Tests to see whether *Orthopoxvirus*-specific antigens are present	Antigens in biopsy specimens can be found with this method. This method can be applied to eliminate or locate more suspicious agents	Not unique to the mpox virus. Must be carried out by trained professionals at a notable laboratory
Anti-*Orthopoxvirus* IgM	Tests for the presence of *Orthopoxvirus* antibodies	Can be used to evaluate recent *Orthopoxvirus* exposure, either from a disease or a smallpox vaccine. Patients with a history of smallpox vaccination who are suspected of having the *Orthopoxvirus* may utilize this assay as a diagnosis	Utilizes a cold chain and blood (serum) collection. The mpox virus cannot be detected with this technique. Must be carried out by trained professionals at a reputable laboratory
Anti-*Orthopoxvirus* IgG	Tests for the presence of *Orthopoxvirus* antibodies	Can be used to determine whether a disease or smallpox vaccine has previously exposed a person to an *Orthopoxvirus*	Necessitates a cold chain and the collection of blood (serum). The mpox virus cannot be detected with this technique. Previous smallpox immunization will have an impact on the results. Variable response times apply. Must be carried out by trained professionals at a reputable laboratory

Data extracted and recreated from McCollum and colleagues[20]. Current tests are intended to be used as an aid in identifying the mpox virus, an *Orthopoxvirus*, or other members within this genus. Vesicular specimens collected from persons infected can be tested with reliable diagnostics for identification. RT-PCR: Reverse transcription polymerase chain reaction; DNA: Deoxyribonucleic acid.

F13L gene product, which codes for a phospholipase responsible to produce a protein complex that facilitates the envelopment of intracellular mature viral particles, to prevent the generation of extracellular viruses[17,24].

Despite the limitation of antiviral medication for mpox, smallpox vaccination can prevent mpox epidemics (approximately 85.0% efficient in eradicating mpox)[25]. Given worries of severe side effects in a population with an unclear immunocompromised profile, smallpox vaccinations, which are made of completely replicative vaccinia virus, are not currently used in monkeypox-endemic locations[2,20]. In 2019, a newer vaccine based on the Ankara strain of the modified attenuated vaccinia virus was authorized for the prophylaxis of mpox[2]. Moreover, JYNNEOS is the live vaccination created from the attenuated, non-replicating *Orthopoxvirus* strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN)[26]. There is still a limited supply of this two-dose vaccination, despite its approval and mainstay vaccine usage for mpox from many governmental agencies[2]. Due to the cross-protection provided for the immune response to *Orthopoxviruses*, smallpox and mpox vaccines are created based on the vaccinia virus[2]. Lastly, under the Expanded Access Investigational New Drug (EA-IND) procedure, the ACAM2000 vaccine is also made available in some countries for use against mpox in addition to smallpox[2].

DISCUSSION

Special attention should be given to this outbreak to accomplish guidance, satisfy standards, and

eradicate such a rare infectious illness by examining preventative and control techniques[2]. Transmission by respiratory droplet particles usually necessitates lengthy face-to-face contact, putting health workers, household members, and other close contacts of active cases at greater risk[27]. Due to the infectious nature of mpox, the Centers for Disease Control and Prevention (CDC) recommends that healthcare providers take the necessary steps to reduce transmission and protect themselves by using standard personal protective equipment (PPE) such as gloves, eye guards, gowns, and an N95 filter when treating patients[16]. Close contact with respiratory secretions, skin lesions of an infected individual, or contaminated things such as garments and beddings can result in human-to-human transmission[27].

In an outpatient setting, patients who have mpox or are showing signs of infection need to be isolated and have their lesions covered up. Patients, two years of age and older, need to wear face masks, while those who do not require hospitalization, particularly children and adolescents, are advised to self-quarantine at home[16]. In-patient care should include the considerations mentioned above and arrange a designated room and bathroom for the patient[16]. Infected patients must avoid contact with healthy individuals and pets until the scabs have fallen, a new layer of skin has formed, and the wounds are no longer open[16]. Healthcare providers should use a negative pressure room for situations that could cause the patient to generate oral secretions, such as intubation and extubation, with aerosol production requiring special air handling[16].

Additional guidelines also recommend bypassing actions such as sweeping, dusting, vacuuming, and fans as they can all recirculate dried particles from mpox lesions into the air[16]. There are a limited number of disinfectants approved and designated for use against specific pathogens; to counter this, the United States Environmental Protection Agency (EPA) developed EVP guidance to evaluate the efficacy of disinfectants based on data submitted by manufacturers[28]. In the case of viral disease outbreaks, the CDC recommends sterilization and using high-grade disinfectants with emerging viral pathogens (EVP) claims, a list of which can be found in the EPA's List Q[16]. Medical waste contaminated with mpox virus, including PPE, needles, and bandages that need to be changed is considered Category A waste and should be treated as regulated medical waste[16]. The CDC, along with the EPA, the Department of Labor, the Department of Transportation, the Department of Defense, and the Assistant Secretary for Preparedness and Response classify Category A waste as any substance that can cause permanent injury or a life-threatening illness in healthy individuals after exposure[29].

Currently, there are no vaccination mandates for health care providers; however, CDC recommends those 18 years and older with a risk of direct exposure to mpox get the JYNNEOS, ACAM2000, or LC16m8 vaccine[16,30]. Post-exposure prophylaxis for those with unprotected direct contact with mpox is available with vaccinia immune globulin or tecovirimat if the vaccine is contraindicated[16]. Vaccinia immune globulin can also be used for post-exposure prophylaxis in children less than 6 mo old[16]. The effectiveness of tecovirimat as post-exposure prophylaxis and of vaccinia immune globulin to prevent mpox are still being researched[16]. There are presently no effective treatments available for mpox; although the condition is self-limiting, persons with immune system disorders, inflammatory or exfoliative skin problems, pregnancy, and children under the age of eight are at greater risk[16]. The Strategic National Stockpile has made available smallpox antivirals such as tecovirimat and brincidofovir as they may be effective for treating mpox. Tecovirimat is a first-line mpox treatment; however, its effectiveness is currently based on animal models, and brincidofovir efficacy is still being studied[16]. Vaccinia immune globulin is also a possible treatment; however, its effectiveness has yet to be determined[16]. Cidofovir, another antiviral used for Cytomegalovirus retinitis, is also being allowed access for treatment; however, both cidofovir and brincidofovir also have high toxicity profiles[16,31].

The coronavirus disease of the 2019 (COVID-19) pandemic effects is still being felt today, particularly in Latin America. The pandemic has made it essential to rapidly respond to and examine viral outbreaks in patients by taking multiple samples and various body fluids to determine where the virus resides and identify the virus and its genome[32]. The COVID-19 pandemic has also demonstrated the need to differentiate the characteristics of a viral outbreak such as mpox from other disease processes of the region in Latin America, including smallpox, cowpox, chickenpox, measles, syphilis, and the Peruvian wart[32]. Furthermore, the COVID-19 pandemic also forced healthcare providers to reconsider the potential for co-infection with other infections or conditions local to Latin America, such as carrying the human immunodeficiency virus[32].

The smallpox vaccine is approximately 85.0% effective in its protection against mpox; however, the original vaccine has not been readily available since smallpox was eliminated in 1980[22]. Therefore, another approach implemented to reduce transmission and contain the outbreak is to vaccinate close contacts of infected patients[22]. While a single source of infection has yet to be determined, there have been cases worldwide indicating a trend in sexually transmitting mpox to the community[22]. Even though mpox is not considered a sexually transmitted disease, recent cases reported from England to the UK Health Security Agency revealed an increase in prevalence among those who deny traveling to endemic areas, are gay and bisexual, and men who have sex with other men[22].

Concerns regarding the geographic distribution and continued return of mpox are growing[33,34]. Mpox outbreaks have been documented during the past 50 years in over 10 African nations and 4 non-African nations[33]. In the African region where mpox is endemic, both the weakness of surveillance and laboratories in African countries have been identified as major challenges. Many suspected cases

presently exist in Africa. Democratic Republic of Congo (DRC) and Nigeria have the greatest burden of mpox in the African Region accounting for 92.0% of all cases with the DRC having 80.0% of cases. Although the report of mpox cases is lower in Africa compared to the current global outbreak, it is still a public health concern due to the limited supply of vaccines. The most prevalent explanation for the rise in mpox cases has been diminishing immunity[34], while deforestation may also be a contributing factor or possibly operate as a potentiator[33].

The characteristics of the current outbreak must be defined to determine how to best use the available tools to contain mpox[35]. Implementing screening tools in healthcare settings and maintaining a high level of suspicion with emerging clinical case definitions will aid in the identification of cases and the delineation of the outbreak's scope[35,36]. Thus, promoting epidemiology, integrated surveillance programs, and laboratory diagnosis is crucial in affected African countries[37].

CONCLUSION

Following the eradication of smallpox, ongoing human-to-human transmission in many nations exposes the mpox virus as an emergent *Orthopoxvirus* infection. Moreover, the waning population immunity caused by the discontinuation of smallpox vaccination may have created a favorable environment for the resurgence of monkeypox. This study highlights the global prevalence, diagnostics, and containment measures of mpox considering the current re-emergence of cases. Scientific findings underline the significance of unusual clinical manifestations of human mpox and the demand for additional and ongoing clinico-epidemiological studies. As human-to-non-human transmission has been evidenced, the isolation of pets from mpox virus-infected individuals should be included in the control measures.

FOOTNOTES

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Benjamin Wilde, Ali Canbay, Antonios Katsounas

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Abstract

The hepatorenal syndrome (HRS) is one major extrahepatic complication of end-stage liver diseases. While circulatory dysregulation is considered as primary etiology for HRS, cirrhosis-related (systemic) inflammation and/or cardial dysfunction may also play a key pathogenic role in HRS development. Exclusion of other causes of acute kidney injury (AKI) is required for diagnosis of HRS-AKI by the definition of the International Club of Ascites. However, the pathophysiology of HRS is not understood completely and there are still limited therapeutic options. Reversibility of renal dysfunction after liver transplantation indicates that HRS-AKI is a functional disorder caused by altered cellular function. The interplay between systemic inflammation and the onset of kidney-related hypometabolism may have a key role and needs to be studied in depth. This minireview challenges simplified views of the HRS in the context of diagnostics and therapy stressing the need for further evidence to advance the knowledge on this syndrome.

Key Words: Hepatorenal syndrome; Liver disease; Cirrhosis; Inflammation; Chronic kidney disease; Acute kidney injury

Core Tip: This minireview challenges simplified views of the hepatorenal syndrome in the context of diagnostics and therapy stressing the need for further evidence to advance the knowledge on this syndrome.

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INTRODUCTION

The hepatorenal syndrome (HRS) occurs in patients with advanced liver disease, cirrhosis and ascites[1-4]. It is characterized by renal failure, which can be rapidly progressive [HRS type I or HRS-acute kidney injury (HRS-AKI)]. More rarely, HRS can present with a more mild course of renal dysfunction [HRS type II or HRS-chronic kidney disease (HRS-CKD)][1-4]. The definitions by the "International Club of Ascites" were revised in 2015; HRS-AKI is now defined in analogy to the definitions of acute kidney injury published by the "Kidney Disease: Improving Global Outcomes"[1-4]. Accordingly, there is no fixed threshold for serum creatinine anymore; rather, the dynamics of renal function reflected by serum creatinine have to be considered. Thus, an increase in serum creatinine by ≥ 0.3 mg/dL from baseline within 48 h or an increase in serum creatinine by ≥ 50% from baseline is considered as AKI in the context of HRS. In addition, some clinical criteria need to be met: (1) No clinical response to withdrawal of diuretics and volume expansion with albumin over a period of 48 h; (2) Absence of shock, and (3) No current or previous administration of other, potential nephrotoxic drugs[1-4]. Furthermore, an underlying, primary renal disease needs to be excluded. Renal ultrasound should be with normal findings. Moreover, urinary analysis should reveal no major pathology, *i.e.*, proteinuria should be less than 0.5 g/d and hematuria should be absent. However, more recently it has been recognized that patients with liver disease may also develop HRS without fulfilling the criteria for AKI, *i.e.*, non-AKI, (HRS-non-acute kidney injury, formerly HRS- type II)[1]. These patients may present with progressive, slow decline of renal function over weeks. Patients without full recovery after an episode of AKI may also fit this category. If renal impairment is present for less than 90 d, this condition shall be termed HRS-acute kidney disease (AKD); in case it persists for more than 90 d with an eGFR < 60 mL/min *per* 1.73 m², then it is termed HRS-CKD. There are no conclusive data available on the prognostic impact of HRS-AKD or HRS-CKD. Recently, Patidar *et al*[5] investigated the incidence and outcome of AKD in patients with cirrhosis and AKI; AKD was found in 2004 (31.6%) out of 6250 patients. Mortality was significantly higher in patients with AKD. Although this study did not investigate HRS-AKD, it suggests that AKD *per se* is a predictor for poor prognosis in cirrhosis patients. For HRS-AKI, there is indeed a considerable amount of evidence suggesting a negative impact on patient survival[6]. Thus, this Minireview focuses on HRS-AKI, formerly known as HRS-type 1.

DIAGNOSIS

The diagnosis of HRS-AKI can be challenging and other etiologies of AKI have to be considered[3,7]. The reduced effective plasma volume can result in pre-renal AKI and non-responsiveness to volume expansion is therefore an important clinical flag to distinguish HRS-AKI from pre-renal AKI. Furthermore, acute tubulus necrosis (ATN) may also cause AKI and distinction from HRS-AKI can be challenging. In the past, fractional excretion of sodium (FeS) has been used to distinguish both entities[3,7]. In HRS-AKI, FeS is below 0.2% and the urinary sodium concentration is lower than 10 mEq Na/L. In contrast, ATN-AKI is characterized by an FeS ≥ 1% and a high urinary sodium concentration ≥ 30 mEq Na/L. Newer biomarkers, *e.g.*, Neutrophil Gelatinase-Associated Lipocalin (NGAL), have the potential to identify tubular damage and ATN but have not yet been used as routine biomarkers in the clinic[8]. Gambino *et al*[9] studied the value of urinary NGAL (uNGAL) to differentiate between ATN-AKI and HRS-AKI. In general, uNGAL levels were higher in ATN-AKI and significantly lower in HRS-AKI as well was in prerenal AKI. Interestingly, uNGAL levels were also significantly lower in patients with HRS-AKI responding to terlipressin/albumin treatment as compared to non-responders. Thus, uNGAL may not only serve as diagnostic biomarker but also as prognostic tool. In addition, structural renal diseases, *i.e.*, glomerulonephritis (GN), need to be excluded, too[10,11]. IgA nephropathy (IgAN) is a common GN and a specific type with distinct histopathologic findings was described in patients with liver cirrhosis[10,11]. In most patients with IgAN, supportive therapy is the treatment of choice and immunosuppressive therapy is only needed in specific clinical settings. In patients with hepatitis B or C induced liver disease, membranous nephropathy or membranoproliferative GN may cause AKI[7,12]. In these cases, antiviral therapy has to be combined with immunosuppressive therapy. GN should be suspected if urinary abnormalities are present, such as proteinuria and/or acanthocytes. Although certainly not possible for all patients, a renal biopsy should be pursued if GN is suspected to establish the exact diagnosis.

PATHOPHYSIOLOGY

Currently, HRS-AKI is regarded as a functional and not a structural disorder of the kidney mainly mediated by reduced perfusion[13,14]. Splanchnic vasodilatation seems to be of major importance for the development of HRS-AKI; this condition is leading to vascular underfilling compensated by vasoconstrictive mechanisms and salt retention[13,14]. As a result, renal blood supply is sharply reduced. A study by Epstein *et al*[15] provided evidence in patients with advanced cirrhotic liver disease. Renal arteriograms were performed in five patients twice: once at recruitment and then again post-mortem. Renal blood flow was sharply diminished at recruitment and cortical blood flow of the kidney was virtually absent. Post-mortem, renal blood was normalized with a physiological perfusion pattern. These findings indicate that HRS-AKI is a transient, functional disorder. In another study by Koppel *et al*[16], seven renal grafts from cadaveric donors with hepatic failure and HRS were transplanted to seven recipients. In four out of seven recipients, the renal allograft was still functional at six months after renal transplantation providing further evidence for the transient nature of HRS. In a case series from the early 70s, full renal recovery was reported after orthotopic liver transplantation (OLT) of three patients with liver failure and AKI[17]. In addition, a recent clinical study investigated the recovery of native kidney function after patients underwent simultaneous liver-kidney transplantation. 28 out of 31 patients recruited suffered from HRS. After transplantation, in 26 patients with HRS a significant recovery of native kidney function was observed with a native-only estimated mean glomerular filtration rate of 49.9 ± 9.4 mL/min/1.73 m^2[18].

Recently, an immunologic component has been added to the puzzle[19]. Data of two prospective cohort studies introduced the hypothesis that ongoing systemic inflammation contributes to decompensation of liver cirrhosis promoting organ failure[19,20]. Especially IL-6 has been associated with increased severity of organ failure and higher mortality in decompensated liver cirrhosis. Data from the PREDICT and CANONIC trials revealed that patients with severe failure of multiple organs show the highest levels of circulating IL-6[19]. In another study by Solé *et al*[21], patients with HRS-AKI had significantly elevated serum levels of IL-6 and vascular cell adhesion molecule 1 (VCAM-1)[21]. Notably, patients who achieved resolution of HRS-AKI had markedly lower serum levels of VCAM-1 compared to those patients with persistent HRS-AKI. VCAM-1 serum levels predicted mortality in patients with HRS-AKI. Nevertheless, mechanisms by which systemic inflammation is induced and sustained remain unclear; in this context, bacterial translocation (BTN) was proposed as one of the drivers of inflammation[19,22]. BTN occurs at gastrointestinal sites and is defined as migration of bacteria or bacterial products to extraintestinal sites[23]. Indeed, patients with cirrhosis are susceptible to infections that stem from the intestine; one common infectious complication is spontaneous bacterial peritonitis, most probably facilitated by increased BTN. Data from human studies have confirmed that BTN is promoted by increased intestinal permeability and alterations of the gut microbial flora in patients with liver cirrhosis. BTN may also trigger the release of pathogen-associated-molecular-patterns (PAMP) such as lipopolysaccharide and thereby cause and/or exaggerate a systemic inflammatory response[19]. Some evidence also indicate that AKI might be (at least co-) facilitated by PAMP and systemic inflammation. Shah *et al*[24] could demonstrate that urinary Toll-like receptor 4 (TLR4) was increased in patients with liver cirrhosis and AKI as compared to patients with stable, uncomplicated cirrhosis. Moreover, the authors found increased TLR4 expression in renal tubular cells. However, there were only few patients with HRS-AKI included and TLR4 expression seemed lower in HRS-AKI when compared to non-HRS-AKI[24]. In an animal model of HRS, the role of TLR4 was studied further. Mice were subjected to bile duct ligation to induce HRS. Additional renal injury was caused by unilateral ureter obstruction. Renal function as measured by blood urea nitrogen and serum creatinine was significantly better in animals with TLR4 deficiency indicating the potential key role in development of HRS[25]. Most importantly, PAMP may induce cell hypometabolism causing a persistent metabolic disorder in peripheral organs. This pathway may be a causal driving force towards functional organ failure as in the case of HRS-AKI in association with liver cirrhosis. The close interplay between infection, inflammation, hypometabolism, loss of function and HRS is summarized in Figure 1.

TREATMENT

The outcome of HRS-AKI is fatal if not treated[2,3,26]. As mainstay of pharmacologic therapy in Europe, the vasoconstrictor terlipressin is widely used in combination with albumin[2,3,26]. A recent placebo-controlled, randomized phase 3 trial investigated the efficacy of terlipressin in patients with HRS-AKI [27]. Recovery rate from HRS was significantly higher in the terlipressin group *vs* the placebo group (32% *vs* 17%, P = 0.006). However, survival was not significantly improved in patients treated with terlipressin as compared to placebo (49% *vs* 55%). In fact, death due to respiratory failure occurred more frequently in patients who received terlipressin (11% *vs* 2%). This trial showed that treatment with terlipressin is efficacious in reversal of HRS-AKI. However, the patients in this trial showed advanced renal dysfunction as indicated by the baseline serum creatinine of 3.5 mg/dL at recruitment[27]. This may have biased the study outcome and explain the lack of survival benefit in the terlipressin group

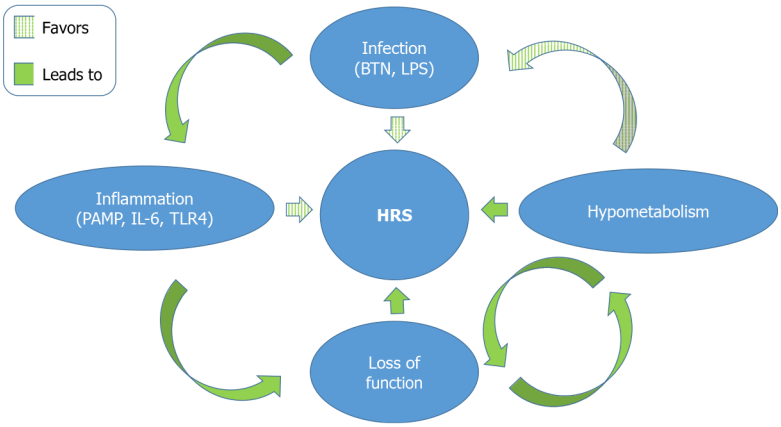

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Figure 1 Pathophysiology of hepatorenal syndrome. The interplay between infection, inflammation, hypometabolism, loss of function and hepatorenal syndrome is depicted. HRS: Hepatorenal syndrome; IL-6: Interleukin 6; BTN: Bacterial translocation; PAMP: Pathogen associated molecular patterns; TLR4: Toll-like receptor 4; LPS: Lipopolysaccharide.

despite reversal of HRS-AKI. Another recent, randomized, controlled trial compared the administration albumin *vs* placebo in patients with liver cirrhosis and HRS-AKI[28]. Interestingly, treatment with albumin alone did not show any beneficial effect on HRS-AKI or survival further underscoring the potential clinical value of terlipressin. Renal replacement therapy (RRT) should be considered in patients who are unresponsive to pharmacologic therapy. The application of RRT is limited by the hemodynamic status of the patient. Tatum *et al*[29] assessed the survival of 55 Liver transplant candidates who received RRT before transplantation[29]. In-hospital mortality was highest in patients on RRT for at least four days reaching 63.5% (4-6 d of RRT) and 59.1% (at least 7 d of RRT). Allegretti *et al*[30] studied the outcome of 341 non-transplant-listed patients with liver cirrhosis who became RRT-dependent during the hospital-stay. The 6-mo-survival of 56/341 patients with HRS was 16% with 4% being RRT-free. There is currently no evidence that extracorporeal liver support systems offer a lasting beneficial effect with respect to HRS[31]. Thus, RRT in the context of HRS is especially useful in patients awaiting liver transplant.

TRANSPLANTATION

Liver transplantation is the treatment of choice for HRS-AKI. Takahashi *et al*[32] studied a cohort of 324 patients who underwent living-related liver transplantation (LrLTX). Patients (285/324) were stratified into three groups: patients without HRS (56%), patients with HRS and treatment response (HRSr, 19%), and patients with HRS lacking treatment response (HRSn, 25%). 29/70 patients in the latter group were dialysis-dependent prior to LrLTX, whereas only 9/55 patients in the HRSr group received dialysis at any time-point prior to LrLTX. When patients with RRT were compared to the patients without RRT prior to LrLTX, the 1- year and 10-year survival was significantly decreased (79.0% *vs* 93.5% and 61.5% *vs* 80.1%, $P = 0.035$). Interestingly, 1-, 3- and 5-year survival was comparable between patients without HRS, HRSr and HRSn. Piano *et al*[4] reported similar findings in patients undergoing cadaveric OLT, *i.e.*, 82 patients with AKI-HRS *vs* 259 patients without AKI-HRS. However, survival probability at year 1 after LT was not different when the AKI-HRS group was divided into responders and non-responders *vs* controls (80% *vs* 86% *vs* 90%). Finally, the incidence of CKD during the first-year post-transplantation was significantly higher in non-responders as compared to responders or controls. Liver transplantation is considered as potent and efficacious treatment modality in patients with HRS-AKI. However, patients with severe, refractory HRS-AKI may be at higher risk for CKD after liver transplantation.

CONCLUSION

HRS is a multifactorial syndrome and the importance of immunological processes driving the pathology of HRS has been recently noted. The therapeutic options are limited and prognosis remains poor in patients who are not eligible for transplantation. Further studies are needed to unravel the patho-physiology of HRS and to develop new therapeutic strategies.

FOOTNOTES

Author contributions: Wilde B performed the majority of the writing and performed research of scientific literature; Canbay A prepared the figure and performed research of scientific literature; Katsounas A designed the outline, performed research of scientific literature, coordinated the writing and performed final editing.

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Rehab A Rayan

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Abstract

A noteworthy public health problem, antimicrobial resistance (AMR) has been impeded in many ways by the coronavirus disease 2019 (COVID-19) pandemic. This narrative review discusses the two-sided impact of COVID-19 on the magnitude of AMR. The pandemic has put tremendous strain on healthcare systems, diverting resources, personnel, and attention away from AMR diagnosis and management toward COVID-19 diagnosis and contact tracking and tracing. AMR research has been severely hampered, and surveillance and antimicrobial stewardship (AMS) programs have been de-emphasized, delayed, or halted. Antibiotics, particularly broad-spectrum, were prescribed more frequently without diagnostic confirmation of bacterial infection than before the pandemic. Nonetheless, the COVID-19 pandemic has highlighted the vulnerability of healthcare systems in controlling infectious disease threats and raised awareness of the importance of infection prevention and control. Yet, the pandemic has created opportunities to capitalize on positive effects on AMR management. The review concludes that it is now more important than ever to focus on AMR and strengthen AMS programs to ensure appropriate antibiotic use and other AMR prevention measures in healthcare. We must ensure that one of the COVID-19 legacies is increased support for AMR research, diagnostic implementation, appropriate diagnostic stewardship, and the strengthening of our health systems. The COVID-19 pandemic has demonstrated that prevention is better than cure. Countries will need to step up their efforts to combat AMR as a multidisciplinary community. We must prepare our public health systems to combat multiple threats at the same time.

Key Words: One Health; Antimicrobial resistance; Coronavirus pandemic; Antimicrobials; Antibiotics; Antimicrobial stewardship

Core Tip: If given the resources, the globe can continue to develop robust public health and healthcare systems to protect its citizens against antimicrobial resistance (AMR). The findings from this narrative review indicate that the pandemic's overuse of antibiotics highlights the need to strengthen antimicrobial stewardship (AMS) programs so that they can guide disciplines. This review recommends that it is now more important than ever to focus on AMR and strengthen AMS programs to ensure appropriate antibiotic use and other AMR prevention measures in healthcare. Performing rapid and accurate point-of-care tests before an antibiotic prescription is an efficient way to optimize antibiotic administration and prevent the development of antibiotic-resistant bacteria.

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INTRODUCTION

One of the world's most serious public health threats is antimicrobial resistance (AMR). AMR, also known as the silent pandemic, happens when bacteria, viruses, fungi, and parasites change and stop responding to medication. As a result, infections become more challenging to cure, raising the risk of a serious disease and death. Drug resistance renders antibiotics and other antimicrobial medications ineffective, making it more challenging or impossible to treat infections. AMR poses a concern on a worldwide scale, especially in developing nations. Antibiotic and antifungal resistance increased dramatically during the coronavirus disease 2019 (COVID-19) pandemic, reversing previous gains. Antibiotic-resistant bacteria cause 1.3 million direct deaths and five million indirect deaths each year[1]. Estimates were made in 2019 before the COVID-19 pandemic worsened the situation. Unfortunately, those most susceptible to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which causes COVID-19, are also the most susceptible to drug-resistant infections[2]. People over the age of sixty-five, as well as those with underlying medical conditions such as cardiovascular diseases, diabetes, chronic respiratory diseases, and cancer, are at a higher risk of developing a serious illness, regardless of the cause.

Before the COVID-19 pandemic, the World Health Organization (WHO) classified AMR as one of the top ten most critical global health problems[3]. According to one study, if no action is taken, AMR will cause ten million deaths yearly researching 2050, with a financial effect of over 100 trillion USD[4]. Efforts for addressing AMR as a significant universal health issue have just lately increased. Taking part in the WHO Global Antimicrobial Resistance and Use Surveillance System grew exponentially between 2017 and 2019, aggregating data from over 64000 surveillance sites in sixty-six countries[5]. This surveillance system had ninety-four countries enrolled in August 2020[6]. This level of participation represents a meaningful accomplishment in the global fight against this health threat. Antimicrobial stewardship (AMS) programs and National Action Plans had made considerable progress in many countries before COVID-19 in slowing AMR.

However, there are growing fears that the COVID-19 pandemic has slowed present and upcoming efforts against AMR[7]. Antibiotics, for example, were prescribed more frequently without diagnostic confirmation of bacterial infection than before the pandemic. Because of the COVID-19 emergency in healthcare systems, many planned activities were deprioritized, and already implemented preventive measures were reversed. The pandemic has put tremendous strain on healthcare systems, diverting resources, personnel, and attention away from AMR diagnosis and management toward COVID-19 detection and contact tracing. AMR studies have been largely hampered, and surveillance and AMS programs have been de-emphasized, lagged, or stopped[8]. Furthermore, during the first two years of the COVID-19 pandemic, hard lessons were learned about prioritizing COVID-19 transmission surveillance at the expense of decreased AMR surveillance[9].

To find out the magnitude of AMR considering COVID-19, we carried out a narrative literature review in various distinguished and reliable journals, news, governmental, and organizational websites on Google, Google Scholar, and PubMed. We denoted appropriate studies by searching for reports on One Health, AMR, antimicrobials, antibiotics, and AMS, in relation to the coronavirus pandemic. Findings from studies were considered if they explicitly noted the linkage between AMR and the COVID-19 pandemic. The search was carried out in December 2022 and covered published peer-reviewed studies accessible from the attack of COVID-19 in December 2019 to December 2022.

This review aims to discuss the impact of COVID-19 on the magnitude of AMR, as shown in Figure 1. First, it highlights the negative aspect of the situation (obstacles) in terms of overprescribing antibiotics during the pandemic, especially broad-spectrum ones. Besides, it augments the argument with data drawn from the case study of the United States concerning the effect of the COVID-19 pandemic inside

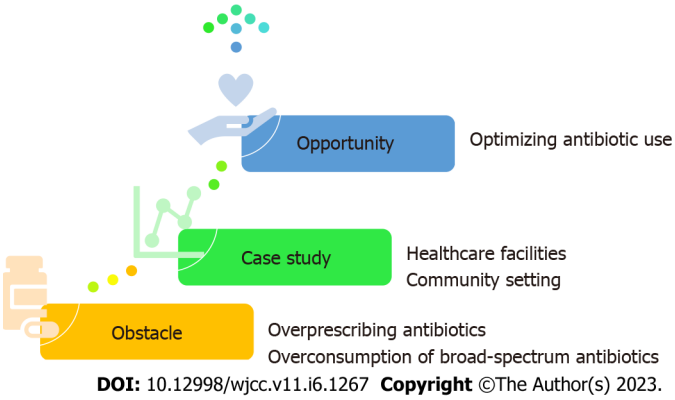

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Figure 1 The impact of the coronavirus disease 2019 pandemic on the magnitude of antimicrobial resistance.

and outside healthcare facilities. Next, it shows the positive side (opportunities) highlighting optimizing the use efforts to prevent AMR. Finally, it concludes with a global call for action now to curb the silent pandemic of AMR.

IMPACT OF THE COVID-19 PANDEMIC: OBSTACLES

Antibiotics and antifungals can save lives, but they can also contribute to resistance when used in humans, animals, or plants. During the pandemic, antibiotic use differed throughout healthcare settings. Antibiotics were frequently administered to COVID-19 patients, yet antibiotics are ineffective against viruses such as that lead to COVID-19. Preventing infections from starting is vital in both our communities and medical settings. In hospitals, many infection prevention and control (IPC) regulations were impeded by pandemic-related issues, which unfortunately led to some AMR advancements being reversed. Hand hygiene, disinfecting tools, segregating patients, and properly handling personal protective equipment (PPE) are all IPC practices. During the pandemic, there were more and sicker patients who needed catheters and ventilators more frequently and for longer periods. This might increase the risk of hospital-acquired infections (HAIs) and pathogen spread, particularly when combined with PPE and lab supply issues, reduced staff, and longer lengths of stay[9].

A considerable lag in tracking AMR, including detection and reporting data, was brought on by changes in patient care, testing, and treatment, as well as personnel availability at healthcare institutions and health departments, because of the COVID-19 pandemic. Knowing where and how resistance changes occur helps to provide strategies (such as outbreak response) to avoid resistance spread and slow resistance. For instance, 23% fewer specimens or isolates were received by the United States Center for Diseases Prevention and Control AMR Lab Network in 2020 than in 2019 for evaluation. Throughout 2020, it kept gathering isolates using tried-and-true methods, while other isolates went untested because of testing halt. This could be for the fact that health facilities and population health personnel had to direct their efforts to COVID-19. Many AMR systems were used to assist the global response to COVID-19, covering testing and providing surge capacity to overburdened laboratories. The Centers for Disease Prevention and Control (CDC)'s National Tuberculosis Molecular Surveillance Center, for example, studied SARS-CoV-2 using its AMR Lab Network sequencing capabilities[10].

FREQUENT PRESCRIPTION OF ANTIBIOTICS

Antibiotics do not cure viral infections like COVID-19, but bacterial coinfections can occur alongside viral infections. Antibiotic treatment of COVID-19 patients was more of a rule than an exception in many countries, particularly during the early pandemic. Concerns about bacterial confections and difficulties distinguishing COVID-19 from community-acquired pneumonia led to the overuse of antibiotics. For instance, antibiotics were prescribed to 80%-100% of COVID-19 hospitalized patients in the United States and China during the first six months of the COVID-19 pandemic, even though they were rarely indicated at the time. Bacterial coinfections were reported in only 7%-8% of hospitalized patients and 14% of intensive care unit (ICU) patients, implying that antibiotics were frequently used inappropriately in the treatment of COVID-19[11]. According to another study's findings based on data collected from over 30000 patients, the estimated rate of bacterial coinfection was also less than 9%[12].

On the contrary, and because of the reduction in healthcare-seeking behavior during the pandemic, infections that do warrant antibiotics, such as tuberculosis, gonorrhea, and pneumococcus, may have gone untreated. But we do not have the same amount of information on how superbug resistance

patterns are developing in the community context as we do in the inpatient situation, where hospitals track the bacteria inside their walls and their susceptibility patterns[13,14].

MORE CONSUMPTION OF BROAD-SPECTRUM ANTIBIOTICS

In both primary care settings and hospitals, the use of broad-spectrum antibiotics has grown in European nations. In addition, broad-spectrum antibiotics were commonly used in hospitalized COVID-19 patients in the United States Antibiotics with a broad spectrum of activity are effective against a wide variety of bacteria. Hospitals were flooded with critically ill patients, particularly early in the pandemic, and those patients stayed for extremely prolonged periods. Those suffering from fever and pneumonia were given broad-spectrum antibiotics. When it was not clear what the course of severe COVID-19 illness would be, there was an impulse to treat severely pneumatic ICU-admitted patients with broad-spectrum antibiotics. And this is despite years of steady decline in HAIs, which AMS committees, IPC programs, and hospitals worked hard to achieve. Broad-spectrum antibiotics should not be used as a first-line treatment and should only be used to treat severe bacterial infections. It is critical to use them correctly to avoid the development of drug resistance.

The COVID-19 pandemic highlights healthcare workers' human desire to intervene, especially when a patient is critically ill, which can lead to a suspension of evidence-based medicine at the bedside. Uncertainty about the COVID-19 diagnosis, combined with a desire to assist patients, concerns about bacterial coinfections, and misleading results from a variety of diagnostic tests, all contributed to an increase in antibiotic overuse early in the pandemic.

CASE OF THE UNITED STATES

In the United States, 29400 people died in the first year of the pandemic from infections that were frequently associated with medical care and were resistant to antibiotics. Nearly 40% of these patients contracted an infection while hospitalized[9,13,14]. Although the overall number of AMR deaths in the United States may be significantly higher, it is impossible to analyze because of data gaps brought on by the epidemic. Since 2013, the United States has been sounding the alarm about AMR, citing the threat it posed to the healthcare system, food supply, environment, and community. Before the pandemic, 50000 Americans died from antimicrobial-resistant infections or *Clostridioides* difficile infections (often associated with antimicrobial use)[13,14]. According to the CDC's 2019 projections; every year, over 35000 Americans die from at least 2.8 million infections that are resistant to antibiotics[13]. However, significant nationwide investments in improving IPC as well as antimicrobial use resulted in antimicrobial-resistant infections falling by 27% along with reduced antimicrobial-resistant infection deaths by 18% between 2012 and 2017 and by 30% in hospitals[13,14]. These declines persisted until 2020. In contrast, the pandemic led to an increase in antibiotic resistance, a rise in antibiotic usage, and a decrease in data and preventative measures[15].

IMPACT OF COVID-19 ON HEALTHCARE FACILITIES

Antimicrobial-resistant infections in healthcare facilities in the United States increased, particularly in hospitals. Hospitals cared for sicker patients who needed medical devices like catheters and ventilators more frequently and for longer periods. Hospitals also faced issues with PPE supply, staffing shortages, and longer patient visits. From March to October 2020, 80% of COVID-19 patients hospitalized in the United States received an antibiotic[13,14]. Ceftriaxone, which was commonly prescribed with azithromycin, was given to half of the hospitalized patients. This is because of challenges in differentiating COVID-19 from community-acquired pneumonia when patients are admitted in a healthcare facility for evaluation. Both resistant hospital-onset infections and mortality jumped by minimally 15% between 2019 and 2020[13].

Following years of consistent declines in HAIs, in 2010, four of the six kinds of HAIs were significantly higher in United States hospitals. Several such HAIs are resistant to antibiotics. There was a 78% increase in infections caused by the carbapenem-resistant *Acinetobacter*, a 32% increase in infections caused by the multidrug-resistant Pseudomonas aeruginosa, a 14% increase in infections caused by the vancomycin-resistant *Enterococcus*, and a 13% increase in infections caused by the methicillin-resistant *Staphylococcus aureus* (MRSA)[13,14]. Furthermore, antifungal-resistant infections such as *Candida Auris* (that generally grew 60%) and *Candida* species (without *Candida Auris*) surged in 2020, with a rise of 26% in hospital infections. Over twenty outbreaks caused by resistant infections, such as *Candida Auris* and *Acinetobacter*, occurred in COVID-19 treatment and observation units. Unknown factors may have a long-term impact on a region's antimicrobial-resistant bacteria outbreak[9,13].

IMPACT OF COVID-19 ON COMMUNITY SETTINGS

We have limited data on the spread of antimicrobial-resistant pathogens in communities, such as drug-resistant gonorrhea and food-borne germs. Yet, antibiotic use in outpatient clinics fell critically during 2020 in comparison to 2019 because of limited access to outpatient healthcare and lower magnitude of other respiratory conditions, which frequently result in administering antibiotics. Patients had reduced access to care and testing because public health staff were redirected to the global pandemic response. In reaction to COVID-19 issues, several medical institutions and clinics reduced access, received less patients, or shut their doors completely. Prior to the COVID-19 pandemic, data between 2012 and 2017 displayed that numerous resistant infections commonly discovered in the community were on the rise. In 2020, potentially resistant infections spread undetected and untreated in communities. In 2021, outpatient antibiotic consumption increased, yet it remained generally less during 2021 in comparison to 2019. Between 2020 to December 2021, azithromycin was the highest prescribed antibiotic for adults, and increases in azithromycin prescribing followed peaks in COVID-19 cases[9].

Even while antibiotic use in nursing homes has grown in response to COVID-19 outbreaks, it is still very low. However, compared to the same months in 2019, usage of azithromycin rose by 150% in April and 82% in December 2020. Using azithromycin remained high until October 2020. Overall, antibiotic use in 2021 was 5% less than that during 2019. This decline could be attributed to limited residents in nursing homes in this period[9].

IMPACT OF THE COVID-19 PANDEMIC: OPPORTUNITIES

Nonetheless, the COVID-19 pandemic has emphasized the fragility of healthcare systems in managing threats of infectious diseases and raised attention of the value of IPC. The pandemic has created opportunities to capitalize on positive effects on AMR management. COVID-19 has had a substantial impact on our social interactions. Subjects are much more aware of protective healthcare measures like washing hands, putting on face masks, and maintaining physical distance[16]. These behavioral shifts will aid in the prevention of infectious diseases, covering those impacted by AMR; however, there is a recidivism risk after the COVID-19 pandemic has passed[17]. Maintaining high-quality IPC training is needed for all healthcare professionals and facilities other than hospitals, such as nursing homes and other long-term care facilities. This includes educating the public on how to prevent the spread of germs and infection in the communities where they live and work.

Because of fewer visits to primary care, overall antibiotic consumption in primary care decreased in many countries during COVID-19. Overall, outpatient antibiotic prescribing trended downward during the first pandemic year. For instance, the Epocrates app, which provides a window into what clinicians are thinking, saw a significant decrease in lookups for antibiotics that are sometimes inappropriately used for upper respiratory infections as early as March 2020. However, during the first year of the pandemic, changes in clinician accessibility and office hours, stay-at-home directives, and mask regulations—all of which we made to stop the spread of COVID-19—had a positive impact on limiting the spread of respiratory infections.

COVID-19 has raised awareness of the importance of laboratory capacity and surveillance[18]. The COVID-19 mitigation response relies heavily on robust diagnostic and laboratory surveillance systems. Repurposing this capacity for AMR will be efficient because such elements are required for the proper detection of infectious conditions and for evaluating the capacity of AMS programs inside the healthcare system, particularly in developing nations[19]. At the same time, the same healthcare authorities' readiness to spend money on additional diagnostics, including point-of-care testing for rapid bacterial infectious illness and AMR[20]. This investment may encourage healthcare authorities to replicate quickly assembled infrastructure, like polymerase chain reaction and lateral flow examinations, for the detecting COVID-19 at scale, to detect AMR. Expanding electronic data automation would provide healthcare facilities and systems with the information they need on antibiotic use and AMR. This also entails using well-established networks like the AMR Lab Network to share information during emergencies, employing telehealth to track down contacts, and making efforts to guarantee that there are laboratory supplies and tools accessible for IPC and patient care.

AMR is a One Health problem that impacts the wellbeing of people, animals, plants, and the environment. Maneuvers to detect antimicrobial-resistant microorganisms, trace the spread of resistance, and assess the impact of the consumption of antimicrobials need monitoring of human, animal, and plant populations, as well as the environment. Increasing the capacity of the National Wastewater Surveillance Systems to collect AMR data from wastewater treatment plants and healthcare facilities, as well as researching resistance in community and healthcare wastewater on a domestic and global scale. This includes increasing global capacity to combat AMR in the environment and monitoring AMR across One Health.

The COVID-19 pandemic has highlighted the importance of improving IPC and hygiene, as well as a reminder that following IPC protocols is critical in reducing hospitalizations. These protocols, which are required to prevent the transmission of SARS-CoV-2, have the potential to significantly reduce AMR

prevalence[18]. The COVID-19 pandemic has raised attention and reaffirmed the importance of a worldwide One Health tract. One Health tract has the possibility to efficiently fight COVID-19 infection [21], and it could combat the growing AMR. Vaccines, which efficiently guard against SARS-CoV-2 will support lowering COVID-19 magnitude and inappropriate antibiotic use, hopefully decreasing the prevalence of AMR worldwide. Encouraging the administration of vaccines for preventable infectious conditions could have a significant effect on the spread of AMR[22].

OPTIMIZING ANTIBIOTIC USE TO PREVENT AMR

The future of AMR is dependent on antibiotic prescribing decisions made today, as well as the care teams responsible for IPC. To regain some of the ground lost during the pandemic, we must revisit basic AMS and IPC principles. Vaccinations, both routine, and catch-up, are needed to prevent infections. The COVID-19 pandemic had a significant impact on preventive vaccination uptake rates in a variety of patient populations. Pneumonia caused by MRSA and other bacteria is a leading cause of death in influenza patients, and influenza vaccination may reduce the risk of bacterial superinfection. Antibiotic use should be optimized across all healthcare settings. Additionally, we should promote tracking for companion animals and agriculture, as well as effective antibiotic and antifungal usage[11].

Viral infections should no longer be treated with antibiotics. Using viral diagnostics and procalcitonin measurements may aid in identifying patients who can be weaned off antibiotics. Recognizing the patient's symptoms, providing symptom relief, and educating the patient about the risks associated with inappropriate antibiotic use if a viral infection is suspected. It is also critical to follow the recommendations of specialty societies when treating viral infections. Treatment must be tailored to the antibiotic spectrum. Referring to the most recent and local data on antimicrobial susceptibility when making decisions. When obtaining blood cultures, take precautions to avoid contamination and narrow the spectrum based on the results. Examining the veracity of documented antibiotic allergies, particularly those related to penicillin[23]. We must adhere to the most recent specialist society recommendations for antibiotic treatment durations and employ the shortest durations possible to prevent unwanted antibiotic exposures. A greater emphasis on IPC procedures because of the COVID-19 pandemic has the potential to reduce other HAIs.

Patient education is vital to antibiotic treatment adherence. Years ago, there was an emphasis on "taking the full course" of antibiotics. Now, the focus has shifted to the shortest and clinically appropriate effective duration of therapy. Each additional day of antibiotic treatment increases the risk of patient harm. The length of antibiotic therapy must be optimized at the time of hospital discharge; for instance, most of the unnecessary antibiotic usage for community-acquired pneumonia occurs after discharge.

AMS is our most potent weapon against AMR, and it deserves high priority and investment from healthcare systems. The key components of the initiative include IPC, quick-cycle research, and education activities, reduced diagnostic ambiguity regarding bacterial infections, avoidance of improper antibiotic usage and durations, and rapid de-escalation based on outcomes. New antibiotics alone will not be enough to fix this issue. Antimicrobial drugs with novel modes of action are scarce, and it takes a while for them to reach the market. The post-antibiotic era has already begun because of the disparity between AMR rates and the development of novel antibiotics. Resistance will certainly develop in the presence of new agents. Novel treatment approaches, such as antibody therapy, bacteriophages, and fecal microbiota transplantation, are being investigated.

The shift in trend indicates that AMR prevention efforts must be revisited and reintegrated into healthcare systems. Despite a great desire to assist patients when there are few treatment choices available, medical personnel should use antibiotics and diagnostic tests cautiously in the early phases of an epidemic. We can learn a lot from the COVID-19 pandemic about upcoming viral pandemics. Faced with new infectious disease outbreaks, hospitals and healthcare workers should improve antibiotic prescribing. They should follow the recommendation in cases where an antibiotic should be considered in a respiratory viral epidemic, as well as in cases where diagnostic tests are indicated. The COVID-19 pandemic has demonstrated that prevention is better than cure. We must prepare our public health systems to combat multiple threats at the same time[24].

The strength of this narrative review lies in its findings indicating that the pandemic's overuse of antibiotics highlights the need to strengthen AMS programs so that they can guide disciplines. Yet, the major limitations are basing the argument on data drawn mainly from one country and the lack of a systematic approach to studying the impact of the COVID-19 pandemic on AMR on a global scale.

CONCLUSION

We must not overlook the possibility that the pandemic will increase AMR globally. Even before the SARS-CoV-2 pandemic, overcoming AMR demanded immediate global action. Understanding the pathogenesis (how a disease develops) of SARS-CoV-2 infection, as well as the possibility of bacterial

coinfections, is critical now that we are amid a pandemic. We must ensure that one of the COVID-19 legacies is increased support for AMR research, diagnostic implementation, appropriate diagnostic stewardship, and the strengthening of our health systems. As we emerge from the pandemic, there is a significant opportunity for the healthcare systems to promote cooperation with policymakers, the population, and the mass media to pay more attention to AMR and engagement to complement the legacy of COVID-19 physical separation, washing hands, face masks, producing vaccines, and keeping away from unneeded antibiotic consumption. States will have to step up their capacities to combat AMR in muti-sectoral contexts. Multi-sectoral, coordinated, and targeted research on such resistance, under the One Health approach, will be vital for competent curbing of AMR in the context of the pandemic, as well as for presenting opportunities for addressing AMR. Eventually, more research is needed to study the impact of the COVID-19 pandemic on AMR systematically on a global scale, pooling data from different countries and taking into consideration the economic variations between countries.

FOOTNOTES

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MINIREVIEWS

Implications of metabolic dysfunction associated fatty liver disease in COVID-19

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Abstract

Metabolic associated fatty liver disorder (MAFLD) characterizes the contributing etiologies (*i.e.*, type 2 diabetes mellitus, metabolic syndrome, overweight) of individuals with fatty liver disease that affects 1/3rd of the world population. In 2020, the coronavirus disease 2019 (COVID-19) crisis was unprecedented, and people with different comorbidities became more susceptible to the infection caused by severe acute respiratory syndrome coronavirus 2. MAFLD patients are frequently obese with added metabolic menace like diabetes, hypertension, and dyslipidemia leading to greater jeopardy of COVID-19. MAFLD patients are 4 to 6-fold more prone towards infections. COVID-19 induces liver injury with elevated levels of aspartate aminotransferase and alanine aminotransferase and insignificantly elevated bilirubin. Hence, MAFLD in COVID-19 patients worsens the condition significantly. The evidence highlighting the interaction between MAFLD and altered liver functioning in COVID-19 suggested that COVID-19 patients with pre-existing MAFLD are at greater risk of morbidity or intensive care unit admission. Direct hepatic injury, enhanced levels of inflammatory cytokines, declined hepatic mitochondrial activity, and compromised immunity are considered as some underlying mechanisms. The main focus of this review is to discuss the implications of metabolic dysfunction associated with fatty liver disease in COVID-19 patients. The review systematically analyzes the effect of

striking two worldwide pandemics (MAFLD and COVID-19) together in the present era.

Key Words: Metabolic associated fatty liver disorder; COVID-19; Metabolic dysfunction; Hepatic damage; Cytokine storm

Core Tip: Metabolic associated fatty liver disorder (MAFLD) is associated with fat accumulation and inflammation in hepatocytes, thus compromising liver function and making people more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Therefore, cytokine storm in SARS-CoV-2 infected MAFLD patients is considered severe and requires urgent attention. In addition, direct hepatic injury caused by SARS-CoV-2, enhanced levels of inflammatory cytokines, declined hepatic mitochondrial activity, compromised immunity, and altered expression of host angiotensin-converting enzyme 2 receptor are considered as some underlying mechanisms. Thus, patients with MAFLD require special attention to protect themselves from the SARS-CoV-2 infection or severe illness caused by SARS-CoV-2.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a novel beta coronavirus, namely, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 originated in Wuhan, Hubei province of China in 2019 and was declared a pandemic by the World Health Organization on March 12, 2020[1]. It is an acute atypical respiratory disease targeting the lungs, and symptoms range from mild to severe. Common symptoms of COVID-19 include cough, fever, nasal congestion, shortness of breath, and difficulty breathing, and severe COVID-19 can lead to pneumonia, kidney failure, acute severe respiratory syndrome, septic shock, multiple organ failure, and death[2,3]. Gastrointestinal symptoms include abdominal pain, vomiting, and diarrhoea[4]. The risk factors associated with COVID-19 are older age and comorbidities (diabetes, hypertension, obesity, and coronary artery disease) leading to multi-organ failure and death[5]. In addition, SARS-CoV-2 activates antiviral immune response and releases proinflammatory cytokines causing an uncontrolled inflammatory response leading to immune abnormalities, which may lead to septic shock, multiple organ failure, and infection by microbes[6].

Metabolic dysfunction associated fatty liver disease (MAFLD) (formerly named non-alcoholic fatty liver disease) poses an economic and health burden on society, affecting a quarter of the world population[7]. There is a dramatic increase in the prevalence of obesity and metabolic syndrome in Western and Asian countries due to changes in diet and lifestyle that have significantly increased the occurrence of MAFLD. Based on histopathological features, it can be classified into simple steatosis and non-alcoholic steatohepatitis that can progress to liver cancer and cirrhosis. Obesity, increasing age, and diabetes are the major risk factors associated with cirrhosis in MAFLD patients[8]. MAFLD is a hepatic manifestation of various metabolic dysfunctions, including obesity, dyslipidemia, type 2 diabetes mellitus, insulin resistance, oxidative stress, adipokines, and apoptosis[9].

MAFLD AND COVID-19

MAFLD is associated with fat accumulation and inflammation in hepatocytes, thus compromising liver function and making people more susceptible to SARS-CoV-2 infection. COVID-19 induces liver apoptosis and is observed with hepatic steatosis and damaging hepatocytes due to increased levels of inflammatory mediators, such as IL-1, IL-6, and IL-10. MAFLD patients are at a 4 to 6-fold higher risk of severe COVID-19 infection[10] as it exacerbates the virus-related cytokine storm[11] and carries a combination of comorbidities which is also a potential risk factor for COVID-19. Obese and advanced fibrosis MAFLD patients are more prone to severe COVID-19. The severity of COVID-19 in MAFLD patients is not associated with advanced liver diseases, and the mortality in the MAFLD group is associated with enhanced and pronounced inflammatory response in the host[12]. MAFLD patients with COVID-19 tend to have more severe symptoms and require more intensive hospital care and long-

term monitoring than non-MAFLD patients[13]. Morbid obesity, older age, multi-morbidity scores, elevated FIB-4 scores, and hypoxia are independent predictors of mortality in hospitalized MAFLD patients[14]. MAFLD is associated with a higher risk of hospitalization in COVID-19 patients, and metabolic syndrome treatment with metformin, GLP-1RA, and bariatric surgery can mitigate the risk [15].

A preliminary analysis was done by Ji *et al*[16] on the implications of MAFLD in 202 COVID-19 patients. Persistent abnormal liver function was observed in 33% of patients from hospitalization to follow-up. MAFLD is an independent risk factor for the progression of COVID-19, causing liver damage and more prolonged viral shedding. The rate of liver abnormalities was 50% at the time of hospitalization and increased to 75% during the hospital stay. The same observation was supported by Huang *et al*[17] on 280 patients with COVID-19; 35.7% of patients reported abnormal liver function during admission. The alanine aminotransferase (ALT) level was higher in MAFLD patients compared to non-MAFLD ones on admission and during hospitalization. Older age (> 50 years) and concurrent MAFLD are risk factors for liver damage in patients suffering from COVID-19. A meta-analysis of 14 studies, including 1851 MAFLD patients, concluded that there is an increased risk of severe COVID-19 and ICU admission compared to the non-MAFLD group with no difference in mortality between MAFLD and non-MAFLD patients[18,19]. A multicenter cohort study on 65 MAFLD and 65 non-MAFLD patients demonstrated a positive correlation between MAFLD and metabolic risk factors and COVID-19 in non-diabetic patients. MAFLD was associated with a four-fold risk of severe COVID-19 in non-diabetic patients[20].

FACTORS INFLUENCING INTERACTION BETWEEN MAFLD/MAFLD AND COVID-19

A combination of risk factors itself accompanies MAFLD. Hence, several risk factors are allied with the interaction between MAFLD and COVID-19, which will be discussed in this section.

Influence of age

Age is a circuitously affecting factor for the rapport between MAFLD and COVID-19. People with comorbidities like diabetes, hypertension, chronic lung disorder, *etc.* are susceptible to COVID-19, particularly elderly patients. Thus, elderly patients are more susceptible to MAFLD and COVID-19. Hence, ageing can be considered as one of the perpetrators of the speedy attack of both diseases as mentioned above, and their alliance can also be affected by ageing very symptomatically.

A systematic multicenter analysis supported that younger patients with COVID-19 are more prone to gain MAFLD than aged patients. The study included 327 patients of different age groups. The patients younger than 60 years were grouped as younger, while the patients more than 60 years of age were grouped as older or aged patients[21]. According to the data, people with severe COVID-19 who had MAFLD made up 24% of the elderly patients and 55.9% of the younger patients. It is conspicuous that in young patients, but not in elderly ones, MAFLD was interrelated to the sternness of COVID-19. The influence of age on the alliance of MAFLD and COVID-19 still needs a proven mechanism for support. In comparison to younger patients, older patients have more comorbid conditions that involve many organs and greater death rates, which may outweigh the effect of MAFLD on COVID-19[22,23].

Impact of hypertension

In the general population, the prevalence of MAFLD is comparatively much higher in patients suffering from COVID-19. Studies prove that MAFLD plays a significant role in vulnerability to COVID-19. Sequentially, COVID-19 exacerbates MAFLD development. The relationship between MAFLD and COVID-19 is like a web, and both are interconnected with each other very intricately. The metabolic hitches like hypertension and lipid cholesterol levels get promoted by COVID-19. The development of COVID-19 is also accelerated in MAFLD patients due to metabolic comorbidities such hypertension and high lipid or cholesterol levels. In MAFLD patients with COVID-19, monitoring and treating these metabolic conditions can reduce the risk of a deprived projection.

One of the metabolic comorbidities, hypertension, is a crucial menace that affects the incidence and advancement of COVID-19. In a cohort study of patients with COVID-19 and chronic metabolic diseases, COVID-19 had the highest incidence in patients with hypertension, and 49.7% of patients with COVID-19 suffer from hypertension[24]. Hypertension is allied with the anomalous instigation of the renin-angiotensin system and the lessened countenance of angiotensin converting enzyme-2 (ACE-2) [25]. Therefore, ACE-2 levels get reduced in hypertension patients. Hence as per the hypothesis, these decreased ACE-2 Levels are responsible for the easy vulnerability towards COVID-19. Inversely, it has been anticipated that COVID-19 decreases ACE-2 bustle and its receptors, resulting in a higher incidence of hypertension in COVID-19 patients. Hypertension may enhance the menace of MAFLD in COVID-19 patients, with the reason being subordinate aspects, such as the instigation of systemic inflammatory reactions in the case of hypertension rather than ACE-2 receptors directly[26]. Around 126 out of 251 COVID-19 patients had hypertension in a retrospective study. The study exhibited that COVID-19 patients with hypertension had higher levels of interleukin -6 (IL-6) and a higher sensitivity

to C-reactive protein and procalcitonin than the non-hypertensive patients[27].

These statistics suggested that COVID-19 patients with hypertension have a more unadorned systemic inflammatory retort than non-hypertension patients. The retort may affect liver metabolism in unembellished cases and cause subordinate liver damage or organ dysfunction.

Impact of dyslipidemia

Dyslipidemia is a metabolic comorbidity comprising anomalous upgradation in triglycerides (TG) and anomalous reduction in high-density lipoprotein. Dyslipidemia was found to be the subsequent recurrent complication after hypertension in a study among COVID-19 patients. An investigation has revealed that after the commencement of the disease, significant lowering of different cholesterols in the body (total cholesterol (TC)[28,29], TG, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) occurs. The changes in these levels were responsible for brutality and the impermanence of the disease. Like the SARS virus, the SARS-CoV-2 also assaults the host cells through synthesizing and packaging virus particles using lipids, leading to a decree in the blood lipid components, which is counted as one of the consistent characteristics of dyslipidemia. Increased incidences of COVID-19 were observed due to an anomalous rise in triglycerides and total cholesterols in MAFLD patients. Therefore, patients with metabolic syndrome and dyslipidemia repeatedly have liver lipid metabolic surplus that may have a harmonious effect when combined with COVID-19, which may also be one of the reasons for liver injury. However, more specific studies are essential to authenticate this concept.

Impact of obesity

Obesity is a sovereign menace aspect of COVID-19. A cohort study, including around 350 patients infected by SARS-CoV-2, suggested that 52% of the patients were intricated with obesity[30]. A similar study revealed that around 19% of obese patients with COVID -19 suffered from MAFLD[31]. The exact mechanism for this has not been explained to date though numerous probable reasons may enlighten this rapport. The foremost reason is that obese patients frequently suffer from MAFLD due to visceral fat accretion. The inflammatory response of MAFLD itself can result in chronic liver injury. On this ground, COVID-19 and the drugs used to treat COVID-19 may additionally exacerbate liver grievance. The second reason is a liver injury resulting from weakened aeration in obese patients, leading to sleep apnea syndrome and hypoxemia, and further an anoxic atmosphere for liver metabolism. The third reason is the affected immune system due to obesity[32]. Numerous inflammatory responses are produced due to adipocytes and immune cells serving comparable functions[31].

In obese patients, the disparity in the regulation of adipocytes and the immune system may endorse the incidence of a provocative tempest due to COVID-19. Thus, the situation may lead to multisystem organ injury as the ultimate consequence.

Impact of diabetes

One relevant study revealed that around 74% of diabetes patients with COVID-19 suffer liver injury. The results claim that diabetes mellitus is one of the prime factors responsible for COVID-19 and MAFLD[33]. The mechanism for the same is still not very clear. However, the influence of high glucose levels over SARS-CoV-2 replication may be considered one of the strong bases influencing the degree of viral incursion. This phenomenon results in an aggravative systemic inflammatory response, resulting in multiple organ impairments, including the liver. The other reason is diabetes as an autoimmune and enduring inflammatory disorder (disparities of CD4+ or CD8+ T lymphocytes), further exaggerated by COVID-19. The liver is one of the most critical immune organs participating in the phagocytosis of exogenous microorganisms and releasing cytokines, and the hepatic immunomodulatory load may increase in diabetic patients with COVID-19. The last reason is anti-diabetic drugs that cause an irregular upsurge in transaminase and intensified immune-mediated hepatic injury[34]. Diabetes is a sovereign risk feature for COVID-19.

Impact of gender

Primary research findings recommend inequality in occurrences of COVID-19 gender-wise. According to these findings, men were usually at more considerable peril than women. For example, a clinical study in China reported that around 58% of patients were men, and as per WHO records, fatality of COVID-19 was more (approximately 65%) in men than women. This gender inequality was justified through the following clarifications:

Due to the heavy load of non-communicable diseases such as cardiac disorders, cancers, diabetes, *etc.* in males, mortality rates are higher in male COVID-19 patients than in females.

Men are more careless towards good health habits and are more fascinated by lifestyle-generated habits like addiction, smoking, irregular sleep cycle, and more fascination for media, which makes men more prone to SARS-CoV-2 infection.

Much research supports the stronger immune system of women than men, which is also one of the causes of easy COVID-19 and MAFLD attacks.

Instead of a higher percentage of men at higher risk for COVID-19 and MAFLD, few groups of women, like pregnant females, are at greater risk for both diseases.

Nevertheless, advanced studies suggested no gender bar for COVID-19 and MAFLD, as women also have many personal and social responsibilities compared to men, leading them to mental trauma with weak immunity leading to impaired hepatic function and easy attack of COVID-19[35,36].

DRUG-INDUCED LIVER INJURY IN COVID-19 TREATMENT

Drug-induced liver injury (DILI) represents liver lesions or liver dysfunction due to medications. The most probable cause of liver injury in COVID-19 patients may be due to the use of multiple drugs for COVID-19 treatment, like antibiotics, antivirals, analgesics, antipyretics, many traditional Chinese medicines, ayurvedic medicines, *etc*. The order of risk of DILI is depicted in Figure 1. To support this fact, one recent study, including liver biopsy of a patient with COVID-19, was performed, which displayed raised liver enzymes partially due to the drugs used in the treatment of COVID-19 leading to liver dysfunction as a consequence of sepsis and shock.

Although DILI occurrences are rare, due to difficult diagnosis and dangerous consequences of liver failure with mortality or sometimes liver transplantation, it is very alarming and challenging for the medical fraternity. Polytherapy in COVID-19 treatment makes DILI more intricate, as drug toxicity may differ by sex, age, and race. Numerous medicines can impair liver function and harm the liver; some of them may asymptomatically increase hepatic enzymes; in other instances, acute hepatitis may manifest. Furthermore, liver damage range is consistent with the dose of the drug used, while in some instances, the drug dosage is not related to liver injury in all cases. The most common drugs responsible for liver injury or hepatotoxicity are antibiotic, anti-inflammatory, antimalarial, and antiviral agents[37].

MECHANISM OF LIVER INJURY IN PATIENTS WITH COVID-19

More severe cases of COVID-19 can be found in MAFLD patients due to impaired innate immunity. Various mechanisms for liver injury in patients with COVID -19 are listed in Figure 2[38].

Direct cytopathic effect

In direct cytopathic effect, the host cells are being besieged by the entry of corona virus through ACE-2. The virus then infects the upper respiratory tract and lung cells. In severe COVID-19 patients, serum gamma-glutamyl transferase (GGT) (a latent investigative indicator for cholangiocyte injury) has been found at amplified levels up to 72%. This ACE-2 receptor binding to cholangiocytes leads to liver dysfunction[39].

Dysregulated and uncontrolled systemic inflammation

Dysregulated and uncontrolled systemic inflammation is an extremely credible reason for hepatic injury in patients with COVID-19. This systemic inflammation is not a major disease. However, the root cause behind this uncontrolled systemic inflammation is the unregulated activation of natural and cellular immunity, which results in multiple organ damage, including hepatic dysfunction owing to abandoned cytokine "hurricane". Again, impaired innate immunity is the main culprit for this uncontrolled systemic inflammation. The latest research findings declare that obesity is undeniably associated with MAFLD and endorses the swing of M2 macrophages (that are inflammation suppressing) to proinflammatory M1 macrophages. This exclusive divergence of macrophages is instigated by fatty acids that advance to ectopic lipid accretion and local and systemic chronic inferior tenderness. This metabolic and immunological dysregulation might aggravate infection caused by SARS-COV-2 that may lead to more unembellished COVID-19 disease[38].

Drug-induced liver injury

The most probable cause of liver injury in COVID-19 patients may be due to the use of multiple drugs for COVID-19 treatment, like antibiotics, antivirals, analgesics, antipyretics, many traditional Chinese medicines, and ayurvedic medicines. To support this, one recent finding, including liver biopsy of a patient with COVID-19, displayed raised liver enzymes partially due to the drugs used in the treatment of COVID-19 Leading to liver dysfunction as a consequence of sepsis and shock. Although DILI occurrences are rare, due to difficult diagnosis and dangerous consequences of liver failure with mortality or liver transplantation, it is very alarming and challenging for the medical fraternity. Polytherapy in COVID-19 treatment makes DILI more intricate, as the liver toxicity of drugs may differ per sex, age, and race[39]. Many drugs that we used may alter the hepatic function leading to liver damage. Asymptomatic elevation of hepatic enzymes and acute hepatitis are some examples for such condition. Hepatic injury may vary according to the dose of the drug; for example, paracetamol in excess dose produces acute hepatotoxicity. It is assumed that pre-existing metabolic liver disorders can

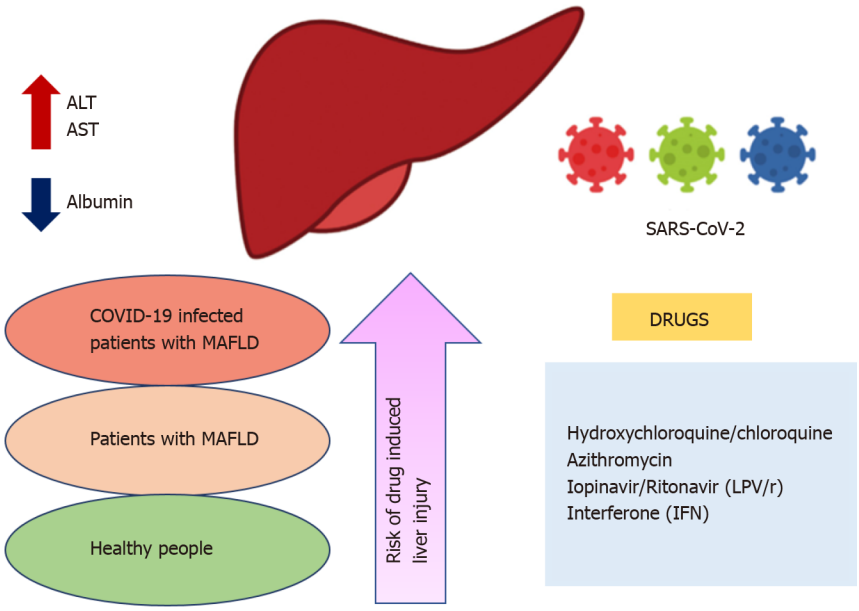

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Figure 1 Order of risk of drug-induced liver injury. ALT: Alanine transaminase; AST: aspartate transaminase; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MAFLD: Metabolic associated fatty liver disorder.

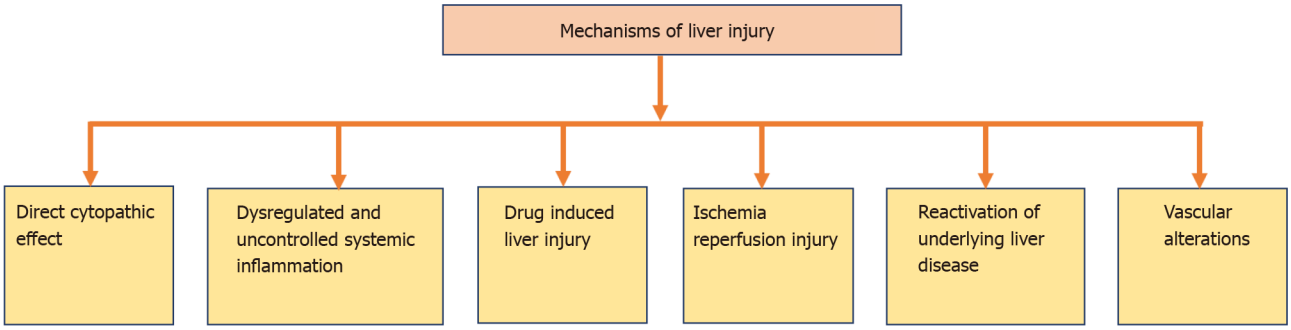

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Figure 2 Mechanisms of liver injury.

increase medication hepatotoxicity because they impair the operation of digestive enzymes, cause oxidative stress, impair mitochondria, and affect lipid balance. Conversely, some xenobiotics might lead to the waning of MAFLD, *i.e.*, prompting a changeover of fatty liver to non-alcoholic steatohepatitis (NASH) and thus persuading necroinflammation and subsequently fibrosis and speedy expansion of liver cirrhosis[39].

Ischemia-reperfusion injury

Complementary to the dysregulated and uncontrolled immune system, one more phenomenon is ischemia-reperfusion injury through respiratory disappointment or sepsis. When systemic inflammatory response syndrome develops in severe COVID-19 instances, the uncontrolled release of proinflammatory cytokines causes peripheral arteries to dilate, which lowers blood pressure and may result in comprehensive tissue hypoxia[40]. If acute respiratory distress syndrome (ARDS) befalls concurrently, it leads to deprived blood oxygenation that intensifies liver ischemia and previously underprivileged blood supply. Furthermore, reactive oxygen species (ROS) increase in the presence of stress and hypoxia, accelerating the oxidation of proteins, DNA, and lipids. Peroxidation products and ROS themselves trigger hepatic stellate cells to generate the extracellular matrix and innate liver immune cells that further result in liver injury through the generation of proinflammatory cytokines[40].

Reactivation of underlying liver diseases

One of the probable causes of liver injury in COVID-19 patients might be the renaissance of primary liver disorder. According to clinical studies, 20%-35% of patients with COVID-19 had altered liver enzymes upon admission, and 15%-30% of patients with COVID-19 had primary liver disease. COVID-

19 patients with preliminary liver disease displayed greater elevated liver enzymes compared to the COVID-19 patients without any pre-existing liver disease. Hepatitis B recurrence may be brought on by immunosuppressive medications used to treat severe COVID-19, such as corticosteroids, IL-1 receptor antagonists, IL-6 receptor antagonists, and JAK inhibitors. However, the risk of recurrence is modest to little. Recent strategies endorse screening for HBsAg and anti-HBc prior to the use of immunosuppressive therapy. Prophylactic anti-HBV therapy is required for all patients who are in danger of developing hepatitis B again, ranging from low to high[41].

Vascular alterations

Vascular modifications are a probable alternative source of liver injury. This is reinforced by the study in which analysis of liver samples of individuals who died with COVID-19 due to respiratory failure was performed and negligible inflammatory infiltrate was detected. It was seen that the portal and sinusoidal veins had partial or complete luminal thrombosis, the portal tract had fibrosis, and the portal vein branches had dilated. However, these were undoubtedly attributable to diminished flow inside the liver and clotting cascade tempted by the virus. While the sample size was small, another autopsy investigation in COVID-19 patients found that 88% of patients had fatty alterations in their livers despite having no hepatic occlusion[38].

LIVER ENZYME VARIATION IN COVID-19

SRAS-CoV-2 infection may trigger the pathogenesis involved in the multi-organ impairment, including liver injury. There are different reasons for liver injury in patients suffering from COVID-19, such as injury of cells by direct virus attack and entry of SARS-CoV-2 into hepatocytes *via* ACE2 expressed in liver and bile duct cells. The damage of hepatocytes, cell apoptosis, and lobular inflammation seen in specimens of liver biopsy and acidophilic bodies are the results due to SARS-CoV-2.

Omrani-Nava *et al*[42] evaluated the changes in hepatic enzymes in patients suffering from COVID-19. The researchers evaluated the laboratory investigation of direct bilirubin, total bilirubin (TBIL), ALT, aspartate aminotransferase (AST), and alkaline phosphatase (ALP). The levels of direct bilirubin, TBIL, ALT, ALP, and AST were higher in COVID-19 patients than in controls. When the levels of AST were elevated, the mortality rate also surged. The investigators found an abnormality in liver enzymes in COVID-19 patients. Yu *et al*[43] performed a cohort study in China with 1099 COVID-19 patients. The researchers found that 21.4% and 22.3% of patients have elevated AST and ALT levels and 10.7% have abnormal bilirubin levels. The TBIL levels were more than 17.2 mmol/L, ALP was greater than 135 U/L, and GGT was more than 50 U/L. The researchers concluded that liver enzyme levels were increased in patients suffering from COVID-19. Cai *et al*[44] also performed a clinical examination of COVID-19 patients, with special reference to an abnormality in liver enzymes. The laboratory outcomes and clinical investigation of 417 patients were obtained from a referral hospital in Shenzhen, China. The researchers observed that during 2 wk of hospitalization, 50 (24.4%), 33(15.2%), 27(11.7%), and 52 (24.5%) patients had elevated levels of ALT, TBIL, AST, and GGT three times from the normal limit. The seven large-scale hospital investigations have revealed that 15%-50% of patients suffering from COVID-19 have superior levels of ALT and AST. These enzymes increased significantly in patients with severe COVID-19[45]. Notwithstanding the potential association reported across the globe between COVID-19 and varying degrees of altered liver enzymes, more detailed study is required to establish the linkage between SARS-CoV-2 infection and liver damage.

RELATION BETWEEN MAFLD AND SARS-COV-2 INFECTION

Metabolic syndrome is a cluster of conditions such as obesity, diabetes, hyperlipidemia, hypertension, and insulin resistance that are responsible for or worsen the conditions of COVID-19 patients[46]. Diabetes mellitus was the second most common disease prevalent in COVID-19 patients and enhanced mortality in infected patients. Hu *et al*[47] performed a meta-analysis, having 40000 patients from Wuhan, China. The researchers found that 8% of total patients were diabetic. The second most prevalent comorbidity in the patients after DM was hypertension.

A study examined 214 patients suffering from COVID-19, belonging to three hospitals in Wenzhou, China. Out of the 214 COVID-19 patients, there were 66 with MAFLD (45 with obesity and 21 without obesity). The investigators observed that obese MAFLD patients had higher levels of ALT and AST as compared to non-obese MAFLD patients. The researchers found that obese MAFLD patients had a six times more risk of COVID-19 as compared to non-obese MAFLD patients[48]. A meta-analysis was performed by Pan and his colleagues about the association between the severity of COVID-19 and MAFLD. The researchers performed this meta-analysis based on PubMed, Medline, EMBASE, and MedRxiv. After screening, the researchers included a total of six studies, and employed 1293 participants. The meta-analysis studies revealed a high percentage of COVID-19 patients suffering from

MAFLD. The researchers observed that MAFLD enhanced the risk of disease progression in patients suffering from COVID-19. The researchers concluded that patients with MAFLD who have been exposed to SARS-COV-2 require better intensive treatment and monitoring[49]. Another study in Chinese hospitals reported that individuals with MAFLD had increased serum IL-6 compared to patients without. The researchers concluded that individuals with MAFLD and enhanced serum IL-6 risk develop severe illness from COVID-19[50]. Zhou *et al*[22] investigated 327 adult patients more than 18 years old suffering from COVID-19 from four different centres (Wenzhou Central Hospital, Hospital of Wenzhou Medical University, Ningbo No. 2 Hospital, and Ruian People's Hospital) in China in January 2020. The 74 patients (23%) were above the age of 60 suffering from MAFLD, and the rest 93 patients also had MAFLD. Moreover, in elderly patients, 18 suffered from diabetes and 32 were diagnosed with hypertension. Of the younger patients (less than 60 years of age), 45 suffered from hypertension and 29 were diagnosed with diabetes. Hypertension and diabetes prevalence was higher in elderly patients than in younger patients. In contrast, the researchers found a strong correlation between MAFLD and COVID-19 in younger patients (χ^2 test $P = 0.001$) compared to elderly patients (χ^2 test $P = 0.66$). The investigators observed that the rate of severe COVID-19 was two times higher in younger MAFLD patients (age less than 60 years) than in non-MAFLD patients. The researchers recapitulated that younger MAFLD patients were at higher risk of COVID-19 than elderly MAFLD patients. In an investigation of 310 COVID-19 patients, out of 310, 94 suffered from MAFLD. The researchers used fibrosis-4 (FIB-4) index as a prime criterion for fibrosis evaluation. The researchers observed that the FIB-4 index was less than 1.3 in 44 patients, while this value was between 1.3 to 2.6 in 36 patients. The MAFLD patients with a high FIB-4 value were more likely to be obese, older, and diabetic, and had higher C reactive protein, elevated liver enzyme level, and lower lymphocyte count and platelet count as compared to MAFLD with a low score of FIB-4. It is evident from the studies that MAFLD patients having high FIB-4 scores were more prevalent to have COVID-19[51]. Ji *et al*[16] studied 202 MAFLD patients suffering from COVID-19. Most patients had a liver injury with a mild hepatocellular pattern, and only 3% had a mixed or ductular pattern. The different liver enzymes were elevated in patients, such as TBIL at 9%, ALP at 2.5%, AST at 17%. and ALT at 50%. The researchers observed that MAFLD patients had a higher risk of COVID-19 progression and longer shedding time of the virus than non-MAFLD patients.

COVID-19 was found to alter glucose homeostasis, induce cytokine storm, and increase oxidative stress[52]. The elevated levels of IL-6 have been seen in MAFLD patients, mainly in obese ones, contributing to an increased risk of COVID-19[53]. MAFLD can characterize an enhanced predisposition to cytokine storm syndrome, increased C-reactive protein and IL-6 levels, and activation of NLR family pyrin domain containing 3 (NLRP3). An individual with pre-existing MAFLD makes him/her more vulnerable to infection caused by SARS-CoV-2 and its associated complications. Different studies pointed out that severe COVID-19 is more common in people with MAFLD, which results in critical illness and even the development of non-alcoholic steatohepatitis[54]. A critical analysis of the PubMed database reported that patients less than 60 years and suffering from MAFLD (obesity and severe fibrosis) are more prevalent to have severe COVID-19. The investigators found that the severity of COVID-19 was enhanced by 4 to 6 fold in MAFLD patients compared to non-MAFLD patients[10]. Thus, elevated levels of cytokines and altered liver function can be conceded as important with the severe illness of COVID-19 in MAFLD patients.

LIVER INJURY MECHANISM IN COVID-19 AND MAFLD

The potential mechanism responsible for COVID-19 facilitating MAFLD progression includes direct toxicity of the virus, systemic inflammatory response syndrome, DILI, hypoxic injury, intestinal microbiota imbalance, and hepatic lipid metabolism dysregulation[55]. The expression of hepatic ACE2 and transmembrane protease serine 2 (TMPRSS2) is enhanced in COVID-19 patients who already have MAFLD. These two factors may be responsible for escalated susceptibility of MAFLD patients towards COVID-19[56]. Different innate immune cells such as natural killer cells, natural killer T cells, and macrophages are present abundantly in the liver[57]. MAFLD and obesity are commonly associated with enhanced production of proinflammatory cytokines by Kupffer cells and adipose cells (TNF-α). There are two types of responses from stimulated macrophages, M1 and M2. The M1 macrophages are responsible for initiating the inflammatory processes, while M2 macrophages have reparative and anti-inflammatory functions with high expression of chemokines. It is predicted that dysregulated hepatic innate immunity is responsible for the pathogenesis of MAFLD[58]. Possibly hepatic macrophages are more likely to shift from M1 macrophages (promoting inflammation) to M2 macrophages (suppressing inflammation), leading to COVID-19 progression. MAFLD with noteworthy fibrosis may intensify the virus-induced cytokine storm, probably by the hepatic release of proinflammatory cytokines, significantly contributing to severe COVID-19.

It was reported that ACE2 receptors are present in the liver in hepatocytes and cholangiocytes. The coronavirus targets these ACE2 receptors to enter and it is assumed that it leads to damage to hepatocytes and cholangiocytes[59]. In contrast, another research group recapitulated that MAFLD is

not associated with enhanced expression of genes encoding for protein receptors necessary for coronavirus infection such as TMPRSS2, ACE2, and phosphatidylinositol 3-phosphate 5-kinase (PIKfyve). The researchers concluded that enhanced ACE2 expression in MAFLD-COVID19 patients is not relevant justification for escalated liver injury[60]. The SARS-CoV-2 infection reduced the hepatic mitochondrial activity and facilitated the mitochondrial swelling of hepatocytes confirmed by ultrastructural examination and transcriptomic analysis. These results strongly recommend that SARS-CoV-2 is directly responsible for cytopathic effects and positively contributes to MAFLD progression [61]. SARS-CoV-2 infection encourages activation of cGAS-STING in endothelial cells by releasing mitochondrial DNA, resulting in type I IFN production and cell death. Mitochondrial swelling in hepatocytes happens due to SARS-CoV-2 infection, signifying that cGAS-STING signalling activation may aggravate MAFLD in patients suffering from COVID-19[62]. The upsurge of inflammatory cytokine levels was reported in patients suffering from MAFLD and COVID-19[10,63]. Thus, COVID-19 in MAFLD patients resulted in serious illness from cytokine storm. Altered expression of host ACE2 receptor, direct viral attack on hepatocytes, interruption of cholangiocyte function, dysregulated immune responses, hyperinflammation, hepatic ischemic and hypoxic injury, abnormal coagulation and thrombosis, DILI, and altered glucose and lipid hemostasis are some multifactorial mechanisms that can explain the worse outcome of COVID-19 and MAFLD[21].

MANAGEMENT OF COVID-19 PATIENTS ALREADY SUFFERING FROM MAFLD

The first line of management is early and accurate liver biochemical monitoring of COVID-19 patients. The tests related to MAFLD should be carried out as early as possible to monitor the proper functioning of the liver. MAFLD patients may be vulnerable to DILI, so repeated medication should be avoided and focus should be given to dosage and duration of medication. Metabolic control should be enhanced in diabetic patients, and is a primary preventive step for SARS-CoV-2 infection. The influenza vaccination declines the risk of pneumonia by 45%-50% among people suffering from diabetes mellitus, which can be employed for patients suffering from COVID-19[64]. ARDS developed in COVID-19 patients commonly due to dysregulated immune response facilitating cytokine release syndrome. Metformin, the first-line treatment for T2DM, enhanced the immune response and prevented the ARDS compared to other anti-hyperglycemic drugs. Moreover, glucagon-like peptide-1 receptor agonists such as SGLT2 and GLP-1RA also potentially manage hyperglycemia in COVID-19 patients[21,65]. The management of COVID-19 includes improvement in targeted interventions for metabolic pathologies. The vaccination response against SARS-CoV-2 should be carefully examined in obesity and DM patients[66]. COVID-19 in MAFLD patients requires special attention and early hospital admission is recommended. Further, in such patients, treatment of arterial hypertension should be continued. Rigorous lifestyle modification, including follow-up of nutritional guidance, measures for weight loss, and management of hyperglycemia, is required to prevent the development of a severe illness in case of SARS-CoV-2 infection[67]. Due to SARS-CoV-2 infection, hypoxia may occur in hepatocytes of MAFLD patients, followed by severe lung damage leading to enhanced expression of hypoxia-induced factors and ACE2 receptors. The MAFLD patients suffering from fibrosis are another challenge to manage in COVID-19. Thus, the MAFLD patients require special care during SARS-CoV-2 infection and adequate lifestyle intervention to avert the consequence of COVID-19.

CONCLUSION

MAFLD patients are at higher risk of COVID-19, and adequate lifestyle intervention is essential to minimize the damage caused by SARS-CoV-2 infection. MAFLD patients suffering from COVID-19 are at greater risk of hepatic damage. COVID-19 was found to alter glucose homeostasis, enhance the generation of inflammatory cytokines storm, and increase oxidative stress, thus worsening the situation in MAFLD patients. Abnormalities in cardiac, kidney, and liver function markers as well as muscle injury and coagulation parameters must also be monitored in patients with COVID-19. In addition, COVID-19 induces liver injury with an elevated level of ALT and AST. Polytherapy in COVID-19 patients is common; thus, such patients are also vulnerable to DILI as some of them can cause the elevation of liver enzymes asymptomatically. Thus, SARS-CoV-2 infected MAFLD patients are considered severe and require urgent attention.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Hyperglycemia in COVID-19 infection without diabetes mellitus: Association with inflammatory markers

Harinivaas Shanmugavel Geetha, Garima Singh, Abinesh Sekar, Maya Gogtay, Yuvaraj Singh, George M Abraham, Nitin Trivedi

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Abstract

BACKGROUND

New onset hyperglycemia is common in patients with severe coronavirus disease 2019 (COVID-19) infection. Cytokine storm due to COVID-19 infection is an essential etiology for new-onset hyperglycemia, but factors like direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced pancreatic β-cell failure have also been postulated to play a role.

AIM

We plan to investigate further the mechanisms underlying SARS-CoV-2 infection-induced hyperglycemia, particularly the rationale of the cytokine-induced hyperglycemia hypothesis, by evaluating the association between inflammatory markers and new onset hyperglycemia in non-diabetic patients with COVID-19 infection.

METHODS

We conducted a retrospective case-control study on adults without diabetes mellitus hospitalized for COVID-19 infection. The serum levels of glucose and inflammatory markers at presentation before initiation of corticosteroid were collected. Hyperglycemia was defined as glucose levels ≥ 140 mg/dL. C-Reactive protein (CRP) ≥ 100 mg/L, ferritin ≥ 530 ng/mL, lactate dehydrogenase (LDH) ≥ 590 U/L, and D-dimer ≥ 0.5 mg/L were considered elevated. We used the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables

and calculated the logistic regression for hyperglycemia.

RESULTS

Of the 520 patients screened, 248 met the inclusion criteria. Baseline demographics were equally distributed between patients with hyperglycemia and those who were normoglycemic. Serum inflammatory markers in patients with or without new-onset hyperglycemia were elevated as follows: CRP (58.1% *vs* 65.6%, $P = 0.29$), ferritin (48.4% *vs* 34.9%, $P = 0.14$), D-dimer (37.1% *vs* 37.1%, $P = 0.76$) and LDH (19.4% *vs* 11.8%, $P = 0.02$). Logistic regression analysis showed LDH odds ratio (OR) = 1.623 ($P = 0.256$). We observed significantly higher mortality (24.2% *vs* 9.1%, $P = 0.001$; OR = 2.528, $P = 0.024$) and length of stay (8.89 *vs* 6.69, $P = 0.026$) in patients with hyperglycemia.

CONCLUSION

Our study showed no association between CRP, ferritin, LDH, D-dimer levels, and new-onset hyperglycemia in non-diabetic patients with COVID-19 infection. It also shows an increased mortality risk and length of stay in patients with hyperglycemia. With new-onset hyperglycemia being closely associated with poor prognostic indices, it becomes pivotal to understand the underlying pathophysiological mechanisms behind the SARS-CoV-2 infection-induced hyperglycemia. We conclude that the stress hyperglycemia hypothesis is not the only mechanism of SARS-CoV-2 infection-induced hyperglycemia but rather a multicausal pathogenesis leading to hyperglycemia that requires further research and understanding. This would help us improve not only the clinical outcomes of COVID-19 disease and inpatient hyperglycemia management but also understand the long-term effects of SARS-CoV-2 infection and further management.

Key Words: COVID-19; Inflammatory markers; Hyperglycemia; C-reactive protein; Mortality; Severity; Mechanisms; Diabetes mellitus

Core Tip: Our study suggests that there is no correlation between the inflammatory marker levels and the presence of hyperglycemia in non-diabetic patients with coronavirus disease 2019 (COVID-19) infection. With an increased need to understand the mechanism underlying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-induced hyperglycemia, we assessed the validity of the most accepted COVID-19 infection-induced cytokine storm-related stress hyperglycemia theory. However, our study did not show any correlation between inflammatory marker levels that correlate with the cytokine storm and the level of hyperglycemia. This suggests the possibility of other mechanisms playing a role in the SARS-CoV-2 infection-induced hyperglycemia. Our study also demonstrated that new-onset hyperglycemia was an independent risk factor for higher mortality and length of stay, thereby emphasizing the need to understand the mechanisms leading to hyperglycemia.

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INTRODUCTION

At the end of 2019, a novel coronavirus rapidly spread worldwide, resulting in a global pandemic. The virus was designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the illness it caused was coronavirus disease 2019 (COVID-19). The spectrum of COVID-19 in adults ranges from asymptomatic infection to mild respiratory tract symptoms to severe pneumonia with acute respiratory distress syndrome and multiorgan dysfunction.

The presence of hyperglycemia was an independent factor associated with poor outcomes. One study of hospitalized, elderly COVID-19 patients in Wuhan reported that 21.6% had a history of diabetes, 20.8% were newly diagnosed with diabetes [fasting admission glucose ≥ 7.0 mmol/L or glycated hemoglobin (HbA1c) ≥ 6.5%], and 28.4% were diagnosed with dysglycemia (fasting glucose 5.6–6.9 mmol/L or HbA1c 5.7%–6.4%)[1].

Although there is clear evidence demonstrating the association between COVID-19 disease and hyperglycemia, there exists a lack of sufficient literature explaining the mechanism of action of SARS-CoV-2-induced hyperglycemia. The pathophysiological mechanisms of hyperglycemia in COVID-19 patients remain poorly understood. Several complex processes have been hypothesized, including previously undiagnosed diabetes, stress hyperglycemia, steroid-induced hyperglycemia, and direct or indirect effects of SARS-CoV-2 on the pancreatic β-cell[2].

Studies have shown that patients with newly diagnosed diabetes have higher inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate, and white blood cells. Acute inflammation seen in cytokine storms may worsen insulin resistance. One study shows that neutrophils, D-dimers, and inflammatory markers are significantly higher in those with hyperglycemia than those with normal glucose[3].

We assessed the rationale of the cytokine-induced hyperglycemia hypothesis by evaluating the association between routinely tested inflammatory markers like CRP, ferritin, Lactate dehydrogenase (LDH), and D-dimer and new onset hyperglycemia in non-diabetic patients with COVID-19 infection.

MATERIALS AND METHODS

Study design and participants

We conducted a retrospective, single-center case-control study of hospitalized patients between Dec 1, 2019, and Jan 1, 2022, at a 329 bed community teaching hospital in central Massachusetts. The study inclusion criteria included: (1) Inpatients diagnosed with SARS-CoV-2 infection; (2) Age > 18 years; and (3) Patients with documented inflammatory markers and glucose levels on admission. The exclusion criteria included: (1) Pregnant patients; (2) Patients with previous diagnoses of Type 1 or Type 2 Diabetes mellitus (DM), and (3) Patients who received steroids before admission. The data were obtained by reviewing the patients' medical records, including demographic information, past medical history, medication, labs, and course during hospitalization. The Institutional Review Board approved this study.

Exposure and outcomes

The primary endpoint measured was hyperglycemia, defined as glucose levels ≥ 140 mg/dL. The patients with hyperglycemia were defined as cases, and the control group included patients with normoglycemia (glucose levels < 140 mg/dL). We assessed the level of inflammatory markers between the two study groups, including CRP, ferritin, LDH, and D-dimer levels. We used prespecified cutoffs for the inflammatory markers described by previous studies[4-6]. The inflammatory markers were categorized as binary variables, *i.e.* either elevated or normal. A CRP ≥ 100 mg/L, ferritin ≥ 530 ng/mL, LDH ≥ 590 U/L, and D-dimer ≥ 0.5 mg/L were considered elevated. Demographic data collected included age, sex, weight, height, body mass index (BMI), and vaccination status. Relevant clinical data that is associated with hyperglycemia in previous studies which included a family history of diabetes, past medical history of prediabetes, American Diabetes Association (ADA) diabetes risk score, hypertension, chronic liver disease (CLD), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and chronic kidney disease (CKD) was collected. We also collected data about the outcomes of these patients that included mortality rate, use of steroids, use of remdesivir, and length of hospital stay. The ADA diabetes risk assessment tool that provides a risk stratification index for developing Type II DM was also used.

Statistical analyses

The data were subjected to the normalcy test (Shapiro-Wilk test) that showed non-normalcy distribution. Hence, non-parametric tests were employed. The baseline demographic characteristics between the two study populations were assessed using χ^2 analysis for categorical variables and the Mann-Whitney *U* test for continuous variables. The association between the covariates and primary endpoints was evaluated using a bivariate logistic regression with hyperglycemia as a dependent variable and other variables significant in the univariate analysis as independent variables. The level of significance was set at 5%.

RESULTS

Patient characteristics

A total of 520 patients were screened, among which 248 met the inclusion criteria, with 186 patients (75%) being normoglycemic on admission and 62 patients (25%) being hyperglycemic on admission. Patients with hyperglycemia were more likely to have a history of hypertension (58.1% *vs* 43.5%, P = 0.047) and increased ADA Diabetes risk scoring (66.1% *vs* 51.6%, P = 0.048) when compared to patients with normoglycemia (Tables 1 and 2). The demographic data like sex distribution, vaccination status,

Table 1 Demographic information

Patient characteristic	Normoglycemia	Hyperglycemia	Total	*P* value[2]
Male sex	102	33	135	0.83
	54.8%	53.2%	54.4%	
Vaccinated for COVID	34	10	44	0.87
	18.3%	16.1%	17.7%	
Hypertension	81	36	117	0.047[1]
	43.5%	58.1%	47.2%	
Family history of diabetes	16	8	24	0.32
	8.6%	12.9%	9.7%	
Prediabetes	5	1	6	1[3]
	2.7%	1.6%	2.4%	
ADA - At risk	96	41	137	0.05*
	51.6%	66.1%	55.2%	
Chronic liver disease	7	2	9	1.00
	3.8%	3.2%	3.6%	
Chronic obstructive pulmonary disease	27	7	34	0.39
	14.5%	11.3%	13.7%	
Congestive heart failure	33	7	40	0.23
	17.7%	11.3%	16.1%	
Chronic kidney disease	31	11	42	0.85
	16.7%	17.7%	16.9%	

[1]Significant.
[2]χ^2 test.
[3]Fisher's exact test.
ADA: American Diabetes Association; COVID: Coronavirus disease.

Table 2 Demographic information

Variable	Category	*n*	Mean	Std dev	Median	IQR	*P* value[1]
Age, yr	Normoglycemic	186	63.38	18.52	68.50	23.00	0.366
	Hyperglycemic	62	66.32	15.64	65.00	29.00	
Weight, kg	Normoglycemic	186	84.96	26.24	82.50	31.00	0.982
	Hyperglycemic	62	84.71	25.63	82.00	29.00	
Height, cm	Normoglycemic	186	168.48	10.67	166.00	18.00	0.376
	Hyperglycemic	62	167.02	10.99	168.00	17.00	
BMI	Normoglycemic	186	29.62	7.75	28.50	9.00	0.566
	Hyperglycemic	62	30.02	7.52	28.00	9.00	

[1]Mann Whitney *U* test.
BMI: Body mass index; IQR: Interquartile range; Std dev: Standard deviation.

and history of CLD, COPD, CHF, and CKD were similar between the two groups.

Inflammatory markers and hyperglycemia

The association between the levels of inflammatory markers like CRP, ferritin, D-dimer, and LDH in

patients with normoglycemia and patients with hyperglycemia was assessed (Tables 3 and 4). Although there was a difference in the mean levels of CRP (106.56 mg/L *vs* 85.65 mg/L), ferritin (1404.40 ng/mL *vs* 470.38 ng/mL), D dimer (0.15 mg/L *vs* 1.71 mg/L) and LDH levels (319.11 U/L *vs* 224.45 U/L), there were statistically no significant differences between serum inflammatory markers except LDH in patients with or without new-onset hyperglycemia [CRP (58.1% *vs* 65.6%, P = 0.29), ferritin (48.4% *vs* 34.9%, P = 0.14), D-dimer (37.1% *vs* 37.1%, P = 0.76) and LDH (19.4% *vs* 11.8%, P = 0.02)]. On further binary logistic regression analysis to predict hyperglycemia, there was no difference in LDH levels between the two groups (OR = 1.623, P = 0.256).

Hyperglycemia and prognosis

We further analyzed the prognostic indices like mortality rate and length of stay between the two groups (Tables 5 and 6). There was significantly higher mortality (24.2% *vs* 9.1%, P = 0.001) and length of stay (8.89 d *vs* 6.69 d, P = 0.026) in patients with hyperglycemia compared to patients with normoglycemia. Further analysis with binary logistic regression shows an increased risk of mortality in patients with hyperglycemia (OR = 2.528, P = 0.024). The administration of remdesivir initially showed a statistically significant difference in patients with hyperglycemia (59.7% *vs* 44.6%, P = 0.04) but did not show any significant difference in binary logistic regression (OR = 1.620, CI: 0.882 - 2.974) (Table 7). There was also no significant difference in the rate of steroid administration between the two groups.

DISCUSSION

COVID-19 and Hyperglycemia

The SARS-CoV-2 infection that was first noticed in December 2019 has resulted in the worldwide COVID-19 pandemic that has claimed over 6.5 million lives worldwide[7]. Initially thought to be a pathogen that affects only the respiratory system, as we continued to learn more about the virus, its effects on multiple organ systems are being slowly discovered, with several studies assessing its association in different disease states[8,9]. Studies have revealed the association of certain risk factors with increased predisposition and severity of the disease. DM has been shown to increase the risk of morbidity and mortality due to its associated metabolic, microvascular, and macrovascular complications and reactive hyperglycemia being a predictor of severity in previous SARS-CoV-1 and Middle East Respiratory Syndrome coronavirus-CoV infections. We noticed an increased prevalence of hyperglycemia in patients with COVID-19 infection, irrespective of the presence of pre-existing diabetes mellitus. An Italian study of 271 patients admitted for COVID-19 showed that hyperglycemia was independently associated with increased mortality[10]. However, this study failed to elucidate the underlying pathophysiological mechanisms explaining SARS-CoV-2 infection-induced hyperglycemia. In our study, we investigated the association of hyperglycemia at presentation with inflammatory markers and the impact of hyperglycemia on mortality and morbidity in non-diabetic COVID-19 patients. The results showed no association between CRP, ferritin, LDH, and D-dimer levels and new-onset hyperglycemia in non-diabetic patients with COVID-19 infection.

Although age and male sex were the initially associated risk factors, further studies revealed the increased prevalence of hypertension and diabetes mellitus in patients with severe disease compared to those with milder forms of infection[11,12]. Our study showed a similar finding of increased hypertension in patients with hyperglycemia. This was further analyzed by binary logistic regression to account for hypertension as a potential confounding agent, given the increased mortality and length of stay in the hyperglycemia group. However, further analysis demonstrated the absence of a significant difference in the presence of hypertension between the two groups. Other risk factors such as male sex, increased BMI, and vaccination status and comorbidities such as chronic liver disease, congestive heart failure, chronic obstructive pulmonary disease, and chronic kidney disease were similar between the two groups, eliminating potential confounders. Although we accounted for major potential confounders, the demographic prevalence of prediabetes was not accounted for due to the non-availability of baseline HbA1c levels.

Covid and Inflammatory markers

With the advent of the COVID-19 pandemic, the utility of inflammatory markers has been on the rise. Biomarkers are quantitative measurements that reflect the pathophysiology of the disease and help gauge the underlying disease severity. Initial studies demonstrated increased levels of inflammatory markers in COVID-19 patients that directly correlated with the disease severity.

Although a milieu of inflammatory markers like Interleukin(IL)-6, IL-1β, and IL-8 exist, these are not routinely assessed in labs. It would not be cost-effective to employ them in the routine monitoring of every patient with SARS-CoV-2 infection, thus necessitating the use of other inflammatory markers that are cost-effective and can be utilized to assess the severity of the disease. This led to further research on the utility of markers like C-reactive protein, ferritin, LDH, and D-dimer. Studies have demonstrated the utility of these biomarkers in correlating with the severity of the disease. The meta-analyses by Malik *et al*[13] showed an increased association between the elevated levels of different inflammatory markers

Table 3 Inflammatory marker levels between the two study groups on admission

Variable	Category	*n*	Mean	Std dev	Median	IQR	*P* value[2]
CRP levels on admission	Normoglycemic	186	85.65	74.12	84.00	149.00	0.278
	Hyperglycemic	62	106.56	94.09	74.00	109.00	
Ferritin levels on admission	Normoglycemic	186	470.38	984.06	385.50	1109.50	0.028[1]
	Hyperglycemic	62	1404.40	4758.84	124.00	647.50	
LDH levels on admission	Normoglycemic	186	224.45	245.15	276.00	319.50	0.041[1]
	Hyperglycemic	62	319.11	326.57	231.00	389.00	
D-dimer levels on admission	Normoglycemic	186	1.71	4.63	1.00	1.25	0.470
	Hyperglycemic	62	2.15	6.26	0.00	1.00	

[1]Significant.
[2]Mann-Whitney *U* test.
CRP: C-reactive protein; IQR: Interquartile range; LDH: Lactate dehydrogenase; Std dev: Standard deviation.

Table 4 Inflammatory marker levels between the two study groups

Variable	Normoglycemia	Hyperglycemia	Total	*P* value[2]
CRP ≥ 100 mg/L	122	36	158	0.29
	65.6%	58.1%	63.7%	
Ferritin ≥ 530 ng/mL	65	30	95	0.14
	34.9%	48.4%	38.3%	
LDH ≥ 590 U/L	22	12	34	0.02[1]
	11.8%	19.4%	13.7%	
D-dimer ≥ 0.5 mg/L	69	23	92	0.76
	37.1%	37.1%	37.1%	

[1]Significant.
[2]χ^2 test.
CRP: C-reactive protein; LDH: Lactate dehydrogenase.

Table 5 Analyses of outcomes

Variable	Normoglycemia	Hyperglycemia	Total	*P* value[2]
Mortality	17	15	32	0.001[1]
	9.1%	24.2%	12.9%	
Received remdesivir	83	37	120	0.04[1]
	44.6%	59.7%	48.4%	
Received steroids	157	56	213	0.25
	84.4%	90.3%	85.9%	

[1]Significant.
[2]χ^2 test.

and the severity of COVID-19 disease. Elevated CRP levels (> 10 mg/L) showed a fourfold increase in poor outcomes. Elevated D-dimer values (≥ 0.5 mg/L) were associated with a threefold higher risk of poor outcomes in COVID-19 patients. Elevated LDH showed a fivefold increased risk of poor outcomes. The Meta-analysis by Huang *et al*[14] demonstrated that patients with poor composite outcome had higher levels of Ferritin. Although various studies used different values of CRP such as Koozi *et al*[4] ≥

Table 6 Analyses of outcomes

Variable	Category	*n*	Mean	Std dev	Median	IQR	*P* value[2]
Length of stay	Normoglycemic	186	6.69	4.38	6.50	6.00	0.026[1]
	Hyperglycemic	62	8.89	6.80	5.00	6.00	

[1]Significant.
[2]Mann-Whitney *U* test.
IQR: Interquartile range; Std dev: Standard deviation.

Table 7 Binary logistic regression for hyperglycemia

Variable	*P* value	OR	95%CI for OR	
			Lower	Upper
LDH ≥ 590 U/L	0.256	1.623	0.704	3.745
Hypertension	0.375	1.355	0.692	2.651
Mortality	0.024[1]	2.528	1.129	5.662
ADA	0.256	0.616	0.267	1.421
Received remdesivir	0.120	1.620	0.882	2.974

[1]Significant.
ADA American Diabetes Association; CI: Confidence interval; LDH: Lactate dehydrogenase; OR: Odds ratio.

1000 mg/L, Ryoo *et al*[5] ≥ 140 mg/L, and Liu *et al*[6] ≥ 41.8 mg/L, we uniformly observed increased risk of COVID-19 severity with elevated levels of CRP. Despite its value in predicting a poor outcome in COVID-19, it should be noted that various factors could affect serum CRP levels, including age, sex, smoking status, weight, lipid levels, blood pressure, and liver injury[15].

Mechanisms of new-onset hyperglycemia in COVID-19

As we continued to discover the close association between COVID-19 disease and hyperglycemia, several theories were postulated on the underlying pathophysiology between SARS-CoV-2 infection and the onset of hyperglycemia (Figure 1).

Stress hyperglycemia

The most widely accepted hypothesis explaining the mechanism of new-onset hyperglycemia in SARS-CoV-2 infection is the stress hyperglycemia theory. Previous studies have shown that any acute illness, including myocardial infarction or severe infection, tends to drive lipolysis production and an increased number of free fatty acids in the blood[16] which in turn causes production of proinflammatory cytokines. In COVID-19 infection, we expect a similar mechanism or even greater response due to the profound cytokine storm triggered by the SARS-CoV-2 infection. Since previous studies had established the correlation between the levels of inflammatory markers like C-reactive protein, ferritin, LDH, and D-dimer and the severity of SARS-CoV-2 infection, we employed these markers to assess the presence of hyperglycemia in correlation with the disease severity. Our study showed no difference in the levels of C-reactive protein, ferritin, and D-dimer between the two groups. Although initial results showed a significant difference in the LDH levels between the two groups, further binary logistic regression did not reveal any significant change. The mean levels of C-reactive protein, ferritin, LDH, and D-dimer were higher in patients with hyperglycemia. However, no significant difference was observed when a cutoff for severity was imposed based on the established inflammatory marker levels for severe COVID-19 disease.

Preadmission diabetes

One of the first theories postulated was the presence of undiagnosed preexisting diabetes in the population that was brought to light when such patients were admitted to the hospital for COVID-19 infection. Studies also supported this hypothesis, such as recently increased weight gain and worsening hyperglycemia due to mandatory isolation, reduced physical activities, social distancing, and poor mental health that led to eating disorders[17]. These changes could potentially lead to metabolic syndrome that culminates in insulin resistance resulting in hyperglycemia. However, our study accounted for such changes by calculating the ADA diabetes risk score, a validated tool by the American

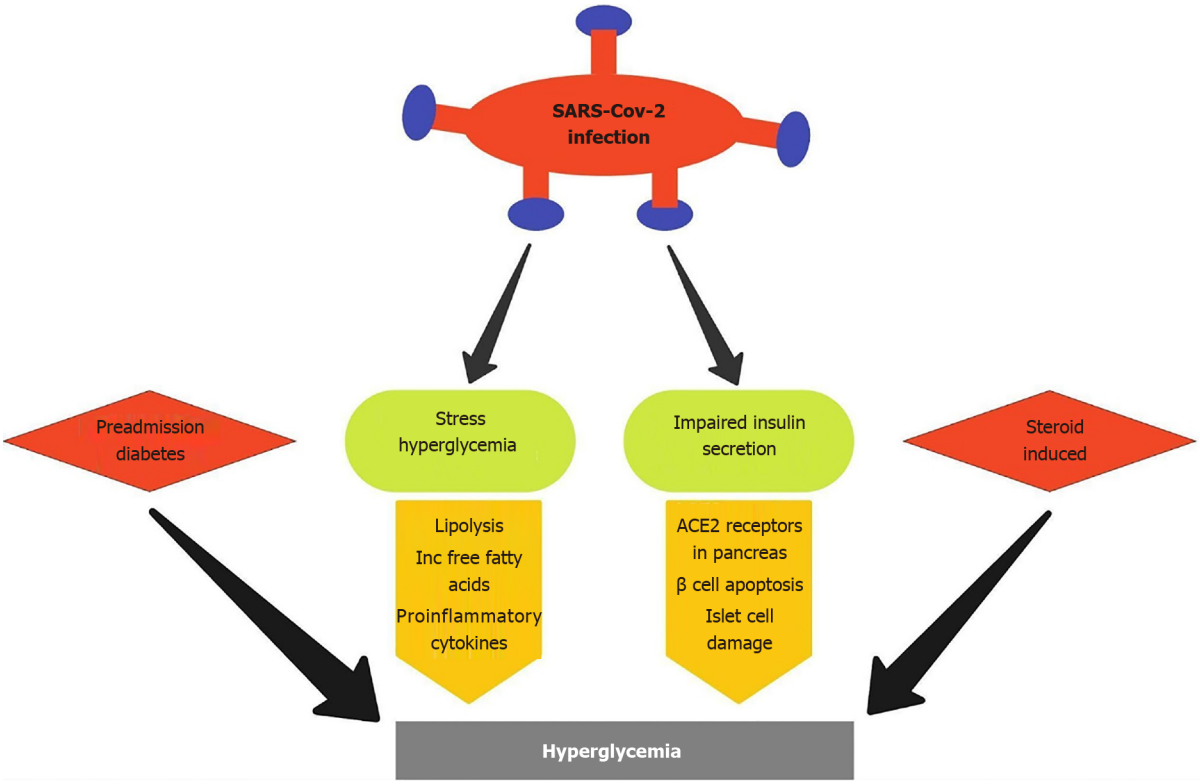

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Figure 1 Mechanisms of hyperglycemia in patients with severe acute respiratory syndrome–coronavirus–2 infection. ACE: Angiotensin converting enzyme; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus–2.

Diabetes Association, to detect an individual's risk of developing diabetes mellitus[18]. A cutoff score of 5 or greater indicates a greater risk of developing diabetes when compared to the general population. In our study, although the initial χ^2 analysis showed a significantly greater ADA risk score in the hyperglycemic study group, further analysis with binary logistic regression showed no statistically significant difference in the ADA risk score between the two groups. This finding emphasizes the poor validity of the preexisting undiagnosed diabetes hypothesis.

Impairments in insulin secretion

The first association between SARS-CoV-2 infection and pancreatic damage was postulated when the presence of Angiotensin converting enzyme 2 receptors, the binding site for SARS-CoV-2, was identified in the pancreatic islet cells[19,20]. More recent studies have observed that SARS-CoV-2 can infect pancreatic cells permitting entry of the virus, leading to attenuation of pancreatic insulin levels and consequently leading to β-cell apoptosis[21,22].

Steroid-induced diabetes

A meta-analysis of 13 studies showed that 32.3% of patients treated for COVID-19 infection with dexamethasone developed glucocorticoid-induced hyperglycemia and 18.6% of patients developed new-onset diabetes[23]. Since steroid-induced hyperglycemia would confound our results, we negated the effects of glucocorticoids by obtaining blood glucose levels on admission before administering steroids. We also excluded patients who had received steroids at outside facilities or in the ED before collecting their on-admission blood glucose levels.

Clinical outcomes of new-onset hyperglycemia

There is growing evidence that hyperglycemia in COVID-19 patients bears significant prognostic implications. Hyperglycemia in critically ill patients is a common manifestation directly correlated with increased mortality or morbidity[24]. More importantly, hyperglycemia was found to worsen the progression of respiratory failure.

Mortality related to hyperglycemia

Platelet activation incited by Fc glycosylated immune complexes is consistent with platelet hyperactivity in severe COVID-19 patients. Excessive macrophage stimulation by enhanced Fc-glycosylated immune complexes is consistent with the macrophage activation syndrome. The resulting hypercoagulability with compromised microperfusion, pulmonary endothelial fluid leakage, and severe respiratory distress

syndrome can result in death[25]. In our study, we observed a significantly increased rate of mortality in patients with new onset hyperglycemia compared to those without. This correlated with the findings of existing literature, such as that by Bode *et al*[26] (2020), who demonstrated that uncontrolled hyperglycemia without prior diabetes was related to an increase in mortality in comparison to normoglycemic subjects. Our study also observed an increased mortality rate in both groups, patients with hyperglycemia (24.2%) and normoglycemia (9.1%), compared to other studies. Our center is one of the referral hospitals receiving the most severe COVID-19 patients, which might explain the higher mortality rate compared to previous studies from China and the United States.

Impact of new-onset hyperglycemia on length of stay

We also observed a significant increase in the mean length of stay in patients with hyperglycemia compared to patients with normoglycemia. This impact of hyperglycemia in those without an established diagnosis of diabetes is a more concerning matter for clinicians, and research has shown that this could be explained by the acute hyperglycemia causing impairment in innate immunity, leading to a heightened risk of infections and increasing the length of stay (LOS) in hospital. In the study by Bode *et al*[26], among 493 discharged patients, the median LOS was longer in 184 patients with hyperglycemia compared with 386 patients without diabetes or hyperglycemia (5.7 *vs* 4.3 d, $P < 0.001$). Our study results are parallel and support the findings of increased mortality and length of stay in patients with hyperglycemia compared with patients with normoglycemia. These results suggest that disease severity and mortality risk significantly increase with newly diagnosed hyperglycemia after hospital admission.

Limitations

One of the most important limitations of the study is the small study population. Since the study was based on a community hospital in the United States, the generalizability of the study is limited. Although due consideration was provided regarding the possible confounding factors, due to the study's retrospective nature, it is possible that all potential confounding factors were not adequately adjusted for. Furthermore, the current study was performed during a period of travel limitations and limited physical activity, which could have contributed to the increased risk of dysglycemia in the study population. Our study is also limited by the inflammatory markers used since it did not include markers like IL-6, IL-1β, and IL-8, which better correlate with the level of inflammation. We were also limited by the non-availability of baseline HbA1c levels in the study population in order to negate any pre-existing diabetic conditions.

Future implications

Further studies are needed to analyze the different potential mechanisms underlying SARS-CoV-2 infection-induced hyperglycemia. Basic science research that would help better understand the underlying pathophysiology and further clinical studies that assess the utility of different treatment strategies in managing hyperglycemia are required to improve the clinical outcomes of COVID-19.

CONCLUSION

Our study investigated the association of hyperglycemia at presentation with inflammatory markers and the impact of hyperglycemia on mortality and morbidity in non-diabetic COVID-19 patients. The current study showed no association between CRP, ferritin, LDH, and D-dimer levels and new-onset hyperglycemia in non-diabetic patients with COVID-19 infection. It also shows an increased mortality risk and length of stay in patients with hyperglycemia. With new-onset hyperglycemia being closely associated with poor prognostic indices, it becomes pivotal to understand the underlying pathophysiological mechanisms behind the SARS-CoV-2 infection-induced hyperglycemia. This will help us better control the glycemic status and prevent new-onset hyperglycemia, thereby improving the clinical recovery of patients. Although current guidelines recommend the treatment of hyperglycemia using an Insulin sliding scale, these recommendations are based on the hypothesis that hyperglycemia secondary to COVID-19 infection is due to cytokine storm-induced stress hyperglycemia. However, if hyperglycemia arises due to other possible mechanisms, such as viral infection-induced direct suppression of insulin secretion, treatment modalities of achieving glycemic control have to be adjusted to better manage the disease and improve prognosis. Our study results indicate the low probability of the stress hyperglycemia hypothesis being the sole mechanism of SARS-CoV-2 infection-induced hyperglycemia but rather a multicausal pathogenesis leading to hyperglycemia that requires further research and understanding. This would help us improve not only the clinical outcomes of COVID-19 disease and inpatient hyperglycemia management but also understand the long-term effects of SARS-CoV-2 infection and further management.

ARTICLE HIGHLIGHTS

Research background

New onset hyperglycemia is common in patients with severe coronavirus disease 2019 (COVID-19) infection. Cytokine storm and direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced pancreatic β-cell failure have been postulated to play a role in new-onset hyperglycemia.

Research motivation

Based on evidence regarding the "Immune-mediated inflammatory storm" during the COVID-19 illness. It has also been proposed that COVID-19 is likely associated with an increased risk of developing diabetes. This motivated us to study the underlying mechanisms contributing to new onset hyperglycemia in hospitalized COVID-19 cases.

Research objectives

To assess the validity of the cytokine-induced hyperglycemia hypothesis by evaluating the association between inflammatory markers and new onset hyperglycemia in non-diabetic patients with COIVD-19 infection.

Research methods

A retrospective case-control study was conducted on adults without diabetes mellitus hospitalized for COVID-19 infection. The serum levels of glucose and inflammatory markers at presentation before initiation of corticosteroid were collected. Hyperglycemia was defined as glucose levels ≥ 140 mg/dL. Prespecified cutoffs were used for the inflammatory markers. Statistical methods of analysis were used to calculate the logistic regression for hyperglycemia.

Research results

Of the 520 patients screened, 248 met the inclusion criteria. Our study showed no association between C-reactive protein, ferritin, Lactate dehydrogenase, D-dimer levels, and new-onset hyperglycemia in non-diabetic patients with COVID-19 infection. We observed significantly higher mortality and length of stay in patients with hyperglycemia.

Research conclusions

With new-onset hyperglycemia being closely associated with poor prognostic indices, it becomes pivotal to understand the underlying pathophysiological mechanisms behind the SARS-CoV-2 infection-induced hyperglycemia. This will help us better control the glycemic status and prevent new-onset hyperglycemia, thereby improving the clinical recovery of patients. Our study results indicate the low probability of the stress hyperglycemia hypothesis being the sole mechanism of SARS-CoV-2 infection-induced hyperglycemia but rather a multicausal pathogenesis leading to hyperglycemia that requires further research and understanding.

Research perspectives

Basic science research that would help better understand the underlying pathophysiology and further clinical studies that assess the utility of different treatment strategies in managing hyperglycemia are required to improve the clinical outcomes of COVID-19.

FOOTNOTES

Author contributions: Geetha HS and Trivedi N conceived the idea for the study; Geetha HS, Gogtay M, Abraham GM, and Trivedi N designed and undertook the literature review; Geetha HS, Singh G, Sekar A, and Gogtay M collected data; Gogtay M and Singh Y performed the statistical analysis, figures, and appendix and analyzed and interpreted the data; Geetha HS, Singh G, Sekar A, Singh Y and Gogtay M wrote the first draft of the manuscript; Geetha HS, Singh G, Sekar A, Gogtay M, Singh Y, Abraham GM, Trivedi N revised the subsequent drafts of the manuscript; All authors reviewed and agreed on the final draft of the manuscript.

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ORIGINAL ARTICLE

Clinical Trials Study

Efficacy of invisible advancement correction for mandibular retraction in adolescents based on Pancherz analysis

Lei Kong, Xin-Qiang Liu

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Abstract

BACKGROUND

Mandibular retraction is the main etiological mechanism of class II malocclusion in China and the subsequent distal molar relationship can cause functional discomfort in mastication, breathing and the temporomandibular joint. The use of mandibular advancement (MA) devices has recently emerged as an adolescent mandibular retraction treatment; however, current studies regarding the effect thereof are relatively few, and there is lack of sufficient clinical support.

AIM

To investigate the clinical effect of invisalign MA on the treatment of mandibular retraction in adolescents.

METHODS

This study included 30 adolescent patients who underwent treatment with the MA appliances from December 2017 to June 2021. The lateral cephalometric data before and after treatment were collected and imported into Dolphin Imaging software. The changes were measured by linear measurement superimposed with lateral cephalometric trajectory based on the Pancherz technology.

RESULTS

There was no significant difference in the length and position of maxilla before and after the treatment. The position of the mandible moved 3.13 mm, the length increased 4.14 mm, the mandibular ramus length increased 4.09 mm, the body length increased 4.25 mm, and the position of the condyle moved 1.03 mm forward after treatment. Additionally, changes in the incisor sagittal position and labial inclination were observed. The position of the upper incisor point moved back 1.33 mm, without statistical difference, the inclination and tooth angle

decreased by 3.44° and 4.06°, respectively; the position of the lower incisor point was moved 2.98 mm, and the inclination and tooth angle increased by 2.62° and 1.23°, respectively. Furthermore, changes in the incisor overjet and molar relationship were seen. Overjet decreased by 4.31 mm, of which 1.78 mm was due to dental factors, accounting for 41.3% of the effect as opposed to 58.7% due to skeletal factors. Molar relationship improved 3.87 mm, with 1.34 mm due to dental factors, and dental and skeletal factors were accounted for 34.6% and 65.4% of the effect, respectively.

CONCLUSION

For adolescent patients with mandible retraction, invisalign MA can effectively promote the mandible growth, and it was proven to be mainly due to skeletal effects.

Key Words: Mandibular retraction; Adolescent; Pancherz technology; Functional correction; Invisible appliance; Mandibular advancement

Core Tip: This study aimed to investigate the clinical effect of invisalign mandibular advancement (MA) in the treatment of mandibular retraction in adolescents. In addition to the conventional cephalometric analysis method, Pancherz analysis was used to separate the skeletal and dental effects. The results of this study show that invisalign MA can effectively promote the adolescent mandible growth, improve the incisor overjet and molar relationship, and it was proven to be mainly due to skeletal effects.

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INTRODUCTION

Skeletal II malocclusion is a common deformity in clinical orthodontics, usually manifesting clinically as maxillary protrusion, mandibular retraction, and deep overjet. The subsequent distal molar relationship can cause functional discomfort in mastication, breathing, and the temporomandibular joint[1]. Studies have shown that mandibular retraction is the main etiological mechanism of class II malocclusion in China[2,3]. Therefore, early intervention should be carried out for these patients, and facial shape and function should be improved through functional orthodontics to guide the mandible forward[2]. The best time for this intervention is at the peak of youth growth and development[4].

Commonly used functional appliances include Twin-Block, Activator, and Herbst. Although these have been proven to be effective, they all have various problems, such as large volumes, heavy foreign body sensation, and a long course for the second fixed treatment for fine adjustment[5,7]. In 2016, a mandibular advancement (MA) device (Figure 1) was developed to combine the concept of growth regulation with tooth movement to support simultaneous dental arch expansion, tooth alignment, and mandibular advancement[3,8,9]. MA has recently emerged as an adolescent mandibular retraction treatment[5,10]; however, current studies regarding the effect thereof are relatively few, and there is lack of sufficient clinical support. We aimed to accurately measure and analyse the differences of skeletal and dental changes before and after MA appliance treatment using Dolphin Imaging software 3D fixed point and Pancherz overlap analysis[8,11]. These were combined with traditional methods to evaluate clinical efficacy in the treatment of skeletal class II mandibular retrogression patients.

MATERIALS AND METHODS

Sampling

From December 2017 to June 2021, adolescents with skeletal II mandibular retraction treated with an MA appliance in the Department of Orthodontics, the Affiliated Hospital of Qingdao University were analysed. Thirty patients were screened according to the inclusion and exclusion criteria as study samples. This study was reviewed and approved by the Medical Ethics Committee of the Affiliated Hospital of Qingdao University (authorisation number: QYFYWZLL26729). Initially, an information letter and informed consent forms were sent to caregivers of all participants. They were asked to carefully read the study objectives and procedures, fill out their contact information, and sign the

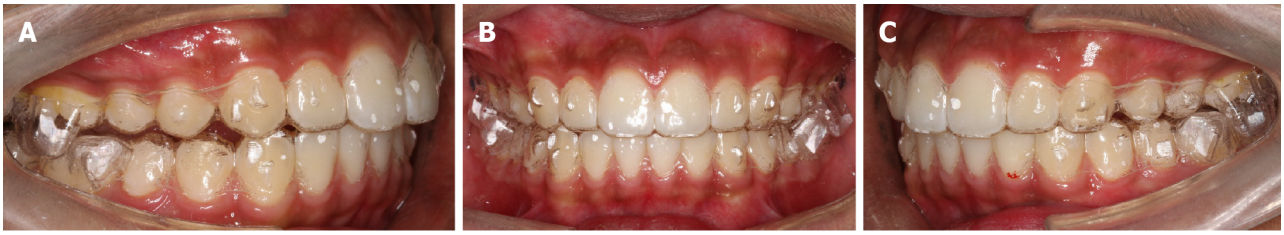

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Figure 1 Clinical mandibular advancement appliance as worn by patients. A: Right interoral occlusion; B: Frontal interoral occlusion; C: Left interoral occlusion.

consent form if they agreed to participate. Adolescents whose parents did not agree to participate were excluded from the study.

We included participants who[4,12-14]: Were at early peak of youth growth and development or peak of youth growth and development [cervical vertebral maturation stage (CVMS) between CVMS1 and CVMS3]; with convex type, retraction of the mandible, the angle between SN and NB (SNB) ≤ 78°, maxillary normal or mild protrusion, the angle between SN and NA (SNA) = 80° ± 2°; stable late mixed dentition or early permanent dentition; mixed dentition the angle between NA and NB (ANB) ≥ 6°, permanent dentition ANB ≥ 5°; and horizontal growth or average growth, SN/MP ≤ 37°. We excluded those with combined severe facial deviation; substantial disease of the temporomandibular joint; previous history of trauma and cleft lip and palate surgery; and previous orthodontic treatment history.

MA appliance treatment process

The treatment process of invisalign MA generally consists of three stages: Pre-MA; MA; and post-MA. In the pre-MA stage, the curve of spee is mainly level, the positional relationship between the upper and lower dental arches is adjusted using the expansion arch, the anterior teeth are aligned or adducted with the space, the posterior teeth are repositioned, and the reverse is removed. During the MA phase, there is coordinated further levelling of the dentition, leading to skeletal advancement to correct the class II molar relationship. This stage requires at least 26 steps, often increasing by 2 mm every seven days and eight steps (approximately two months). The final stage may be more than eight steps to achieve balance and stability and can be combined with class II traction when necessary. After reaching the target site and stabilization, an oral scan was performed, followed by post-MA to complete fine adjustment. Stage T0 and stage T1 radiographs were taken at the beginning and end of the treatment, respectively. For image data acquisition, lateral cranial radiographs taken at T0 and T1 stages on 30 patients meeting the inclusion criteria were collected for comparative analysis.

Method of measurement

The lateral radiographs were imported into Dolphin Imaging software for data measurement, mainly using Pancherz analysis, combined with conventional measurement methods such as Down analysis and Wits analysis. Sagittal changes were studied using linear measurements superimposed on lateral cranial radiographs based on the Pancherz method.

We established the Pancherz analysis method as follows: The occlusal plane (OL) was made on the lateral cephalic radiograph before treatment (through the convex incisal edge point in the upper incisor and distal buccal cusps in the maxillary first molar) as the horizontal reference axis. We used the sella point (S) to OL vertical plane (OLP) as the vertical reference axis and formed a line between the OL and OLP coordinates. S was used as the overlap point, the SN plane, the line connecting the S point and N point line (Figure 2) was overlapped, and its coordinates were transferred to the lateral cranial radiographs after treatment. The post-treatment data were measured. All linear measurements were made on lines parallel to OLP. A total of 22 measurement markers and reference planes, as well as 28 skeletal and dental measurements, were selected to measure and analyse the lateral radiographs of patients before and after treatment (Figure 2 and Table 1).

Statistical analysis

The same researcher conducted three measurements on the patient's cranial lateral radiographs, on the same computer, at an interval of more than two weeks before and after treatment; the average of the three measurements was taken as the final research data. Paired samples *t* test was used to study the changes before and after treatment for all variables within the same group. All data were analysed using the by SPSS 23.0 software, and the significance level was set as $P < 0.05$[15].

Calculation of sample size

In this experiment, Pg/OLP was used as the main analysis index, and the hypothesis test of the population mean of the two groups was used. According to the results of published literature, $\alpha = 0.05$

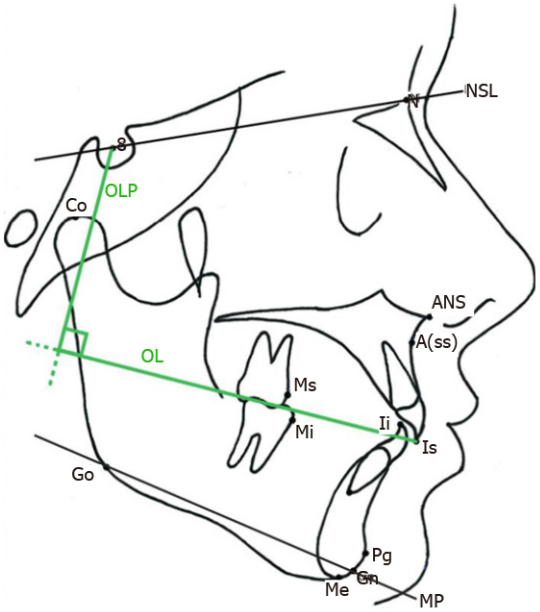

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Figure 2 Mark points and reference planes of cephalometric measurement by Pancherz analysis. S: Sella; N: Nasion; NSL: SN plane, the line connecting the S point and N point; ANS: Anterior nasal spine; Co: Condylion; OL: Occlusal line; OLP: Occlusal line perpendicular; Ms: Molar superius; Mi: Molar inferius; Ii: Incision inferius; Is: Incision superius; Pg: Pogonion; Me: Menton; Gn: Gnathion; Go: Gonion; A(ss): A.subspinale; MP: MP plane, the line connecting the gonion point and gnathion point.

(bilateral test), degree of assurance 1 - β = 0.8 were selected, and the sample sizes of the experimental group and the control group were equal. The following formula was used (Figure 3). A sample size of 25 patients in each group was calculated using Pg/OLP, 25 patients in each group. Considering that the shedding rate was 10%, 28 cases were required for the experimental and control groups to ensure the scientific design of the study. Considering the actual number of patients who had completed clinical work and met the inclusion criteria, 30 patients were finally selected, including 15 males and 15 females. The ages of participants ranged from 10 to 13 years, with an average of 11.6 ± 0.9 years.

RESULTS

Skeletal changes before and after MA correction

ss/OLP value representing maxillary length did not change significantly ($P > 0.05$). The Pg/OLP of the mandible and Co-OLP of the condyle increased by 3.13 mm and 1.03 mm, respectively ($P < 0.05$), indicating that the mandible moved forward and down after MA treatment. The average increase of Pg/OLP + Co/OLP in mandibular length was 4.14 mm, the average increase of Co-Go in mandibular ramus length was 4.09 mm, and the average increase of Go-Pg in mandibular body length was 4.25 mm. The differences were statistically significant ($P < 0.05$).

SNA decreased slightly after MA appliance treatment, but the difference was not statistically significant ($P > 0.05$), indicating that the sagittal direction of the maxilla was not significantly restricted. After treatment, the mean value of SNB increased by 1.96°, ANB decreased by 2.03°, and Wits decreased by 2.90 mm, which were statistically significant compared with T0 ($P < 0.05$), indicating that the sagittal relationship of the mandible was significantly improved.

The SN-MP of the mandibular plane angle increased by 1.65° on average before treatment, and the difference was statistically significant ($P < 0.05$). The ratio of S-Go/N-Me between posterior height and anterior height decreased by 2.04% on average ($P < 0.05$). The ratio of anterior-inferior height to anterior-inferior height (ANS-Me/N-Me) increased by 1.45% on average ($P < 0.05$). The results showed that the sub facial 1/3 height of patients increased significantly after MA appliance treatment (Table 2).

Changes of labial inclination of anterior teeth after MA treatment

After treatment, the position of upper central incisor point is/OLP decreased by 1.33 mm on average, indicating that the incisor end of upper central incisor moved to the palate by 1.33 mm, while the inclination of upper central incisor U1-NA decreased by 3.44° on average ($P < 0.05$), and the angle of upper central incisor U1-SN decreased by 4.06° ($P < 0.05$). The results showed that the upper anterior teeth were adducted after treatment.

Table 1 Skeletal measurement items and notes on lateral radiographs

Measurement	Definition
ss/OLP (mm)	Maxillary position, vertical distance from ss point to OLP
Pg/OLP (mm)	Mandibular position, vertical distance from Pg point to OLP
Co/OLP (mm)	Condyle position, vertical distance from Co point to OLP
Pg/OLP + Co/OLP (mm)	Mandibular length
Co-Go (mm)	Length of mandibular ascending ramus
Go-Pg (mm)	Length of mandibular body
Co-Pg (mm)	The total length of the mandible
SNA (°)	Sagittal relationship of anterior maxilla to basal bone
SNB	Sagittal relationship of anterior mandibular to basal bone
ANB	Sagittal position relationship between upper and lower basal bone
Wits	The distance between upper and lower alveolar points and occlusal plane
SN-MP	The plane angle of the mandible, the plane tangent to the lower edge of the mandible through the point Me
S-Go/N-Me	Posterior height/anterior height
ANS-Me/N-Me	Anterior inferior height/anterior height
is/OLP	Position of upper central incisor
ii/OLP	Position of lower central incisor
ms/OLP	Position of maxillary first molar
mi/OLP	Position of the lower first molar
U1-NA	Inclination of maxillary central incisor
U1-SN	Upper central incisor angle
L1-NB	Inclination of lower central incisor
L1-MP	Lower central incisor angle
is/OLP-ii/OLP	The distance from is point to OLP minus the distance from ii point to OLP is used to represent overjet
ms/OLP-mi/OLP	The distance from ms point to OLP minus the distance from mi point to OLP is used to describe molars
is/OLP-ss/OLP	Changes in the position of the upper central incisor relative to the maxilla
ii/OLP-pg/OLP	Changes in the position of the lower central incisor relative to the mandible
ms/OLP-ss/OLP	The position change of maxillary first permanent molars relative to maxilla
mi/OLP-pg/OLP	Change in the position of the first permanent molars relative to the mandible

NA: The line that connects point N to point A; SN: SN plane, the line that connects point gonion to point gnathion; NB: The line that connects point N to point B; SNA: The angle between SN and NA; SNB: The angle between SN and NB; ANB: The angle between NA and NB; SN-MP: The angle between SN and MP.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta/2}) \times (\sigma_1^2 + \sigma_2^2)}{\delta^2}$$

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Figure 3 Formula for calculating sample size. In the formula: $Z_{1-\alpha/2} = 1.96$, $Z_{1-\beta/2} = 0.84$; $\sigma_1 = 3.25$; $\sigma_2 = 4.53$, $\delta = 72.55\text{-}75.68$.

After treatment, the position of the lower central incisor point ii/OLP increased 2.98 mm on average, indicating that the incisal of the lower central incisor moved 2.98 mm to the labial, while the inclination of the lower central incisor increased 2.62° on average ($P < 0.05$), and the angle of the lower central incisor increased 1.23° ($P < 0.05$). Compared with T0, there was a certain degree of labial inclination in

Table 2 Cephalometric analysis and comparison of changes and calculated measurement items after mandibular advancement treatment

Measurement	Pre-treatment T0	Post treatment T1	Difference T1-T0	*T* value	*P* value
ss/OLP (mm)	71.42 ± 3.76	72.02 ± 4.05	0.60 ± 0.82	-0.532	0.258
Pg/OLP (mm)	72.55 ± 3.25	75.68 ± 4.53	3.13 ± 0.89	-1.561	0.029[a]
Co-OLP (mm)	-8.57 ± 0.65	-9.60 ± 0.45	-1.03 ± 0.79	-1.349	0.000[c]
Pg/OLP + Co/OLP (mm)	82.01 ± 1.57	86.25 ± 2.05	4.14 ± 2.18	-1.687	0.000[c]
Co-Go (mm)	50.03 ± 4.15	54.12 ± 3.65	4.09 ± 1.58	-3.037	0.018[a]
Go-Pg (mm)	76.18 ± 5.43	80.43 ± 3.90	4.25 ± 2.87	-4.581	0.001[b]
Co-Pg (mm)	108.58 ± 7.08	113.60 ± 6.58	5.02 ± 1.83	-3.803	0.038[a]
SNA (°)	80.95 ± 1.90	80.67 ± 1.54	-0.28 ± 0.04	1.915	0.166
SNB (°)	74.89 ± 1.78	76.85 ± 1.65	1.96 ± 2.56	3.218	0.000[c]
ANB (°)	6.11 ± 1.06	4.08 ± 1.34	-2.03 ± 1.32	18.370	0.000[c]
Wits (mm)	6.41 ± 2.45	3.51 ± 1.18	-2.90 ± 1.72	7.138	0.000[c]
SN-MP (°)	31.20 ± 3.62	32.85 ± 3.51	1.65 ± 1.37	-1.478	0.043[a]
S-Go/N-Me	64.12 ± 2.68	62.08 ± 3.09	-2.04 ± 1.68	1.386	0.035[a]
ANS-Me/N-Me	54.40 ± 1.89	55.85 ± 2.18	1.45 ± 1.37	-2.087	0.045[a]
is/OLP	77.98 ± 6.07	76.65 ± 5.71	-1.33 ± 3.08	1.657	0.353
ii/OLP	71.11 ± 5.04	74.09 ± 4.76	2.98 ± 1.08	-1.709	0.071
ms/OLP	46.86 ± 5.34	45.67 ± 4.87	-1.19 ± 0.39	1.687	0.205
mi/OLP	45.30 ± 3.28	47.80 ± 5.18	2.50 ± 1.04	-1.560	0.082
U1-NA	28.89 ± 7.51	25.45 ± 5.40	-3.44 ± 6.89	-7.760	0.010[a]
U1-SN	108.04 ± 3.01	103.98 ± 4.78	-4.06 ± 4.88	4.673	0.000[c]
L1-MP	95.20 ± 2.93	96.43 ± 2.86	1.23 ± 0.40	-0.318	0.000[c]
L1-NB	22.78 ± 4.08	25.40 ± 3.32	2.62 ± 1.63	-3.341	0.030[a]
is/OLP-ii/OLP	6.87 ± 1.51	2.56 ± 0.76	-4.31 ± 1.43	16.30	0.000[c]
ms/OLP-mi/OLP	2.13 ± 1.20	-1.74 ± 1.31	-3.87 ± 0.78	10.61	0.000[c]
is/OLP-ss/OLP	7.04 ± 1.07	6.48 ± 2.09	-0.61 ± 1.71	4.25	0.089
ii/OLP-pg/OLP	-1.12 ± 1.65	0.05 ± 1.70	1.17 ± 0.83	1.75	0.005[b]
ms/OLP-ss/OLP	-23.18 ± 2.69	-24.34 ± 1.98	-1.16 ± 1.78	-15.68	0.000[c]
mi/OLP-pg/OLP	-26.98 ± 2.45	-26.80 ± 2.78	0.18 ± 1.57	3.05	0.185

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Co: Condylion; OLP: Occlusal line perpendicular; Pg: Pogonion; Go: Gonion; ss: Subspinale; MP: MP plane, the line connecting the gonion point and gnathion point; SNA: The angle between SN and NA; SNB: The angle between SN and NB; ANB: The angle between NA and NB; SN-MP: The angle between SN and MP.

the lower anterior teeth at T1 stage (Table 2).

Changes of anterior tooth coverage, molar relationship, and tooth relative to skeleton

Compared with the T0 period before treatment, the anterior tooth overjet is/OLP-ii/OLP decreased by 4.31 mm ($P < 0.05$) and molar relationship ms/OLP-mi/OLP increased by 3.87 mm. The difference was statistically significant ($P < 0.05$), and the upper central incisors moved 0.61 mm compared with the maxillary to lingual side. The difference was not statistically significant ($P > 0.05$).

The lower central incisor migrated 1.17 mm significantly ($P < 0.05$) compared with the mandible lip side. The maxillary first molars migrated 1.16 mm significantly ($P < 0.05$) compared with the mandible to the bistal surface. The mandible first molars moved 0.18 mm compared with the mandible, but this

difference was not significant ($P > 0.05$) (Table 2).

Changes in anterior tooth overjet, molar relationship, and ratio of skeletal and dental factors after MA treatment

After treatment, dental and skeletal overjet changed by an average of 4.31 mm. The total change was due to an upper incisor adduction improvement of 0.61 mm and lower incisor labial inclination improvement of 1.17 mm. Tooth factors were responsible for a total of 1.78 mm, with the remainder due to skeletal factors. Regarding the calculation of cause of overjet change, skeletal factors accounted for 58.7%, and dental factors accounted for 41.3%. The total change of molar relationship was improved by 3.87 mm on average, of which 1.16 mm was contributed to by maxillary molar distal displacement. A total of 0.18 mm was increased by mandibular molar mesial displacement, dental factors totalled 1.34 mm, and skeletal and dental factors accounted for 65.4% and 34.6%, respectively (Figures 4 and 5).

DISCUSSION

In the treatment of adolescent patients with skeletal retraction of the mandible, invisalign MA can effectively promote the growth and development of the mandible and improve the appearance of the mandible. The treatment effect has both dental effect and skeletal effects, and the skeletal effect is of primary importance.

Pancherz analysis was mainly used[8,16]. Firstly, the OL line, OL, on the lateral cranial radiographs before treatment was taken as the X-axis, and a vertical line, OLP passing point S, was made as the Y-axis to establish the rectangular coordinate system. The main reason for choosing the coordinate plane is that it has little change before and after treatment; therefore, the coordinate system is relatively stable; the reference line coincidence is good before and after treatment; and the measurement data is easy to compare. During treatment, it is necessary to select a stationary point, S, as the coincidence point; then select a steady SN plane before growth peak to overlap the datum plane. Coordinates should be moved per slice to the head before and after the treatment side, and a unified coordinate system calculating and analysing the measurements in all types of linear results can use a linear OLP record. The skeletal and dental change, and change in correlation between them, should be analysed so that before and after treatment sagittal direction changes reflect directly on the overlap line spacing. This vividly and accurately expresses the before and after treatment in patients, and we can adopt the formula calculation to determine the proportion of bone and teeth changes, to determine a treatment, the changes of bone and the separation of teeth before and after treatment clearly reflect the curative effect. However, Pancherz analysis is limited in that it usually only focuses on the changes of the mandible and alveola in the sagittal direction, but not the vertical and plane rotation. In addition, the Pancherz analysis method does not involve the change of labial-lingual inclinations and other angles of the incisor, because it uses line distance measurement. Therefore, we combined traditional X-ray cephalometric analysis methods, such as Downs and Wits analysis, to comprehensively analyse the effect of the MA appliance before treatment.

Whether functional appliances can actually inhibit the growth and development of the maxilla has long been debated[7,17,18]. One theory is that functional orthotics inhibit the growth and development of the maxilla by generally making the maxilla grow backward and downward and rotate, while reducing the ability to grow. The other view is that the functional appliance has no effect on the position and growth direction of the maxilla but causes upper alveolar remodelling with the distal movement of the maxillary dentition. Some researchers believe that the functional appliance needs to be combined with traction of an external force to the mouth to form effective maxillary development. In this study, the distance from ss to the OLP plane increased by 0.60 mm on average after MA treatment, indicating an increase in sagittal basal bone length of the maxilla that would be predictable in growing adolescents. The results show that the MA appliance had no significant inhibition on the growth and development of the maxilla.

The key to the function of the advancement appliance is to initiate the response mechanism of adaptive remodelling of the mandibular condyle by guiding the retraction of the mandible forward, so as to maintain the stable position of the mandible and rebuild its relationship with the maxilla. In the study, Pg-OLP distance increased after treatment. Furthermore, Go-Pog of mandibular body length, Pg/OLP + Co/OLP of full mandibular body, Co-OLP of mandibular ramus, and SNB angle all increased, with statistical significance, confirming that the growth and development of the mandible was significantly improved after treatment, and the sagittal relationship between the mandible and maxilla was improved and coordinated. In the leading process, the previously restricted growth space of the mandible is released, which stimulates the downward reconstruction of the growth cent of the condyle and increases the height of the mandibular ascending ramus[19]. After treatment, the effect of mandibular growth is mainly considered to be the sagittal forward movement of the jaw promoted by the function of the appliance, and the growth of the mandible is considered to be due to normal growth and development[20].

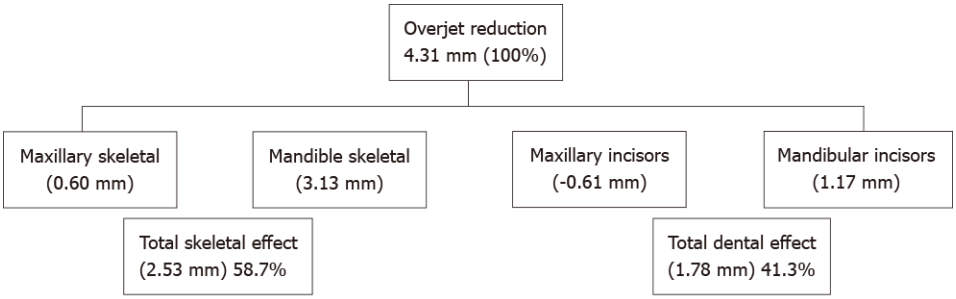

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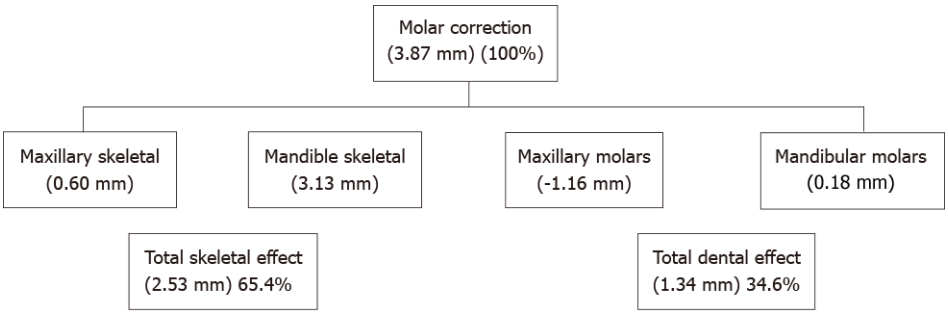
Figure 4 Changes in coverage relationship and proportion of dental and skeletal effect after mandibular advancement treatment. According to calculation and measurement, the proportion of skeletal factors in the total sagittal displacement overjet is 58.7%, the proportion of dental factors is 41.3%. Minus ("-") indicates the position moves backward, positive value indicates the position moves forward.



DOI: 10.12998/wjcc.v11.i6.1299

Figure 5 Molar relationship changes and the proportion of dental and skeletal effect after mandibular advancement treatment. According to calculation and measurement, the proportion of skeletal factors in the total sagittal displacement molar correction is 65.4%, the proportion of dental factors is 34.6%.

In this study, after MA treatment, the ascending ramus height, the ratio of anterior-inferior height to posterior-inferior height, and the mandibular plane angle all increased, while the ratio of posterior-anterior height to anterior-inferior height decreased. The results showed that the lower 1/3 height and mandibular plane angle increased after the use of the invisible appliance to guide the mandible forward, and the mandible may have a certain degree of backward and downward rotation.

The removed mandibular natural growth trend may be due to the process of leading, when the mandible moves forward, the upper and lower teeth form a wedge space at the back and the molars elongate to compensate which causes compensatory mandibular growth and, thus, mandibular clockwise rotation. In addition, the mandible is forced to be in a new jaw position during the extension process, which releases the growth space of the mandible, promotes downward reconstruction of the growth centre of the condyle, and causes elevation of the mandibular ramus to accelerate[19]. As all the cases included in this study were horizontal and average growth types of mandibular retraction, the lower 1/3 height of the patient's face was effectively improved through treatment and the lateral appearance was more beautiful.

Studies have confirmed that the MA appliance can effectively improve the overjet and molar relationship of class II patients. After treatment, the overjet of most patients was significantly improved, and the improvement of the upper and lower first molars was mostly neutral or a mild mesial relationship. The reduction of overjet and the improvement of molar relationship are the results of the changes of bone and teeth in the treatment of class II mandibular retraction. The curative effect is composed of dental and skeletal effects. According to the calculation, the overjet of the front teeth after correction was reduced by 4.31 mm, and the molar relationship was improved by 3.87 mm. Among them, skeletal factors accounted for 58.7% and 65.4% of the total proportion of overjet and molar relationship, respectively. Dental factors accounted for 41.3% and 34.6%, respectively. It is concluded that the MA appliance can be used in the treatment of skeletal II mandibular retraction, and the improvement of the relationship between overjet and molar is more influenced by the skeletal effect.

For adolescent patients with skeletal retraction of the mandible, the correction with invisalign MA can effectively promote growth, development, and improved appears of the mandible. There were both dental and skeletal effects, but the skeletal effect was of primary importance as it may play a role in the reconstruction of the temporomandibular joint.

The clinical retrospective study is summarized and designed on the basis of the existing case data. The integrity of case data are not controlled by the experimental design, and confounding factors and bias are inevitable. Therefore, only sophisticated statistical methods can be used to avoid or minimize

the effects. Due to the insufficient sample size of the control group, this study adopted a method of self before and after control.

CONCLUSION

In the treatment of adolescent patients with skeletal retraction of the mandible, invisalign MA can effectively promote the growth, development, and appearance of the mandible. The treatment effect has both dental and skeletal effects, with skeletal effects having a stronger influence.

ARTICLE HIGHLIGHTS

Research background

In recent years, invisalign treatment with mandibular advancement (MA) has emerged for correcting class II malocclusion in growing teens with patients reporting comfort and satisfaction during the treatment; this approach uses precision wings incorporated into the upper and lower aligners to engage the mandible in an advanced edge-to-edge position while the anterior teeth are being aligned. It was developed to combine the concept of growth regulation with tooth movement to support simultaneous dental arch expansion, tooth alignment and MA. Whether the simultaneous correction of the bite along with dental alignment results in greater efficiency compared to treating the bite relationship and the dental alignment sequentially, there is lack of sufficient clinical research support.

Research motivation

This study aimed to investigate the clinical effect of invisalign MA in the treatment of mandibular retraction in adolescents. Pancherz analysis was used to separate the skeletal and dental effects.

Research objectives

To analyse the dentoskeletal effects of the invisalign MA device in the treatment of skeletal class II malocclusions.

Research methods

Lateral cranial radiographs before and after treatment of 30 subjects were collected, pre-treatment (T0) and post-treatment (T1) lateral cephalograms were mainly traced using Pancherz's cephalometric analysis, the differences were assessed with paired samples *t*-test at the $P < 0.05$ level.

Research results

Improvement in class II relationship resulted from skeletal and dental changes. The position of the mandible moved forward 3.13 mm. There was 4.31 mm overjet reduction of which 58.7% due to skeletal factors, and 3.87 mm molar correction of which skeletal factors were accounted for 65.4%.

Research conclusions

The research show the effectiveness of MA in the management of skeletal class II malocclusions due to mandibular retrusion, highlighting an improvement in the sagittal relationships between the upper and lower bases.

Research perspectives

Further prospective studies should be conducted with a control group and larger sample size.

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Author contributions: Kong L contributed to the conceptualization, methodology, data curation, writing original draft, visualization, investigation of the manuscript; Liu XQ contributed to the clinical treatment, supervision, writing-reviewing of the manuscript.

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ORIGINAL ARTICLE

Observational Study

Survey study of the etiology of non-traumatic altered consciousness in the Emergency Department at Suez Canal University Hospital in Egypt

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Abstract

BACKGROUND

Disorders of consciousness including coma in non-trauma patients can be caused by a wide variety of pathologies affecting the central nervous system. They represent a frequent challenge in emergency medicine and are combined with a very high in-hospital mortality. Hence, early treatment of these patients is vital and increases the likelihood of a good outcome.

AIM

To identify the causes of altered consciousness presentation to the Emergency Department at Suez Canal University Hospital.

METHODS

This was a descriptive cross-sectional study conducted on 87 patients with acute non-traumatic disturbed level of consciousness (DLOC) at the Emergency Department.

RESULTS

The mean age of the studied patients was 60.5 ± 13.6 years. Among them, 60% were males and 40% were females. The most common cause of acute non-traumatic DLOC was systemic infection, such as sepsis and septic shock (25.3%), followed by respiratory causes (24.1%) and neurological causes (18.4%).

CONCLUSION

The most common cause of acute non-traumatic DLOC was systemic infections followed by respiratory and neurological causes.

Key Words: Disturbed level of consciousness; Non-traumatic; Emergency department

Core Tip: Disorders of consciousness including coma in non-trauma patients can be caused by a wide variety of pathologies affecting the central nervous system. This includes life-threatening medical, neurological or neurosurgical emergencies where timely medical intervention is vital. The aim of this cross-sectional observational study was to identify the causes of acute non-traumatic altered consciousness in the Emergency Department at Suez Canal University Hospital. Our study concluded that the most common cause of acute non-traumatic disturbed level of consciousness was systemic infections followed by respiratory and neurological causes.

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INTRODUCTION

Disorders of consciousness including coma in non-trauma patients can be caused by a wide variability of pathologies affecting the central nervous system (CNS). This includes life-threatening medical, neurological or neurosurgical emergencies where timely medical intervention is vital[1]. Five–nine percent of all patients in Emergency Departments (EDs) present with acute non-traumatic disorders of consciousness, and up to two percent of patients are in a coma at admission. Therefore, they represent a frequent challenge in emergency medicine[2,3]. Furthermore, they are combined with a very high in-hospital mortality that accounts for 25%-48% of patients in western populations[4,5].

In a previous study examining the etiology and outcome of non-traumatic coma in a tertiary pediatric ED in Egypt, the most frequent etiologies were metabolic (33%), CNS infection (28%) and intracranial hemorrhage (13%). In the ED, 50% of those patients died[6]. Hypothermia, hypotension, flaccidity and poor Glasgow coma scale (GCS) score at admission correlated significantly with mortality. Forty-eight hours after admission, poor pulse volume, poor GCS, abnormal respiratory pattern/apnea and seizures correlated significantly with mortality[6].

Generally, the underlying pathologies of patients with disturbed consciousness have been classified into primary or focal injury to the CNS and secondary affection of the CNS resulting in a diffuse brain dysfunction, such as in metabolic disorder or intoxication[7]. The reported prevalences of structural *vs* metabolic coma varies from 28%-64% and 37%-75%, respectively[8]. The early treatment of these patients is vital, and diagnoses need to be confirmed or excluded promptly because a good outcome significantly depends on early treatment ("time is brain"), *e.g.*, in meningoencephalitis[9] or basilar artery occlusion[10].

There are no data on the pattern of altered consciousness presentation in the EDs in Egypt, which could make proper preparation of the departments for the potential needs regarding these patients suboptimal. Therefore, in this study, we aimed to identify the causes of altered consciousness presentations to the ED at Suez Canal University Hospital (Ismailia, Egypt).

MATERIALS AND METHODS

Study design

This observational, prospective, cross-sectional study was conducted from January 2021 to January 2022.

Study setting

The study was conducted on data of patients admitted to the ED at Suez Canal University Hospital, Ismailia, Egypt.

Study population

This study comprised 87 patients who were ≥ 18-year-old with acute non-traumatic disturbed level of consciousness (DLOC) *i.e.* GCS < 15. Patients with a history of recent head trauma, or with a history of neurological insult with residual altered consciousness or on medications that caused an altered level of consciousness (ALC) were excluded from the study. All data of the patients included in this study were collected after receiving informed written consent from the patients' first-degree relatives.

A pre-organized questionnaire was prepared, which included age, sex, onset of DLOC, and chronic illnesses. Clinical assessment of the patients included vital signs and grading of level of consciousness using the GCS. The appropriate laboratory and radiological investigations were completed to determine etiology of the DLOC. The outcome of the patients was determined as survival or death, and the mortality rate was calculated.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences for Windows version 22 (IBM Corp., Armonk, NY, United States). *P* values < 0.05 were considered statistically significant. The confidence interval was set at 95%.

RESULTS

Baseline characteristics of the study population

The present study showed that the mean age of the studied patients was 60.5 ± 13.6 years (range: 18-93 years). The majority of patients (64.5%) were ≥ 60 years, and 23% of the patients were between the ages of 50-59 years. The majority of the patients (60.0%) were males, with a male to female ratio of 1.5:1. All characteristics are presented in Table 1.

Chronic illnesses of the cohort

Reported chronic illnesses among the patients is shown in Table 2. Hypertension (HTN) and diabetes were the most common chronic illness (43.7% and 34.5%, respectively).

Distribution of the patients according to GCS

The majority of the patients (42.5%) had GCS between 6 and 11, followed by 33.3% of patients with GCS between 11 and 14, and 24.2% of patients with GCS between 3 and 5 (Table 3).

Radiological investigations of the cohort

Computed tomography (CT) was primarily used for radiological investigations. CT of the brain showed that 53.0% of the patients had normal CT findings, while 23.0% of patients had abnormal CT findings. CT was not performed in 24.0% of patients.

Distribution of the causes of non-traumatic DLOC

The most common cause of acute non-traumatic DLOC was systemic infection such as sepsis and septic shock (n = 22, 25.3%), which included urinary tract infection, cellulitis, infected bedsores and sepsis. The next most common causes were respiratory (n = 21, 24.1%) and neurological (n = 16, 18.4%). Among the respiratory causes, coronavirus disease 2019 (COVID-19) accounted for 15.0% of patients (n = 13) and pneumonia accounted for 3.5% of patients (n = 3). Among the neurological causes, stroke represented 8.1% of patients (n = 7) followed by intracranial hemorrhage (7.0%, n = 6); meningitis and status epilepticus were also present at lower rates. Metabolic causes were also found (11.5%), consisting primarily of diabetic ketoacidosis and dehydration associated with electrolyte disturbances. Further causes are shown in Table 4.

The mortality rate was 25.3% (n = 22), of which 41.0% of the patients died due to systemic infection followed by 31.8% due to respiratory causes (primarily COVID-19) and 13.6% due to oncological causes.

DISCUSSION

This cross-sectional study aimed to determine the causes of non-traumatic disorders of consciousness. We observed that the mean age of these patients was 60.5 ± 13.6 years, with range of 18-93 years, and that more male patients were eligible for participation in this study than females. Our findings were similar to Jung *et al*[11], in which they observed a mean age of 68.81 ± 16.40 years in patients with ALC in the ED. Most of those patients were in their 80 s, accounting for 27.09% of the patients with ALC in the ED; the patients in their 70 s and 80 s also accounted for 53.49% of their study population. Cherukuri and Dhanawade[12] studied patients in the ED of Christian Medical College Hospital, Vellore (India), a tertiary medical care center, from January 2013 to April 2013; moreover, their study population was exclusively > 18 years of age, presenting with acute undifferentiated altered mental state (AMS) *i.e.* GCS < 15, with onset of symptom(s) being no more than 1 wk before ED presentation. Patients with chronic AMS and traumatic brain injuries were excluded from the study. Ultimately, in that study, the mean age was 52.3 ± 17.84 years and they observed a male predominance (62.3%).

Our study observed several chronic diseases, including HTN, diabetes, chronic kidney disease, chronic liver disease, coronary artery disease and cerebrovascular stroke. HTN and diabetes were the

Table 1 Baseline characteristics of the study population, *n* (%)

Variables	*n* = 87	Alive	Dead	*P* value
Age, yr				N/A
mean ± SD	60.5 ± 13.6	60.4 ± 14.1	62.6 ± 12.2	
Median (range)	75 (18-93)	75 (18-93)	48 (30-78)	
Age groups				0.4[b]
18-29	3 (3.4)	3 (4.6)	0 (0)	
30-39	3 (3.4)	2 (3.1)	1 (4.5)	
40-49	5 (5.7)	4 (6.2)	1 (4.5)	
50-59	20 (23.0)	15 (23.1)	5 (22.7)	
≥ 60	56 (64.5)	41 (63.0)	15 (68.3)	
Male	52 (60.0)	40 (61.5)	12 (54.5)	0.3[b]
Female	35 (40.0)	25 (38.5)	10 (45.5)	

[b]*P*: Non-significant.
N/A: Not applicable; SD: Standard deviation.

Table 2 Chronic illnesses of the cohort, *n* (%)

Chronic illnesses	*n* = 87	Dead, *n* = 22	Alive, *n* = 65	*P* value
Chronic obstructive pulmonary disease	10 (11.5)	0 (0)	10 (15.4)	0.04[a]
Chronic kidney disease	12 (13.8)	6 (27.3)	6 (9.2)	0.03[a]
Diabetes mellitus	30 (34.5)	10 (45.5)	20 (30.8)	0.1[b]
Cancer	8 (9.2)	5 (22.7)	3 (4.6)	0.02[a]
Chronic liver disease	14 (16.1)	8 (36.4)	6 (9.2)	0.006[a]
Cerebrovascular stroke	14 (16.1)	2 (9.1)	12 (18.5)	0.2[b]
Coronary artery disease	10 (11.5)	3 (13.6)	7 (10.8)	0.4[b]
Hypertension	38 (43.7)	12 (54.5)	26 (40)	0.1[b]

[a]$P < 0.05$.
[b]*P*: Non-significant.

Table 3 Distribution of the patients according to the Glasgow coma scale, *n* (%)

GCS	*n* = 87	Dead, *n* = 22	Alive, *n* = 65
3-5	21 (24.2)	6 (27.3)	15 (23.1)
6-10	37 (42.5)	10 (45.4)	27 (41.5)
11-14	29 (33.3)	6 (27.3)	23 (35.4)
mean ± SD	8.5 ± 3.7	7.9 ± 3.5	8.6 ± 3.8
Median (range)	11 (3-14)	11 (3-14)	11 (3-14)

GCS: Glasgow coma scale; SD: Standard deviation.

most common chronic illnesses (43.7% and 34.5%, respectively). Our findings agreed with Cherukuri and Dhanawade[12], in which 40% of their patients had type 2 diabetes mellitus and 36.8% had systemic HTN. History of smoking was recorded for 11%. These results were similar to the results of the study by Sarker *et al*[13], in which HTN, diabetes, ischemic heart disease, chronic kidney disease and chronic liver disease were identified as chronic illnesses among their study population. HTN and diabetes mellitus

Table 4 Distribution of the causes of non-traumatic disturbed level of consciousness, *n* (%)

Causes of disturbed level of consciousness	*n* = 87	Dead, *n* = 65	Alive, *n* = 22	*P* value
Neurological	16 (18.4)	15 (23.1)	1 (4.5)	0.5[b]
Intracranial hemorrhage	6 (7.0)	6 (9.2)	0 (0)	
Stroke	7 (8.1)	6 (9.2)	1 (4.6)	
Meningitis	1 (1.1)	1 (1.5)	0 (0)	
Cavernous sinus thrombosis	1 (1.1)	1 (1.5)	0 (0)	
Status epileptics	1 (1.1)	1 (1.5)	0 (0)	
Metabolic	10 (11.5)	10 (15.4)	0 (0)	
Hypoglycemia	1 (1.1)	1 (1.5)	0 (0)	
Diabetic ketoacidosis	6 (7.0)	6 (9.2)	0 (0)	
Dehydration and poor oral feeding	3 (3.5)	3 (4.6)	0 (0)	
Systemic infection sepsis	22(25.3)	13 (20.0)	9 (41.0)	
Respiratory	21 (24.1)	14 (21.5)	7 (31.8)	
COVID-19	13 (15.0)	7 (10.8)	6 (27.3)	
Pneumonia	3 (3.5)	3 (4.6)	0 (0)	
Respiratory failure	5 (5.8)	4 (6.2)	1 (4.5)	
Organ dysfunction	8 (9.2)	7 (10.8)	1 (4.5)	
Hepatic encephalopathy	4 (4.6)	3 (4.6)	1 (4.5)	
Uremic encephalopathy	1 (1.1)	1 (1.5)	0 (0)	
Hypertensive encephalopathy	3 (3.5)	3 (4.6)	0 (0)	
Cardiovascular	2 (2.3)	1 (1.5)	1 (4.5)	
Cardiogenic shock	1 (1.1)	1 (1.5)	0 (0)	
Pulmonary edema	1 (1.1)	0 (0)	1 (4.5)	
Oncological	5 (5.8)	2 (3.1)	3 (13.6)	
Drug overdose	1 (1.1)	1 (1.5)	0 (0)	
Unknown	2 (2.3)	2 (3.1)	0 (0)	

[b]*P*: Non-significant.
COVID-19: Coronavirus disease 2019.

were also the most common (26% and 17%, respectively) in their study.

Our study showed that the mean GCS was 8.5 ± 3.7. The majority of the patients (42.5%) had moderate DLOC, followed by mild and then severe DLOC. In a study by Sarker *et al*[13], more than half of the patients (53%) had GCS between 6 and 10 (moderate), followed by 27% with GCS between 3 and 5 (severe) and 20% with GCS between 11 and 14 (mild) at the time of presentation. They observed a mean GCS of 7.7 ± 3.1.

In our study, the most common cause of acute non-traumatic DLOC was systemic infection such as sepsis and septic shock (*n* = 22, 25.3%), followed by respiratory causes (*n* = 21, 24.1%) and neurological causes (*n* = 16, 18.4%). Similarly, Jung *et al*[11] found that the leading cause of ALC in the ED was systemic infection, which accounted for approximately 30% of the cases. The second most common cause was metabolic (21.07%), and the third most common cause was stroke (18.19%), which was diagnosed when the acute CNS symptoms were compatible with the brain lesions found on neuroimaging. Cherukuri and Dhanawade[12] found that neurological conditions were the most important cause for AMS, accounting for 37.1% of their patients. Other etiologies were metabolic and endocrine causes (18%) followed by infections (13%).

In a study by Schmidt *et al*[14], the main diagnoses were classified into acute primary brain lesions (39%), primary brain pathologies without acute lesions (25%) and pathologies that affected the brain secondarily (36%). In another study by Braun *et al*[9], in which 58% of the studied patients had neurological causes for coma (intracranial hemorrhage, stroke, and epilepsy), followed by intoxication (16.6%), cardiovascular cause (5.8%) and respiratory cause (5.5%), respectively. Also in a study by Idro

et al[15], infections of cerebral malaria were the primary cause of AMS in a study from Ethiopia. Studies of AMS by Sporer *et al*[16] found that substance abuse was the primary cause. The etiology and the characteristics of patients with DLOC varies between different countries and depends on many factors including regional or demographic backgrounds, location of the hospital, the national health care system and medical resources. Accordingly, our cohort was comprised of an elderly population with multiple comorbidities. Typically, elderly people are neglected in our society and do not receive prompt treatment of illnesses, which explains why we observed systemic infections as the most common cause of DLOC. In addition, our study was conducted during the COVID-19 pandemic, which may explain the number of patients that presented with acute DLOC due to respiratory causes (15% of the respiratory causes were due to COVID-19).

In our study, the mortality rate was 25.3% (n = 22), of which 41% of the patients died due to systemic infection followed by respiratory causes (primarily COVID-19) and oncological causes. It was similar to a study by Forsberg *et al*[17], in which the total hospital mortality was 26.5%. Kekec *et al*[18] also reported higher mortality of 20.1% in patients with AMS. In contrast to our results, the mortality rate among AMS patients in the study by Cherukuri and Dhanawade[12] was 11.5%. Kanich *et al*[2], Leong *et al*[19] and Xiao *et al*[20] reported mortality rates ranging from 9% to 11%.

There were several limitations to this study. First, as this was a single-center study, the sample size was small as our center is a tertiary care facility and only receives patients 3 d/wk. Second, the scope of this study was limited to clinical practice in the ED with exclusion of traumatic DLOC, psychiatric causes and patients with cardiac arrest on presentation to ED. ALC has a wide variation of causes, and it can be challenging and time-consuming to achieve a definitive diagnosis, which may require additional evaluation that is not available in the ED. Moreover, two or more causes can occasionally be present concomitantly. The study was also carried out during outbreaks of COVID-19, which affected the causes of mortality. These obstacles make it challenging to study ALC in the ED, indicating that further study and analysis are needed.

CONCLUSION

DLOC including coma in non-traumatic patients can be caused by a wide variety of pathologies affecting the CNS. They represent a frequent challenge in emergency medicine with a very high in-hospital mortality. Early treatment of these patients is vital and good outcomes depend on early treatment. This cross-sectional study revealed that systemic infection was the most common cause of DLOC, followed by respiratory causes and neurological diseases. Patients with systemic infections, COVID-19 and oncological diseases had the highest mortality among our studied patients.

ARTICLE HIGHLIGHTS

Research background

Disorders of consciousness including coma in non-traumatic patients can be caused by a wide variety of pathologies affecting the central nervous system including life-threatening medical, neurological or neurosurgical emergencies where timely medical intervention is vital. The early treatment of these patients is vital, and diagnoses need to be confirmed or excluded promptly.

Research motivation

There are no data on the pattern of altered consciousness presentation in Emergency Departments (EDs) in Egypt, which could make proper preparation for the potential needs of these patients suboptimal.

Research objectives

The primary objective of our study was to identify the causes of altered consciousness presentation to the ED at Suez Canal University Hospital (Egypt). The secondary objectives were to describe the treatment modalities for patients presenting with altered consciousness and to assess the mortality rate among patients presenting with altered consciousness.

Research methods

This study was conducted on 87 patients, all of whom were ≥ 18-year-old with acute non-traumatic disturbed level of consciousness (DLOC) *i.e.* Glasgow coma scale < 15. All data of the patients included in this study had been collected after receiving informed written consent from the patients' first-degree relatives. The outcomes of the patients were determined as survival or death, and the mortality rate was calculated.

Research results

In our study, the most common cause of acute non-traumatic DLOC was systemic infection such as sepsis and septic shock (n = 22, 25.3%), followed by respiratory causes (n = 21, 24.1%) and neurological causes (n = 16, 18.4%). The mortality rate was 25.3% (n = 22) of which 41.0% of the patients died due to systemic infection, followed by 31.8% due to respiratory causes [primarily coronavirus disease 2019 (COVID-19)] and 13.6% due to oncological causes.

Research conclusions

The most common cause of acute non-traumatic DLOC was systemic infections followed by respiratory and neurological causes.

Research perspectives

Further study and analysis are needed to overcome the challenges of a small sample size and outbreaks of COVID-19 encountered in our study.

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FOOTNOTES

Author contributions: Moussa BS and Abd Elatiff ZM collected the data; Moussa BS assessed the results; Kamal Eldin Elhadary GM and Abd Elatiff ZM wrote and revised the manuscript; all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Metformin effect on internal carotid artery blood flow assessed by area under the curve of carotid artery Doppler in women with polycystic ovarian syndrome

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Abstract

BACKGROUND

Insulin resistance (IR) was reported in most polycystic ovarian syndrome (PCOS) cases. Metformin, a biguanide drug, successfully reduced IR. Homeostatic Model Assessment for IR (HOMA-IR) and Doppler parameters assessed metformin's effectiveness.

AIM

To verify whether the area under the curve of the internal carotid artery (AUC-ICA) Doppler wave can be a useful marker for assessing IR among PCOS cases who presented with menstrual irregularity and were treated with metformin over 6 mo.

METHODS

An observational, cross-sectional study recruited 54 eligible PCOS women; the anthropometrics were as follows: age, body mass index (BMI), menstrual cycle days, biochemical serum cholesterol, low and high-density lipoprotein, sex hormone-binding globulin, fasting blood glucose, and HOMA-IR, hormonal testosterone, luteinizing hormone over follicle-stimulating hormone ratio, and ultrasonic pulsatility index (PI) and resistance index (RI), carotid artery intima-media thickness (CIMT) and (AUC-ICA) parameters were initially recorded and repeated 3 mo and 6 mo later with metformin tab 500 mg; three times/day for 6 mo. In addition, AUC-ICA was assessed by taking repeated systolic and diastolic wave height measurements.

RESULTS

Metformin caused a progressive reduction in BMI, menstrual cycle days, biochemical hormonal, and Doppler parameters (CIMT, PI, RI, and AUC-ICA). AUC-ICA correlated strongly to all PCOS parameters. AUC-ICA correlated inversely with treatment time (r = -0.98, P < 0.001) and positively with HOMA-IR (r = 0.98, P < 0.0001). *Via* the best subset regression model, the AUC-ICA had the highest predictive value for HOMA-IR.

CONCLUSION

AUC-ICA preceded PI, RI, and CIMT with a strong, meaningful correlation to all PCOS parameters, making it a reliable marker for the assessment of IR, especially during metformin therapy. Further studies are recommended to promote the application in practice.

Key Words: Carotid artery intima-media thickness; Insulin resistance; Internal carotid artery Doppler; Metformin; Polycystic ovarian syndrome

Core Tip: Women with polycystic ovarian syndrome (PCOS) suffer from insulin resistance and an atherogenic state evidenced by increased carotid artery intima-media thickness (CIMT). Fortunately, this increase in CIMT is reversible with metformin therapy, an insulin-sensitizing drug. Moreover, treated cases have restored ovulatory cycles and exhibited reduced androgen levels. First, we primarily aimed to examine whether the area under the curve of the internal carotid artery (AUC-ICA) Doppler is related to insulin resistance among PCOS women who presented with menstrual disturbances. Second, is to examine if AUC-ICA can be a useful marker in assessing changes in insulin resistance among treated cases with metformin for follow-up.

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is still one of the most frequently challenging problems facing gynecologists worldwide. Despite much work conducted to understand its nature, its long-term complications from cardiovascular, infertility, and obesity-related problems are still major issues facing all affected women[1-3]. PCOS women are characterized by a state of life-long insulin resistance (IR) with permanently elevated serum insulin[4].

This hyperinsulinemia disturbs ovarian steroidogenesis (estrogens and progesterone) and the pituitary secretion of gonadotropins, represented by chronically elevated serum luteinizing hormones (LH) and serum testosterone[5].

Elevated serum testosterone mainly affects lipid metabolism with an elevation of low-density lipoprotein (LDL) and serum cholesterol and a reduction of serum high-density lipoprotein (HDL)[6]. This disturbed lipid metabolism; leads to acute atherosclerotic changes affecting virtually every artery in the body but mostly in the medium-sized artery like the internal carotid artery, which can be scanned by B-mode ultrasound device. The atherogenic state is evidenced by increased carotid artery intima-media thickness (CIMT); fortunately, this increase in CIMT is usually reversible with the use of insulin-sensitizing drugs among young women below 35 years of age, which makes this reduction one of the most important prognostic variables for IR complications[7].

According to Bernoulli's rule, the increased CIMT per se is associated with a reduction in the arterial diameter, which consequently increases the artery's blood flow speed[8].

According to this rule, the narrower the artery lumen is, the more blood speed per unit area in its section (inverse relationship). Modern Doppler devices allow arterial blood speed to be measured and graphed on paper strips directly from scanned arteries. With ultrasound waves beamed at 60 degrees, we can measure the difference in phase shift of the ultrasound wave[9].

The most commonly used Doppler indices to assess arterial blood flow are pulsatility and resistant index (PI and RI), respectively[10].

The PI is an ultrasonic blood flow parameter calculated from the highest, lowest, and mean Doppler frequency shifts during a given cardiac cycle. As for the RI, it estimates the resistance in a pulsatile

vascular tree[11].

However, a new parameter can be easily conducted with current Doppler devices: Measuring the area under the curve (AUC) of one complete heartbeat-associated blood flow graph in an artery represented by a systolic and diastolic wave.

Multiple readings of the heights of a systolic and diastolic wave of a single Doppler wave measure AUC under one Doppler wave. In physical terms, measuring AUC means measuring the amount of blood passing per unit area of the artery cross-section area[12]. For that, the speed of blood flow should increase while the amount of blood passed per unit sectional area of the internal carotid artery should reduce or remain the same according to the resistance distal to the vessel[12].

Metformin is an insulin sensitizer used for type 2 diabetes. Since many PCOS women are IR, metformin administration proved its efficacy in restoring ovulatory cycles and reducing androgen levels. This biguanide inhibits hepatic glycogenesis, increases insulin sensitivity in the periphery, increases glucose uptake, and decreases insulin secretion[1].

Earlier studies in the field have shown reduced atherogenic indicators by insulin sensitizers like metformin and inositol for 3-6 mo, including dyslipidemia, IR, and improved endothelial function and coronary flow. Furthermore, there was a reduction in CIMT among treated women[13]. The aim of the study is to verify whether the AUC of the internal carotid artery (AUC-ICA) Doppler is related to IR among women with PCOS who presented with menstrual disturbances. Second, to examine if AUC-ICA can be a useful marker for the assessment of IR among women treated with metformin for follow-up.

MATERIALS AND METHODS

The current study was a cross-sectional study conducted in AL Yarmouk Teaching hospital between April 2019 till December 2021. The ethical committee of Mustansiriyah University approved the study dated February/21/2019 (IRB No. 115). Participants were briefed about the study's aim and methodology; all gave their consent before enrollment, and the Helsinki declaration was followed.

From the outpatient clinic, unmarried women with PCOS who presented with menstrual cycle abnormality and/or hirsutism, the age range of 18-35 years, and a body mass index (BMI) range of 18 to and 30 were invited to participate in the study. During this period, all patients had been prescribed a metformin tab. (Merck Santé/France) 500 mg TID times /d.

The diagnosis of PCOS was made based on Rotterdam criteria, where 2 out of 3 criteria confirm PCOS diagnosis[14]. (1) Oligomenorrhea is defined as < than six cycles/ 12 mo, or amenorrhea is defined as a complete absence of the menstrual cycle (more than 90 d); (2) Clinical hyperandrogenism, with or without acne; and (3) Ultrasonic features of polycystic ovaries[15,16].

Exclusion criteria

The following groups were excluded from this study: (1) Women with hypertension, diabetes mellitus, and thyroid diseases; (2) Drug intake of insulin sensitizers, lipid-lowering medicines, anti-androgenic therapies, oral contraceptives, and steroids; (3) Participants with a BMI of more than 30; and (4) Those with missing data were also excluded.

Fifty-four participants satisfied our criteria and the patients in this study were all subjected to meticulous clinical examination and all had an initial pelvic ultrasound scan to confirm the appearance of the PCOS ovaries. For each participant, four sets of data were collected; demographic criteria, biochemical and hormonal data, and biophysical data. These data were collected at the initial visit, 3 mo, and then 6 mo later, and the patient was supplied with a data collection sheet for the dates of further scheduled visits. During this period, all patients had been prescribed a metformin tab (Merck Santé/ France) 500 mg TID times /d. At the end of the study, a total of 54 women with complete data of biophysical, biochemical, and hormonal data were assessed at 0, 3, and 6 mo; all were described in the study flowchart Figure 1.

Initial patients' uptake

The initial uptake was based on the clinical criteria of a menstrual cycle (MC) abnormality (oligomenorrhea or amenorrhea). The patients' age was recorded and only BMI was calculated in the outpatient clinic according to the formula: Weight in kg/square meter of height. After exclusion, eligible cases were planned to be further investigated for hormonal, biochemical, and biophysical criteria.

Biochemical and hormonal assays

On the 2nd day of the menstrual cycle and after one night's fast, participants in the study were initially sent to the Teaching labs in Yarmouk Hospital for the following biochemical tests: HDL, LDL, serum cholesterol, homeostatic model assessment for insulin resistance (HOMA-IR), fasting blood glucose (FBS), and sex hormone-binding globulin (SHBG). In addition to the hormones: Follicle-stimulating hormone (FSH), LH, and serum testosterone. The HOMA-IR tested insulin sensitivity based on the formula: HOMA-IR = fasting insulin (micro U/L) × fasting glucose (nmol/L)/22.5[17].

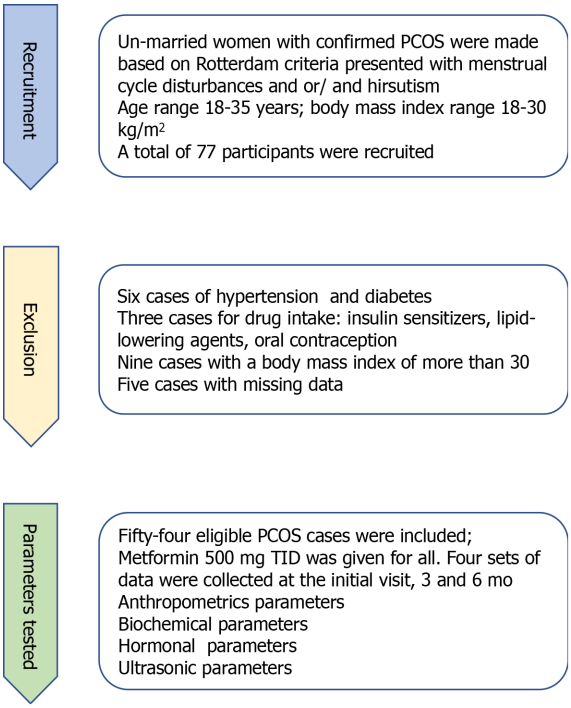

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Figure 1 Study flowchart. PCOS: Polycystic ovarian syndrome.

All patients were given subsequent appointments based on the initial visit to repeat all of the above investigations 3 mo and 6 mo later while on metformin therapy, in addition to recording the days of the MC.

Biophysical data uptake

On the same day of biochemical data uptake, patients were sent for a Doppler assessment of the internal carotid artery.

Examination technique

In the radiology unit, an ultrasound machine TOSHIBA, Logic p5 with a linear array probe, and a frequency range of 5-10 MHZ was used. To measure carotid media intima thickness (CIMT), a special software computer option was used to adjust angle measurements for CIMT with a two–dimensional 2D grayscale maneuver. The assessment was made for both the right and left internal carotid artery (ICA), and the mean of both readings was taken.

CIMT was defined as the distance between the lumen intima to the adventitia media layer line of interference on the far wall in the longitudinal axis[18]. In order to decrease intra- and inter-observer variability for CIMT measurements, all readings were made by the same radiologist in our department after a period of practice to master the technique.

As for blood flow parameters, PI, and RI, a Doppler study of the ICA was performed, and measurements were made to PI and RI.

The patient required no special preparation, and the examination was held while the patient lay in a supine position with their head turned to the other side and did not last more than ten minutes. As mentioned above, patients were provided with scheduled visits for further re-scan 3 mo and 6 mo later.

Measurement of area under curve for Doppler wave

To explain how we calculated the AUC, we will give an example. A sample of ICA Doppler is shown in Figure 2. In this picture, we measured the different heights of the Doppler wave (demarcated by dots in Figure 2A) as it went up and down with a facility supplied by the ultrasound device. Depending on the width of the wave, these measurements averaged between 8 and 10 for each wave; see the horizontal orange line in Figure 2A). The measurement of the heights represents the speed of blood in the systolic and diastolic velocities. The calculated heights were put in an Excel table to analyze later with simple, free software called GRAPH, which can be downloaded from: https://www.padowan.dk/download/ [19].

In Figure 2B, a graphical simulation of the internal Carotid Artery Doppler wave in Graph software is shown, with the different heights (demarcated in red dots) used to measure the systolic and diastolic blood flow for the calculation of AUC.

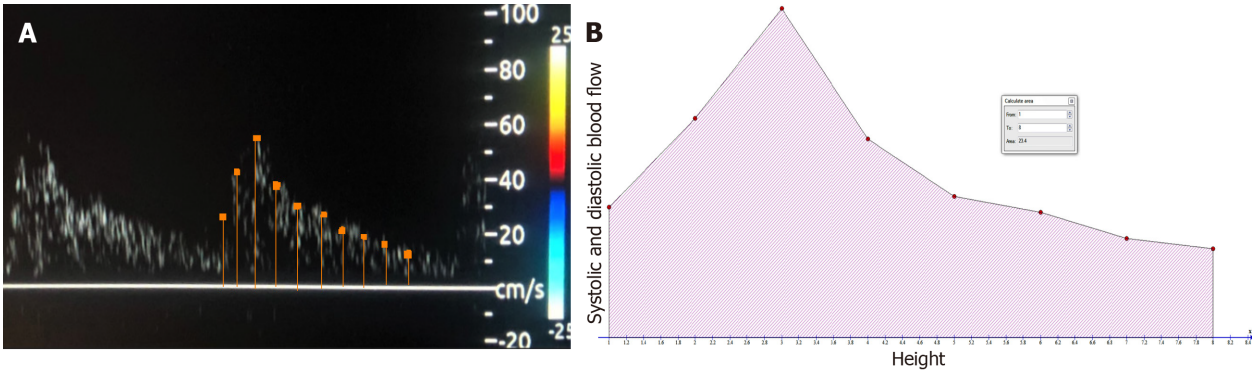

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Figure 2 A sample of internal carotid artery Doppler. A: It shows a real-time internal carotid artery Doppler; we have simulated the way of measuring the area under the curve by Paint app to the last wave. Note how different heights of the systolic and diastolic blood flow (demarcated with orange dots), which are used to measure the area under the curve (demarcated as orange longitudinal lines); B: It shows the graphical simulation of the internal carotid artery Doppler wave with the different heights (demarcated in red dots) used to measure the systolic and diastolic blood flow for the calculation of the area under the curve.

The AUC-ICA was calculated according to the following formula: AUC = ∫ Blood velocity measured at systolic and diastolic velocity for a single Doppler wave[11].

AUC physically means the amount of blood passed per unit area of the internal carotid artery per single heartbeat. It was measured in unit 3. Following the initial measurement of AUC-ICA, a re-assessment was made 3 mo and 6 mo later. All data with associated biochemical and biophysical data were stored in an excel sheet for further data analysis at the end of the study (Figure 2).

Sample size calculation

The sample size was calculated according to the following equation for a cross-sectional study with quantitative variables[20]:

Sample size = (Z1-α/2) 2 SD2/d2.

Z1-α/2 = is standard normal variate = 1.96.

SD = standard deviation of the variable taken from already published studies.

d = absolute error or precision level as an operator decides.

Sample size = (1.96)2 (0.35)2 / (0.1)2 = (3.84 × 0.1225)/ 0.01 = 43 patients.

So the sample size is 43 patients, and our study involved 54 patients.

Statistical analysis

Continuous data were expressed as mean and standard deviation. Data normality was checked with the Shapiro-Wilk test, and the data were normally distributed. One-way ANOVA test was used to assess the statistical data differences at the initial visit, at 3 mo, and 6 mo later for all the above biochemical, hormonal, and biophysical study variables. Linear regression was used to evaluate the decline of the AUC-ICA within 6 mo of metformin treatment with the calculation of the correlation coefficient and associated *P* value. In addition, further linear regression was constructed between AUC as the main dependent variable *vs* all significant biochemical, hormonal and biophysical variables taken in this study with the calculation of the correlation coefficient and associated value to assess the effect of metformin treatment on those correlations for the 6 mo treatment. AUC-ICA was assessed with a freely downloadable software GRAPH and further checked with MedCalc and NCSS software. *P* values less than 0.05 were considered significant.

RESULTS

Fifty-four young, unmarried, PCOS women were collected with full hormonal, biochemical, and biophysical profiles at the initial visit, 3 mo, and 6 mo after starting the metformin tablet 500 mg/TID day. Regarding the anthropometric criteria, the mean age of the participants was 24.81 ± 3.49 years. The days of the MC showed a significant decrease ($P < 0.034$) from 57.6 ± 5.8 in the initial visit to 43 ± 5.6 and 31.97 ± 4.9 d in the second and 3rd visits, respectively. Likewise, BMI showed a significant reduction ($P < 0.04$) from 28.22 ± 0.75 in the initial visit to 25.88 ± 0.64 and 23.81 ± 0.74 kg/m^2, respectively.

The main demographic criteria of these women are given at the three sampling and scanning times expressed as mean and standard deviation and were described in Table 1, while the three columns were compared with a one-way ANOVA test. The results highlight a progressive increase in serum HDL and SHBG throughout the treatment period over 6 mo. FBG showed a trend decrease; however, it fails to have a statistical value. On the other hand, a significant reduction was found in serum cholesterol, LDL,

Table 1 The primary biochemical, hormonal, and ultrasonic criteria at the initial visit, 3 mo and 6 mo later, with their statistical comparison

Parameter	First visit value, *n* = 54	2nd visit at 3 mo, *n* = 54	3rd visit at 6 mo, *n* = 54	*P* value
Cholesterol in mg/dL	384.19 ± 13.64	337.25 ± 18.40	276.82 ± 12.69	< 0.030
HDL in mg/dL	35.70 ± 3.78	48.70 ± 4.31	62.52 ± 4.09	< 0.001
LDL in mg/dL	203.22 ± 8.74	167.41 ± 12.26	132.33 ± 12.62	< 0.040
Fasting blood sugar in mg/dL	92.22 ± 1.80	90.93 ± 2.42	92.07 ± 2.43	0.071
HOMA-IR	2.26 ± 0.07	2.02 ± 0.10	1.74 ± 0.07	< 0.001
SHBG in nmol/L	29.52 ± 7.11	58.29 ± 8.25	81.74 ± 7.49	< 0.001
Testosterone in ng/dL	108.30 ± 8.29	79.74 ± 9.45	51.56 ± 7.96	< 0.010
LH / FSH_Ratio	2.62 ± 0.12	2.23 ± 0.15	1.76 ± 0.13	< 0.001
PI	1.41 ± 0.08	1.13 ± 0.07	0.89 ± 0.07	< 0.034
RI	0.89 ± 0.04	0.77 ± 0.05	0.62 ± 0.04	< 0.040
CIMT in mm	0.92 ± 0.03	0.79 ± 0.03	0.66 ± 0.03	< 0.001
AUC- ICA Doppler	56.44 ± 4.49	42.11 ± 4.06	31.29 ± 3.93	< 0.001

Data are presented as means ± standard deviation. BMI: Body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SHBG: Sex hormone-binding globulin; FSH: Follicular stimulating hormone; LH: Luteinizing hormone; HOMA-IR: Homeostasis model assessment for insulin resistance; PI: Pulsatility index; RI: Resistance index; CIMT: Carotid artery intima-media thickness; AUC: Area under the curve; ICA: Internal carotid artery.

HOMA- IR, testosterone, LH/FSH ratio, PI, RI, and CIMT. As for AUC-ICA, it showed a progressive decrease with the treatment period.

In order to shed more light on the trend of AUC-ICA correlation with various study parameters, a linear regression was constructed in Table 2.

All biochemical markers; cholesterol, HDL, LDL, SHBG, and HOMA_IR; the hormonal markers of testosterone, and LH/FSH_Ratio; and ultrasonic parameters, RI, and CIMT used in PCOS women evaluation were correlated strongly to AUC-ICA, $P < 0.05$.

A highly significant negative correlation exists between AUC-ICA Doppler *vs* HOMA-IR. An inverse correlation was confirmed between the 6 mo time (24 wk) of metformin therapy *vs* AUC-ICA with r = -0.99 and *P* value less than 0.001, which was shown in Figure 3 and highlighted by a real-time Doppler scan in Figure 4, where the wave peak decreased after treatment from 80 to 60 and accordingly; the AUC-ICA was reduced.

To assess the strength of association between HOMA-IR as the primary dependent variable *vs* the predictive biophysical profiles related to the ICA, namely PI, RI, CIMT, and AUC-ICA Doppler; the best subset regression model was constructed with a calculation of Mallow's coefficient described in Table 3. The lowest values are shown on the AUC-ICA Doppler, which means it has the highest predictive value for HOMA-IR. While RI has the highest Mallow's coefficient value, which means it has the lowest predictive value. Both CIMT and PI lie in between the two.

DISCUSSION

Our results showed that metformin therapy for 6 mo caused a progressive improvement in BMI, menstrual cycle days, metabolic markers, hormonal parameters, and Doppler parameters (PI, RI, and CIMT). AUC-ICA exhibits a meaningful correlation to all PCOS parameters. Furthermore, it showed a progressive reduction throughout the treatment period. AUC-ICA correlated inversely with treatment time ($r = -0.98$, $P < 0.001$)and positively with HOMA-IR ($r = 0.98$, $P < 0.0001$). With the best subset regression model, the AUC-ICA had the highest predictive value for HOMA-IR.

Women with PCOS present with multiple anthropometric, metabolic, and hormonal abnormalities which are successfully reversed by metformin therapy; our results were in accordance with published studies[21].

The reduced BMI in our result was in line with a recently published meta-analysis study. Their result discussed that metformin as a monotherapy or in combination with other drugs can improve all anthropometric parameters (weight, waist-to-hip ratio, and BMI) among PCOS women. This was made irrespective of the dose and the duration of metformin use[22].

Table 2 Correlations of area under the curve - internal carotid artery Doppler *vs* study variables over 6 mo with metformin therapy for women recruited to this study

AUC- ICA *vs* parameter	Coefficient of correlation	*P* value
Cholesterol in mg/dL	0.81	0.03
HDL in mg/dL	-0.92	0.002
LDL in mg/dL	0.88	0.04
HOMA_IR	0.98	0.0001
SHBG in nmole/L	-0.90	0.01
Testosterone in ng/dL	0.86	0.001
LH/ FSH_ratio	0.91	0.007
PI	0.87	0.002
RI	0.8	0.009
CIMT in mm	0.95	0.0001
24 wk of metformin therapy	-0.99	0.001

Data are presented as means ± standard deviation. HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SHBG: Low hormone binding globulin; FSH: Follicular stimulating hormone; LH: Luteinizing hormone; HOMA-IR: Homeostasis model assessment for insulin resistance; PI: Homeostasis index; RI: Resistance index; CIMT: Carotid artery intima-media thickness.

Table 3 Best subset regression between homeostasis model assessment for insulin resistance as the main dependent variable *vs* carotid artery intima-media thickness, pulsatility indices, resistance indices and area under the curve of the carotid artery Doppler with calculation of associated Mallow's coefficient

Variable	(Cp) Mallow's coefficient
AUC-ICA	49.6
CIMT	155.5
PI	326.8
R1	637.0

AUC-ICA: Area under the curve for the internal carotid artery; CIMT: Carotid artery intima-media thickness; PI: Pulsatility indices; RI: Resistance indices.

The Abdalla meta-analysis declared a meaningful reduction of serum testosterone with metformin, $P < 0.0001$ with moderate grade evidence and our result was in good agreement with their results[23].

The role of IR in hyperandrogenemia is not well understood. Some authors suggest that hyperinsulinemia plays a dual role in triggering hyperandrogenemia, first *via* direct stimulation of ovarian androgens due to the insulin receptors on the theca cells, and second *via* indirect stimulation of LH secretion and suppression of SHBG production by the liver with a net increase of free androgen levels [24].

Metformin's beneficial effects on PCOS include; antihyperglycemic and reduction of IR by increasing the peripheral uptake of glucose in addition to its indirect effect on insulin levels. Our data showed a progressive reduction of FBS and HOMA-IR with the treatment, as other studies pointed out[20]. It has an anti-androgenic effect *via* reducing CYP17 cytochrome activity involved in androgen production, not to mention increasing SHBG, which consequently reduces free androgens[20].

The favorable effect of metformin in cardiovascular disease (CVD) protection has several benefits. First, it protects endothelial integrity, which is a key player in the triggering and progression of CVD, consequently reducing future CVD risk. Second, metformin may inhibit hepatic de novo lipogenesis paths to lower plasma cholesterol levels and improves the atherogenic milieu, although the exact mechanism is still unknown. Third, metformin has anti-inflammatory and anti-oxidative effects; both are accredited as an etiological factor in PCOS pathogenesis. Indirect action of metformin; *via* reducing IR and androgen, both were proposed to act independently and synergistically in the progression of atherogenic dyslipidemia and CVD risk among PCOS women[22-25].

Regarding the menstrual cycle, Yilmaz *et al*[26] studied menstrual irregularities and hirsutism in women treated with two insulin-sensitizing medications, Rosiglitazone and metformin. Their data showed an improvement in cycle regularity and hirsutism score; however, they advised Rosiglitazone

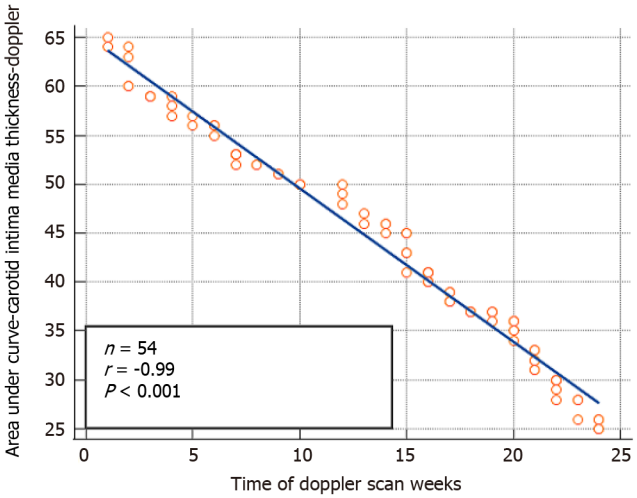

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Figure 3 Highlights an inverse correlation of area under the curve of the internal carotid artery *vs* metformin treatment time (*r* = -0.99, *P* < 0.001).

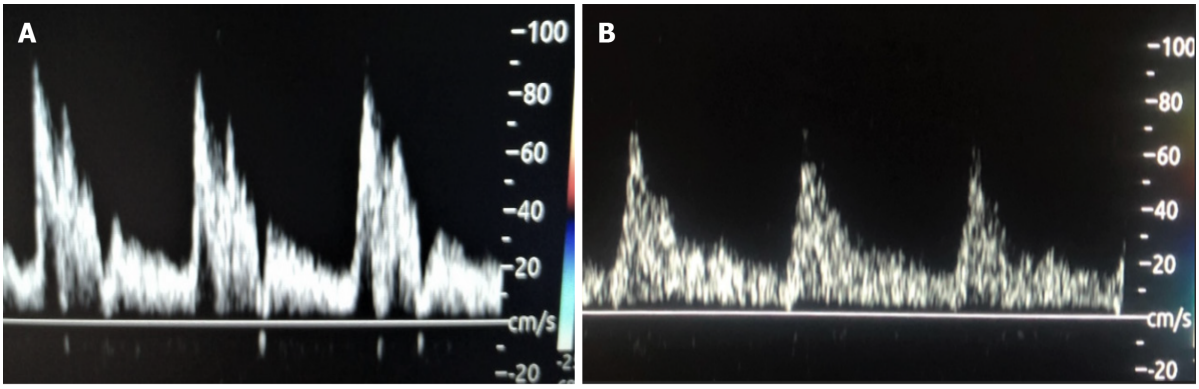

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Figure 4 A real-time Doppler scan. A: A real-time Doppler scan showing progressive reduction of the area under the curve of the internal carotid artery with treatment. Note the decrease in the peak of the wave in a subsequent visit 3 mo apart; from 80 to 60; B: A real-time Doppler scan showing the progressive reduction of the area under the curve of the internal carotid artery with treatment. Note the reduced wave peak to 60 following treatment compared to previous Figure 4A.

over metformin for greater patient acceptance and hirsutism improvement. In line with their result, our data showed significant improvement in MC days and regularity[26].

Androgen excess tends to associate with hyperinsulinemia and IR. This alliance seems to worsen menstrual cycle abnormalities. Several studies showed that many women with metformin therapy have ovulated and had a pregnancy. In contrast, patients with higher levels of serum testosterone were more likely to be infertile[27,28].

There was a debate on which contributes more to improving MC by metformin therapy, reduced IR, reduced androgen, or reduced BMI caused by metformin. The Ezeh *et al*[29] study results highlighted that menstrual cycle abnormality correlated positively with IR severity and not with hyperandrogenemia with adjustment of IR confounders, including BMI. In fact, amenorrheic PCOS women had the worst IR. Our results showed an improved IR and menstrual cycle pattern with metformin use, which suggests a clinical implication for daily practice; tracking down MC changes is easy and is free of charge, and it can reflect an improvement in the IR that underlies PCOS syndrome[29]. Prior studies demonstrated that MC abnormalities among adolescents would not impact future reproductive performance[30]. However, that was not the case for older women (> 30 years) who presented with oligomenorrheic and hirsute; they had lower reproductive performance than their age-matched controls [31].

IR lies at the heart of PCOS pathogenesis and severity and is a prognostic marker for response to treatment[32]. IR is universally assessed by HOMA-IR, calculated from the fasting serum insulin levels and blood sugar. Nevertheless, the assessment of HOMA-IR is costly and time-consuming, and this has pushed many researchers to find alternatives to assess IR[33,34].

Since 2010 many papers have reported that women with PCOS have universally increased intima-media thickness IMT in all medium-sized arteries like the carotid and ovarian artery[35]. Since then, many researchers have declared an excellent correlation between CIMT and HOMA-IR, and the current study results are in good agreement with the aforementioned studies[36].

Blood flow parameters were used to monitor HOMA-IR among PCOS cases during metformin use. In this study, both PI and RI had a progressive reduction, consistent with results obtained by Kaya *et al* [37]. Their study highlighted the beneficial role of adding metformin to combined contraceptive pills among PCOS women compared to those treated with combined contraceptive pills alone. CIMT and flow-mediated dilatation (FMD) was improved with the metformin group. The author attributes this to the effect of metformin on endothelial integrity, which is responsible for nitric oxide release, reducing oxidative stress, and the correction of altered cellular signaling pathways[27,37,38].

The foundation of this study is a simple physical fact. Bernoulli's rule states that fluid velocity has an inverse correlation to the diameter of a vessel[8]. The increased ICA-IMT will cause the passing of blood to be faster. Since the area under the curve physically means the amount of blood passed per one sectional area in the vessel wall, consequently, AUC might represent a sensitive marker to HOMA-IR [11].

Scientists have discussed that measuring insulin sensitivity through surrogate markers of insulin sensitivity (HOMA-IR and QUICKI) is no longer enough and raised the necessity for more acute ways [37-40]. Although IMT and FMD were investigated in PCOS, we believe that estimating the change of blood speed mirrored by AUC is more accurate, as described in earlier work[38,39].

Indeed, the strong correlations of AUC-ICA with all biochemical, hormonal, and Doppler parameters (PI, RI, and CIMT) support our hypothesis; furthermore, the progressive reduction of AUC-ICA represents the initial positive predictive ability of AUC-ICA as a possible novel marker for predicting IR. The best subset regression added more strength to our result, which confirmed; that AUC-ICA had the highest predictive value; it preceded PI, RI, and CIMT. The parameters mentioned above are already validated in IR, and thus AUC-ICA use needs no external validation.

Study limitations

The treatment period is relatively short, so we cannot be sure of the future implications of metformin treatment in the long run. The study type is another limitation, as in any cross-sectional study, the exact cause-and-effect link cannot be determined because the IR and AUC-ICA were simultaneously measured[40]. Intra- and inter-observer variability for AUC-ICA measurements is another limitation. Finally, the COVID-19 pandemic has seriously affected the duration of the study due to the repeated lockdown conducted in Iraq at that time[40,41].

Study strengths

AUC is a novel marker proposed by the current study, calculated by serial readings of Doppler wave height using freely downloadable software from the web, namely GRAPH software. It was easily calculated, free of extra charge, as it can be integrated into pelvic scan sessions. Its strong association with HOMA-IR and the duration of the treatment added to its cost make it superior to HOMA-IR in terms of cost-benefit analysis. For that, AUC-ICA is recommended as a reliable predictive marker for IR, follow-up, and prognostic value, especially during metformin therapy. Further studies are warranted for AUC-ICA application in clinical practice.

CONCLUSION

Measurement of the area under the curve of ICA is a promising marker for assessing IR in polycystic ovarian syndrome cases during the metformin therapy period. AUC-ICA showed strong significant correlations to PCOS parameters and had a superior cost-benefit analysis over HOMA-IR. Further studies are recommended to explore future applications in practice.

ARTICLE HIGHLIGHTS

Research background

Insulin resistance (IR) is implicated in many aspects of polycystic ovarian syndrome (PCOS) pathogenesis. Metformin effectively decreased IR. Improved IR was evaluated *via* homeostatic model assessment for IR (HOMA-IR) and Doppler parameters; mainly carotid artery intima-media thickness (ICA-IMT). The area under the curve of the internal carotid artery (AUC-ICA) Doppler wave was examined as a helpful marker for determining IR among PCOS cases presented with menstrual irregularity and treated by metformin over 6 mo.

Research motivation

Much research has shown that surrogate measures of insulin sensitivity are no longer sufficient for evaluating insulin sensitivity, which has increased the need for new direct methods. Demonstrating changes in blood flow mirrored by AUC appeared to be more dependable; as indicated in earlier work, ICA-IMT was already examined in PCOS.

Research objectives

To ascertain if IR is related to the AUC-ICA Doppler in PCOS-affected women with menstrual irregularities. The second goal is to analyze the reliability of AUC-ICA as a helpful marker for monitoring IR in women who have received metformin treatment.

Research methods

The study enrolled 54 PCOS women in a cross-sectional study. *Anthropometric* data included patient age, body mass index (BMI), menstrual cycle days, *biochemical parameters:* serum cholesterol, low and high-density lipoprotein, sex hormone-binding globulin, fasting blood glucose, and HOMA-IR, *hormonal parameters:* testosterone, luteinizing hormone over follicle-stimulating hormone ratio, and *ultrasonic parameters*: (CIMT, PI, RI, and AUC-ICA). Measurements of the systolic and diastolic wave height were repeated in order to evaluate the AUC-ICA following metformin tab-500 mg; three times/d for 6 mo. Metformin caused a progressive reduction in BMI, menstrual cycle days, biochemical hormonal, and Doppler parameters (CIMT, PI, RI, and AUC-ICA). AUC-ICA correlated strongly to all PCOS parameters. AUC-ICA correlated inversely with treatment time (r = -0.98, P < 0.001) and positively with HOMA-IR (r = 0.98, P < 0.0001). *Via* the best subset regression model, the AUC-ICA had the highest predictive value for HOMA-IR.

Research results

BMI, menstrual cycle days, biochemical hormonal, and Doppler markers (CIMT, PI, RI, and AUC-ICA were all gradually reduced by metformin treatment). All PCOS indicators and AUC-ICA had significant correlations. AUC-ICA had a negative correlation (r = -0.98, P < 0.001) with treatment time and a positive correlation (r = 0.98, P0.0001) with HOMA-IR. The AUC-ICA demonstrated the best subset regression model's maximum predictive value for HOMA-IR.

Research conclusions

AUC-ICA was a reliable marker for the assessment of IR, especially during metformin medication. AUC-ICA preceded PI, RI, and CIMT and showed a high, meaningful correlation to other PCOS markers. For further use in practice, more research is suggested.

Research perspectives

The area under the curve of the internal carotid artery had a significant correlation with HOMA-IR and the length of metformin therapy, not to mention it has a superior cost-benefit analysis over HOMA-IR. AUC-ICA is a reliable indicator of IR, follow-up, and prognostic value, particularly while using metformin.

FOOTNOTES

Author contributions: Akram W and Nori W designed research and reviewed the data, wrote and revised the letter; Zghair MAG collected and analyzed the data; All authors have read and agreed on the final version of the manuscript.

Institutional review board statement: The ethical committee of Mustansiriyah University approved the study dated February/21/2019 (IRB No. 115).

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

Conflict-of-interest statement: All authors declare that they have no potential or real conflicts related to this paper.

Data sharing statement: All data are available on reasonable request from the corresponding author.

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

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ORIGINAL ARTICLE

Observational Study

Effect of continuous nursing combined with respiratory exercise nursing on pulmonary function of postoperative patients with lung cancer

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Abstract

BACKGROUND

Lung cancer is a malignant tumor with high morbidity and mortality among cancers. Surgery is currently one of the primary methods of treating lung cancer. Although it can slow down the progression of the disease by removing the lesion, this invasive surgery inevitably damages the integrity of the patient's chest. Moreover, the patient's pulmonary function may have a low compensatory capacity after surgery, causing various respiratory diseases such as atelectasis, respiratory function decline, and even serious cardiovascular disease. All of these have great negative impacts on the surgical effect and the prognosis of patients. With the continuous exploration and development of nursing, continuous nursing and respiratory exercise nursing have been gradually applied in the nursing of patients after lung cancer surgery, and have achieved good nursing results.

AIM

To investigate the effect of continuous nursing combined with respiratory exercise nursing on the pulmonary function of postoperative patients with lung cancer.

METHODS

A total of 80 patients with lung cancer who underwent surgery in our hospital from January 2021 to December 2021 were selected as the study subjects. All subjects were randomly divided into the control group (n = 40 cases) and the experimental group (n = 40 cases). Patients with lung cancer in the control group were given conventional nursing after surgery, while the experimental group was given continuous nursing combined with respiratory exercise nursing based on conventional nursing. The recovery of pulmonary function and respiratory

symptoms was observed before and after 3 mo of intervention in both groups. The pulmonary function parameters, blood gas analysis, MD Anderson Symptom Inventory-lung cancer module (MDASI-LC) scores, incidence of pulmonary complications, and Morisky compliance scores were compared between the two groups before and after 3 mo of intervention.

RESULTS

There was no significant difference in pulmonary function and blood gas analysis between the two groups before intervention ($P > 0.05$). 3 mo after the intervention, the pulmonary function parameters in the experimental group (SpO_2, VC, MVV, FEV1, FEV1% pred, and FEV1/FVC) were higher than those in the control group, and the differences were statistically significant ($P < 0.05$). There was no significant difference in blood gas analysis between the two groups before intervention ($P > 0.05$). PaO_2 in the experimental group was significantly higher than that in the control group, and $PaCO_2$ was significantly lower than that in the control group 3 mo after the intervention. The difference had statistical significance ($P < 0.05$). 3 mo after the intervention, the MDASI score of respiratory symptoms in the experimental group was significantly lower than that in the control group ($P < 0.05$), and the incidence of pulmonary complications was lower than that in the control group ($P < 0.05$). In addition, the treatment compliance and nursing satisfaction of patients in the experimental group were higher than those in the control group, and the differences were statistically significant ($P < 0.05$).

CONCLUSION

Continuous nursing combined with respiratory exercise nursing can significantly accelerate the recovery of respiratory function in postoperative lung cancer patients, reduce the incidence of postoperative complications of lung cancer as well as improve the treatment compliance of patients.

Key Words: Postoperative lung cancer; Continuous nursing; Respiratory exercise nursing; Pulmonary function

Core Tip: Lung cancer is a malignant tumor disease with high morbidity and mortality among cancers. Continuous nursing and respiratory exercise nursing is a new nursing model, which can improve the long-term prognosis of patients with lung cancer and improve their life quality. Unfortunately, continuous nursing and respiratory exercise nursing for postoperative lung cancer patients are not widely studied. We collected 80 patients with lung cancer and observed the recovery of pulmonary function and respiratory symptoms after 3 mo of continuous nursing and respiratory exercise nursing. The results found that continuous nursing combined with respiratory exercise nursing could significantly accelerate the recovery of respiratory function, reduce the occurrence of postoperative complications of lung cancer, and improve patients' treatment compliance after lung cancer surgery.

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INTRODUCTION

Lung cancer is a malignant tumor originating from the bronchial mucosa and glands of the lung and is divided into small-cell lung cancer and non-small-cell lung cancer according to histological type[1]. At present, surgery, radiotherapy, and chemotherapy are the main methods for lung cancer treatment[2]. Surgical resection is the main method for the radical treatment of lung cancer. Meanwhile, perfect perioperative nursing is also particularly important[3]. Due to the damage to lung anatomy and physiology after lung cancer surgery, patients experience impaired gas exchange and hypoxemia, and some patients also experience complications such as respiratory failure[4,5]. Studies have shown that respiratory function exercise can improve postoperative pulmonary function and reduce the incidence of pulmonary complications in patients with lung cancer[6]. Therefore, early and adequate respiratory function exercise after lung cancer surgery is important for the recovery of pulmonary function and

improvement of hypoxemia.

Conventional nursing covers only nursing during hospitalization as well as health education for patients before discharge, and there is no patient nursing guidance and systematic follow-up after discharge. However, according to previous clinical experience, the completion rate of respiratory function exercise after discharge is generally low in patients after lung cancer surgery[7,8]. Therefore, it is necessary to improve patients' self-nursing ability at home. Continuous nursing is a new type of nursing model, which covers nursing services from hospital to family or society based on holistic nursing theory and humanistic nursing theory. It ensures the nursing quality of patients after discharge and improves the long-term prognosis of patients as well as their life quality[9-11]. By searching the literature, we found that studies have shown that the combination of continuous nursing and respiratory training has a better improvement effect on the life quality, mental health, and self-efficacy of lung cancer patients undergoing chemotherapy[12]. Based on this, we speculated that the application of continuous nursing combined with respiratory exercise nursing in postoperative lung cancer patients can also improve the respiratory function of patients and promote their rehabilitation to a certain extent. In this study, 80 patients with lung cancer undergoing surgery in our hospital were given continuous nursing combined with respiratory exercise nursing to observe the effect of this nursing model on the recovery of pulmonary function in patients after lung cancer surgery.

MATERIALS AND METHODS

General data

A total of 80 patients (49 males and 31 females) with lung cancer who underwent surgery in our hospital from January 2021 to December 2021 were selected as the study subjects. All patients and their families agreed to participate in the study and signed written informed consent. This study was approved by the Ethics Committee of Haikou People's Hospital. Inclusion criteria: (1) Patients diagnosed with primary lung cancer by bronchoscopy and pathological biopsy; (2) Patients with surgical indications, no mediastinal lymph node metastasis within stage II lung cancer[13] and expected survival of more than 6 mo; and (3) Patients with normal cognitive function and no mental illness. Exclusion criteria: (1) Patients receiving targeted therapy, chemotherapy, immunotherapy, and other treatments; (2) Patients with emotional instability, unable to cooperate with the treatment; (3) Patients with a history of thoracic or pulmonary surgery; (4) Patients with a lung infection, active tuberculosis, and severe COPD and other primary lung diseases; (5) Patients with other systemic diseases and dysfunction; and (6) Patients with incomplete clinical data. All patients were randomly divided into a control group (n = 40 cases) and an experimental group (n = 40 cases) according to different nursing models. There was no significant difference in general data such as gender, average age, body mass index, and medical history between the two groups (P > 0.05). The results are shown in Table 1.

Nursing intervention methods

Control group: Patients were treated with conventional nursing and health education after lung cancer surgery. Conventional health education, perioperative nursing, dietary guidance after discharge, medication guidance, and daily nursing guidance were given to the patients.

Experimental group: Continuous nursing combined with respiratory exercise nursing was adopted based on conventional nursing: (1) A continuous nursing team was established for patients after lung cancer surgery and systematic training was provided for all nurses; (2) Information files were established for discharged patients, including the patient's age, course of the disease, surgical methods, and other hospitalization information, as well as the patient's home address and contact information. Medical and nursing support was provided, and a personalized continuous nursing program was developed for discharged patients, including daily diet, medication, exercise, and disease review; (3) Implementation of continuous nursing. We implemented continuous nursing through weekly telephone follow-up and online instant communication. We guided patients to perform respiratory function exercises, encouraged patients to participate in social activities, and build their confidence in overcoming the disease; (4) Postural nursing: patients undergoing lobectomy were placed in the supine, left, or right lateral decubitus positions; patients undergoing segmentectomy or wedge resection were placed in the healthy lateral decubitus position as far as possible to promote dilatation of the lung tissue on the affected side, and those with bloody sputum or bronchial fistula should be placed in the affected lateral decubitus position; (5) Respiratory function exercise: (a) Pursed-lip breathing: Asked the patients to inhale with their noses, close their lips tightly, hold for 5 s after maximum deep inspiration, and then breathe slowly with their mouths like a whistle. Inspiratory time: Exhalation time is approximately 1:2; and (b) Abdominal breathing: Asked the patient to relax, place both hands on the abdomen, slowly distend the abdomen during inspiration, then spit out the gas with pursed-lip breathing, and depress the abdomen during expiration. Balloons can be used for blowing for 15 min 3-4 times a day; (6) Effective cough and expectoration exercise: Instructed patients to inhale deeply during cough and expectoration, hold their breath at the end of deep inspiration, and then expectorate deeply, which can

Table 1 Comparison of general data between the two groups

Clinical information	Test group, *n* = 40	Control group, *n* = 40	*t*/χ^2	*P* value
Average age (yr), mean ± SD	62.76 ± 10.43	62.18 ± 10.39	0.249	0.803
Gender, *n* (%)				
Male	24 (60)	25 (62.5)	0.053	0.818
Female	16 (40)	15 (38.5)		
Average disease duration (mo), mean ± SD	6.47 ± 1.32	63.6 ± 6.5	0.636	0.527
BMI (kg/m^2), mean ± SD	23.52 ± 3.68	23.47 ± 3.97	0.058	0.9536

BMI: Body mass index.

effectively promote sputum drainage; and (7) Nursing team and patient communication group were established for patients and their families to post daily breathing exercises and self-nursing logs. And the nursing plan was timely adjusted with the patient's self-nursing log. Also, timely guidance was given according to the changes in the patient's condition, and patients were well-reminded to come to the hospital for reexamination on time. Patients were guided to return to the hospital if any abnormal conditions occurred.

Observation index

Pulmonary function tests: Pulmonary function parameters were measured by professional physicians using (Master Screen Diffusion, JAEGER, Germany) advanced diffusion spirometry before and after 3 mo of intervention in both groups. Pulmonary function parameters included fingertip pulse oxygen saturation (SpO_2), vital capacity (VC), maximum ventilation (MVV), forced expiratory volume in the first second (FEV1), FEV1 percentage of predicted value (also known as FEV1% pred), and FEV percentage of vital capacity (FEV1/FVC). The data of 3 mo post-intervention were measured at patients' follow-up.

Blood gas analysis: The nursing staff drew blood from the patient's femoral artery, and the arterial blood gas analysis of the patients before and after 3 mo of intervention was detected by the laboratory personnel using an ABL90 blood gas analyzer (RADIOMETER, Denmark). Blood gas analysis parameters included PaO_2 and $PaCO_2$.

Respiratory symptoms: Nursing staff assessed the symptoms of the patients before and after 3 mo of intervention using the revised MD Anderson Symptom Inventory-lung cancer module (MDASI-LC) scale[14]. Items included cough, expectoration, hemoptysis, chest distress, and weight loss. Each item was scored on a scale of 0-10, where a score of 0 indicates the disappearance of symptoms, 1-3 indicates mild symptoms, 4-6 indicates moderate symptoms, 7-9 indicates severe symptoms, and 10 indicates extreme symptoms and severely affects life.

Complications: The number of patients with atelectasis, pulmonary infection, incision infection, wound bleeding, and respiratory failure within 3 mo after the intervention was recorded and counted in the two groups, and the total incidence was calculated.

Compliance: Morisky Medication Compliance Scale (MMAS-8) was used to assess the medication compliance of patients before nursing and 3 mo after nursing intervention[15]. MMAS-8 scale was full of 8 points. A score of 8 points was considered as good compliance, a score of 6-8 points as moderate compliance, and a score of fewer than 6 points as poor compliance.

Nursing satisfaction: Nursing satisfaction was assessed using a nursing satisfaction questionnaire designed by our hospital. The satisfaction survey was distributed by the nursing staff during the follow-up of the patients 3 mo after surgery. A total of 80 copies were distributed and 80 copies were recovered, with a recovery rate of 100% and an effective rate of 100%. The total score of the satisfaction questionnaire scale > 90 points indicates the patients were very satisfied; 80-90 points indicate satisfied; 60-79 points indicate fairly satisfied; < 60 points indicate dissatisfied. Satisfaction = (very satisfied cases + satisfied cases)/total cases × 100%.

Statistical analysis

Data were statistically analyzed using SPSS 19.0 software (SPSS Inc., Chicago, IL, United States). Measurement data were demonstrated as mean ± SD, and a *t*-test was used for comparison between the two groups. Enumeration data were demonstrated as *n* (%) and analyzed using the χ^2 test. $P < 0.05$ was

considered statistically significant.

RESULTS

Comparison of pulmonary function indexes between the two groups of patients

The changes in the indicators related to pulmonary function in the two groups were observed before and after the intervention with the two nursing programs. The results showed that there was no significant difference in the pulmonary function indexes between the two groups before the intervention ($P > 0.05$). During the follow-up visit after 3 mo of intervention, SpO_2 (%), VC (L), MVV (L/min), FEV1 (L), FEV1% pred (%), and FEV1/FVC (%) in the two groups were increased, and the increase of the above indicators in the experimental group was significantly higher than that in the control group ($P < 0.05$). This indicated that, compared with the conventional nursing program, continuous nursing combined with a respiratory exercise nursing intervention program can effectively promote the recovery of pulmonary function in postoperative lung cancer patients, which is conducive to the prognosis of patients, as shown in Table 2.

Comparison of blood gas analysis between the two groups

The changes in the indicators related to blood gas in the two groups were observed before and after the intervention with the two nursing programs. The results showed that the differences in PaO_2 (mmHg) and $PaCO_2$ (mmHg) between the two groups before the intervention were not statistically significant ($P > 0.05$). The PaO_2 in the experimental group was significantly higher than that in the control group and the $PaCO_2$ was significantly lower than that in the control group 3 mo after the intervention ($P < 0.05$). This indicated that, compared with the control group that only adopted conventional nursing, the patients in the experimental group with continuous nursing combined with respiratory exercise nursing intervention had better improvement in blood gas-related indicators, as shown in Table 3.

Comparison of MDASI scores of respiratory system symptoms between two groups

The changes in MDASI scores of respiratory symptoms in the two groups before and after the intervention of the two nursing programs were observed. There was no statistically significant difference can be found between the MDASI scores of respiratory symptoms in the two groups before the intervention ($P > 0.05$). The MDASI scores of cough, expectoration, hemoptysis, chest distress, and weight loss in the experimental group were significantly lower than those in the control group 3 mo after the intervention ($P < 0.05$) This suggested that the improvement level in all respiratory symptoms at 3 mo of intervention was better in patients who adopted continuous nursing combined with respiratory exercise nursing intervention than in those who adopted the conventional nursing program, as shown in Table 4.

Comparison of the incidence of pulmonary complications in the two groups

The incidence rates of surgical incision infection, surgical incision bleeding, pulmonary atelectasis, pulmonary infection, and respiratory failure were compared between the two groups 3 mo after the intervention of the two nursing programs. The incidence of atelectasis and pulmonary infection was significantly lower in the experimental group than in the control group, and the overall complication rate was also lower in the experimental group than in the control group (7.50% *vs* 22.50%, $P < 0.05$). This indicated that continuous nursing combined with respiratory exercise nursing significantly reduced the incidence of postoperative pulmonary complications compared with conventional nursing, as shown in Table 5.

Comparison of treatment compliance between two groups of patients

The level of patient compliance in the two groups before and after the intervention of the two nursing programs was observed. It was found that the difference between the percentage of patients with good, moderate, and poor compliance in the two groups before the intervention was not statistically significant ($P > 0.05$). The percentage of patients with good compliance in the experimental group was higher than that in the control group after 3 mo of the intervention ($P < 0.05$). This indicated that continuous nursing combined with the respiratory exercise nursing program can effectively improve the patient's treatment compliance, as shown in Table 6.

Comparison of nursing satisfaction between the two groups

The nursing satisfaction level between the two groups of patients after 3 mo of intervention by the two nursing programs was compared. The results showed that the number of very satisfied patients in the experimental group was higher than that in the control group, and the overall satisfaction rate was higher than that in the control group (95.00% *vs* 82.50%, $P < 0.05$). This indicated that continuous nursing combined with a respiratory exercise nursing program could significantly improve the nursing satisfaction of postoperative lung cancer patients, as shown in Table 7.

Table 2 Comparison of pulmonary function indicators between the two groups (mean ± SD)

Indicators	Time	Test group, *n* = 40	Control group, *n* = 40	*t* value	*P* value
SpO_2 (%)	Before the intervention	95.68 ± 10.26	95.35 ± 10.17	0.144	0.885
	3 mo after the intervention	98.86 ± 4.26	96.04 ± 3.57	3.209	0.002
VC (L)	Before the intervention	2.96 ± 0.36	2.91 ± 0.33	0.648	0.519
	3 mo after the intervention	3.64 ± 0.63	3.18 ± 0.46	3.567	< 0.001
MVV (L/min)	Before the intervention	83.74 ± 4.18	83.92 ± 4.24	0.191	0.849
	3 mo after the intervention	89.46 ± 7.56	85.02 ± 6.38	2.839	0.006
FEV1 (L)	Before the intervention	1.53 ± 0.24	1.57 ± 0.25	1.095	0.276
	3 mo after the intervention	2.56 ± 0.76	2.09 ± 0.53	3.208	0.002
FEV1% pred (%)	Before the intervention	61.27 ± 8.03	60.94 ± 7.42	0.191	0.849
	3 mo after the intervention	69.48 ± 9.35	63.56 ± 7.94	3.052	0.003
FEV1/FVC (%)	Before the intervention	67.22 ± 8.37	67.16 ± 8.24	0.032	0.974
	3 mo after the intervention	76.82 ± 10.46	70.05 ± 9.68	3.004	0.003

SpO_2: Oxygen saturation; VC: Vital capacity; MVV: Maximum ventilation; FEV1: Forced expiratory volume in the first second; FEV1% pred: FEV1 percentage of predicted value; FEV1/FVC: FEV1 percentage of vital capacity.

Table 3 Comparison of blood gas between the two groups (mean ± SD)

Indicators	Time	Test group, *n* = 40	Control group, *n* = 40	*t* value	*P* value
PaO_2 (mmHg)	Before the intervention	90.67 ± 11.24	90.32 ± 11.15	0.139	0.889
	3 mo after the intervention	98.45 ± 9.46	93.28 ± 8.89	2.524	0.013
$PaCO_2$ (mmHg)	Before the intervention	50.39 ± 5.27	50.12 ± 5.06	0.233	0.815
	3 mo after the intervention	42.85 ± 3.84	46.08 ± 4.38	3.507	< 0.001

DISCUSSION

According to a secondary analysis of global cancer statistics for 2020, lung cancer is the leading cause of cancer-related deaths among men and women in our country, accounting for 40% of lung cancer-related deaths worldwide[16]. Surgical resection is the best treatment option for lung cancer patients with surgical pointers[17]. However, the incidence of postoperative complications in lung cancer has been reported to be approximately 14%-40%[18]. One of the reasons is that lung cancer surgery changes the anatomy and physiological structure of the patient's lungs, which affects the patient's pulmonary ventilation and air exchange function, leading to serious complications such as pulmonary atelectasis and respiratory failure. Effective respiratory function exercise has a positive significance in improving a patient's pulmonary function and preventing complications. Continuous nursing is a targeted nursing program that enables patients to receive professional and effective nursing at home after discharge from the hospital[19]. As a new nursing model, continuous nursing extends nursing into the patient's home through follow-up visits, disease review, and modern communication, providing patients with timely, professional, and targeted nursing that is identical to that provided in the hospital[20]. In addition, continuous nursing solves the problem of transitioning patients from hospital to home, improves patients' self-care ability, reduces postoperative complications, and achieves good social benefits[21,22]. Therefore, it is important to implement continuous nursing for patients to prevent postoperative complications and improve patient nursing satisfaction.

In this study, we found that continuous nursing plus whole-course respiratory function exercise significantly increased pulmonary function parameters, such as SpO_2, VC, MVV, FEV1, FEV1% pred, FEV1/FVC. It also increased the arterial partial pressure of oxygen, decreased the arterial partial pressure of carbon dioxide, and had a lower MDASI score and incidence of pulmonary complications compared with conventional nursing. Zhou *et al*[23] pointed out that physical pulmonary rehabilitation (PMPR) was performed in 44 post-thoracoscopic lobectomy lung cancer patients, after which 3 (6.8%) patients had pulmonary atelectasis and 2 (4.5%) patients had pneumonia. The overall incidence of postoperative complications in lung cancer patients undergoing perioperative PMPR was 11.3%, which was higher than the 5% in this study. This further confirmed that continuous nursing combined with

Table 4 Comparison of MD Anderson Symptom Inventory scores between the two groups (mean ± SD)

Programs	Time	MDASI score		*t* value	*P* value
		Test group, *n* = 40	Control, group *n* = 40		
Cough	Before the intervention	7.28 ± 0.72	7.31 ± 0.74	0.183	0.854
	3 mo after the intervention	5.62 ± 0.53	6.54 ± 0.62	7.134	< 0.001
Expectoration	Before the intervention	7.43 ± 0.78	7.52 ± 0.79	0.512	0.609
	3 mo after the intervention	5.08 ± 0.52	6.29 ± 0.64	9.280	< 0.001
Hemoptysis	Before the intervention	4.63 ± 0.51	4.48 ± 0.49	1.341	0.183
	3 mo after the intervention	3.26 ± 0.36	4.17 ± 0.48	9.592	< 0.001
Chest distress	Before the intervention	5.89 ± 0.63	5.91 ± 0.66	0.138	0.890
	3 mo after the intervention	3.84 ± 0.39	4.52 ± 0.48	6.954	< 0.001
Weight loss	Before the intervention	4.62 ± 0.57	4.39 ± 0.54	1.853	0.067
	3 mo after the intervention	3.08 ± 0.31	3.78 ± 0.39	8.886	< 0.001
Total	Before the intervention	29.85 ± 3.21	29.61 ± 3.22	0.333	0.739
	3 mo after the intervention	20.88 ± 2.11	25.30 ± 2.61	8.329	< 0.001

MDASI: MD Anderson Symptom Inventory.

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

Group	Surgical incision infection	Surgical incision bleeding	Atelectasis	Pulmonary infection	Respiratory failure	Overall incidence rate
Test group, *n* = 40	0 (0.00)	0 (0.00)	1 (2.50)	1 (2.50)	0 (0.00)	2 (5.00)
Control group, *n* = 40	0 (0.00)	0 (0.00)	3 (7.50)	6 (12.50)	0 (0.00)	9 (22.50)
χ^2						5.165
P value						0.023

Table 6 Comparison of treatment compliance between the two groups, *n* (%)

Group	Before the intervention			3 mo after the intervention		
	Good	Moderate	Poor	Good	Moderate	Poor
Test group, *n* = 40	6 (15.00)	28 (70.00)	6 (15.00)	24 (60.00)	11 (27.50)	5 (12.00)
Control group, *n* = 40	9 (22.50)	26 (65.00)	5 (12.00)	13 (32.50)	22 (55.00)	5 (12.00)
χ^2		0.765			6.937	
P value		0.682			0.031	

respiratory exercise nursing intervention was positive and effective in reducing postoperative complications and promoting postoperative recovery in patients with lung cancer. With the development of rehabilitation medicine, respiratory function exercise is considered to be an effective way to promote pulmonary rehabilitation. Active breathing exercise enhances the strength and endurance of respiratory muscles, improves the patient's pulmonary function and respiratory system function, and reduces the incidence of pulmonary complications while enhancing the patient's overall postoperative recovery[24]. In addition, effective breathing exercises increase pulmonary blood circulation, promote alveolar gas exchange, and improve pulmonary ventilation and hypoventilation[25]. Ko *et al*[26] found that 4-8 wk of exercise and bi-weekly continuous telephone communication guided by physiotherapists in patients with chronic obstructive pulmonary disease (COPD) reduced the frequency of acute exacerbations, promoted pulmonary rehabilitation as well as prolonged the time of readmission for acute COPD, which had a better control effect on the remission of COPD patients. Respiratory function exercise is a

Table 7 Comparison of nursing satisfaction between the two groups, *n* (%)

Group	Very satisfied	Satisfied	Fairly satisfied	Dissatisfied	Satisfaction rate
Test group, n = 40	26 (65.00)	12 (30.00)	2 (5.00)	0 (0.00)	38 (95.00)
Control group, n = 40	12 (30.00)	21 (52.50)	5 (12.00)	2 (5.00)	33 (82.50)
χ^2					7.825
P value					0.005

long-term process. However, after discharge from the hospital, most patients discontinue rehabilitation exercises and respiratory exercises due to various reasons such as fear of wound pain, depression, physical fatigue, and lack of professional respiratory exercise instruction. In this study, a complete nursing intervention group was established before the start of the intervention in continuous nursing combined with a respiratory exercise nursing program adopted by the patients in the experimental group. And all team members underwent standardized training to ensure the homogenization of the intervention. Continuous nursing was performed through postoperative visits, questionnaires, and online communication after patients were discharged from the hospital, maintaining the continuity, completeness, and integrity of nursing. The effect of respiratory exercise was evaluated, and the rehabilitation exercise was adjusted timely according to the changes of the patient's condition. What's more, effective cough and expectoration methods were instructed to patients to promote pulmonary sputum drainage and reduce the occurrence of pulmonary infection. Regular health education was given to patients to improve their perception of the importance of breathing exercises. Therefore, continuous breathing combined with respiratory exercise greatly improves pulmonary function, improves hypoxemia, and reduces the incidence of pulmonary symptoms and complications.

In addition, Morisky compliance and nursing satisfaction were better in the intervention group compared to the control group. Mei *et al*[27] performed whole-course high-quality nursing for 30 lung cancer patients who underwent surgery in the Department of Respiratory Medicine and found that this program could also effectively reduce the negative conditions of patients, lower the level of anxiety and depression, and improve patient compliance and satisfaction. This is somewhat similar to the conclusions of our study. Compared with the current continuous nursing combined with respiratory exercise, although both of them achieved positive nursing results, the whole-course nursing program focused on the physiological and psychological nursing of the patients, mostly on the nursing staff's initiative to provide psychological consultation and nursing services. While continuous nursing combined with respiratory exercise nursing in this study focused more on allowing patients and their families to actively participate in the nursing work with the help of nursing staff. It fundamentally promoted the recovery of pulmonary function in patients through scientific and efficient respiratory exercise, and also enhanced postoperative rehabilitation while taking into account the improvement of patients' participation, compliance, and satisfaction, which is more conducive to nurse-patient communication and nursing work. Poor patient compliance outside the hospital was associated with a lack of medical and nursing supervision as well as social support[28]. In the continuous nursing group, the patients were given the whole course of medication, diet, exercise guidance, and one-on-one health education during the home nursing after discharge, which enhanced the enthusiasm of patients for treatment and a good attitude toward life. A reasonable diet improves the nutritional status of patients and shortens the postoperative recovery time. It also strengthens communication between nurses and patients. Therefore, patients in the intervention group had higher treatment compliance and nursing satisfaction. In this study, the application of continuous nursing combined with respiratory function exercise in postoperative lung cancer patients achieved surprising results. This nursing model requires nursing team members to have excellent professional knowledge, the ability to deal with sudden complications as well as the ability to communicate friendly to patients after completing standardized training and assessment. In addition, the nursing members were also required to closely monitor various postoperative vital signs and rehabilitation indicators of patients, guide patients to perform respiratory function exercises as well as provide effective support and guarantee for maintaining a good health status of patients. However, there are still some limitations in this study. For example, the sample size is small and the postoperative observation time is short. It is uncertain whether results consistent with this study can be obtained after expanding the sample size and extending the postoperative observation time. In the subsequent study, we will further investigate and validate a larger sample size with a more rigorous study protocol.

CONCLUSION

In summary, continuous nursing combined with respiratory function exercise can effectively improve postoperative pulmonary function and PaO_2, reduce $PaCO_2$, and promote pulmonary function recovery

in patients. At the same time, it also reduces the occurrence of postoperative complications and improves patients' treatment compliance and nursing satisfaction. It is of great significance to the postoperative recovery of lung cancer.

ARTICLE HIGHLIGHTS

Research background

Lung cancer is the leading cause of cancer death. Therefore, it is particularly important to seek suitable nursing methods for the rehabilitation of lung cancer patients.

Research motivation

Resection surgery is the main treatment for lung cancer. Postoperative complications and mortality are mostly linked to respiratory failure consecutive to respiratory muscle overload. Respiratory movement plays an important role in lung cancer care, as well as the pulmonary rehabilitation.

Research objectives

This study aims to explore the effect of continuous nursing combined with respiratory exercise nursing on the recovery of lung function in patients with lung cancer after operation.

Research methods

Eighty patients with lung cancer were randomly divided into control group (n = 40 cases) and experimental group (n = 40 cases). The patients in the control group received routine nursing after operation, while the experimental group received continuous nursing combined with respiratory exercise nursing on the basis of routine nursing. Observe the recovery of pulmonary function and respiratory system symptoms of the two groups before and after the intervention for 3 mo.

Research results

After intervention, the nursing satisfaction of the study group was higher than that of the control group; PaO_2 in the study group was significantly higher than that in the control group; The MD Anderson Symptom Inventory score of respiratory symptoms in the study group was significantly lower than that in the control group; The treatment compliance and nursing satisfaction of patients in the study group were higher than those in the control group. The difference between the above studies was statistically significant ($P < 0.05$).

Research conclusions

Continuous nursing combined with respiratory exercise nursing can significantly accelerate the recovery of respiratory function of patients with lung cancer after surgery, reduce the incidence of postoperative complications of lung cancer, and improve the treatment compliance of patients.

Research perspectives

This study proves that continuous nursing combined with respiratory function exercise is of great significance for postoperative rehabilitation of lung cancer patients, which may provide a theoretical basis for postoperative treatment of lung cancer patients.

FOOTNOTES

Author contributions: Qiu QX and Feng XH were responsible for the concept and writing of the manuscript; Qiu QX and Li WJ analyzed the data; Li WJ and Ma XM were responsible for revising the paper; all authors have read and approved the final version of the manuscript.

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CASE REPORT

Functioning gonadotroph adenoma with hyperestrogenemia and ovarian hyperstimulation in a reproductive-aged woman: A case report and review of literature

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Abstract

BACKGROUND

Functioning gonadotroph adenomas are extremely rare pituitary tumors that secrete gonadotropins and exhibit distinct clinical manifestations. Here, we report a case of functioning gonadotroph adenoma in a reproductive-aged woman and discuss its diagnosis and management.

CASE SUMMARY

A 21-year-old female patient with abdominal pain, irregular menstruation, hyperestrogenemia, and an ovarian mass was included. Brain magnetic resonance imaging (MRI) revealed a pituitary macroadenoma, and transsphenoidal surgery relieved her clinical symptoms. Before transsphenoidal surgery, plasma CA125, estradiol levels were elevated, while prolactin, luteinizing hormone, follicle-stimulating hormone, PROG, cortisol, FT4, thyroid-stimulating hormone, parathyroid hormone, and GH levels were maintained at normal levels. After transsphenoidal surgery, the patient was diagnosed with a functioning gonadotroph adenoma. During follow-up, pelvic ultrasound confirmed normal-sized ovaries in the patient, the menstrual cycle returned to regular, and her hormones were maintained within a normal range. There was no evidence of tumor recurrence after two years of follow-up.

CONCLUSION

Early diagnosis of functioning gonadotroph adenomas should be considered in

patients with hyperestrogenism, irregular menstruation, large or recurrent ovarian cysts, and visual field defects. Pituitary MRI should be performed, and transsphenoidal surgery is recommended for the management of this disease.

Key Words: Functional gonadotroph adenoma; Ovarian hyperstimulation; Hyperestrogenemia; Transsphenoidal surgery; Case report

Core Tip: Functional gonadotroph adenomas (FGAs) are rare pituitary gland tumors. Here, we describe a case of FGAs in a woman of reproductive age with abdominal pain, irregular menstruation, hyperestrogenemia, and ovarian mass. We would like to share our experience of diagnosis and treatment, which will help clinicians make appropriate decisions in the future.

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INTRODUCTION

Gonadotroph adenomas are the most common histological subtype of pituitary adenomas that originate from the adenohypophysis. Functioning gonadotroph adenomas (FGAs) are extremely rare, accounting for less than 1% of all gonadotroph adenomas[1]. Gonadotroph adenomas are classified as functioning and non-functioning gonadotroph adenomas, and the former is distinct from other hormone-secreting pituitary adenomas, which are also easily misdiagnosed due to their low proportion. FGAs secrete one or more biologically active hormones, such as gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH)[2], and this leads to different clinical manifestations, such as menstrual irregularity, infertility, ovarian hyperstimulation syndrome in females, testicular hypertrophy, sexual dysfunction, erythrocytosis in males, and isosexual precocious puberty in children[2,3]. Non-functioning gonadotroph adenomas (NFGAs) patients always present with mass effect symptoms, such as visual disorders, headache, and cranial nerve dysfunction, or are discovered as incidental imaging findings, and they often lack hormone hypersecretion symptoms[4]. The most common presenting clinical manifestations of FGAs are menstrual irregularity, including oligomenorrhea, secondary amenorrhea, menorrhagia, and irregular vaginal bleeding[2,5,6]. The pathogenesis of FGAs remains unclear; however, early diagnosis facilitates the selection of proper therapeutic methods by clinicians and would be beneficial to the prognosis of the disease. Here, we describe a case of functioning gonadotroph adenomas in a reproductive-aged woman with abdominal pain, irregular menstruation, hyperestrogenemia, ovarian mass, and fibroadenoma of the breast and discuss the diagnosis and management of the disease.

CASE PRESENTATION

Chief complaints

A 21-year-old female patient with abdominal pain, irregular menstrual cycles, hyperestrogenemia, and recurrence of an ovarian mass was transferred to our hospital in July 2020.

History of present illness

Four months prior, the patient was referred to another hospital because of abdominal pain and irregular menstrual cycles. Ultrasonography revealed a large multilocular cystic mass in the abdominal cavity. As the abdominal pain increased, the patient underwent single-port laparoscopic removal of the bilateral ovarian cysts. During surgery, the bilateral ovaries were enlarged in a multilocular mass with yellow fluid inside, and histopathology revealed multiple luteinized follicular cysts of the ovary.

After one month of clinical treatment, the patient experienced abdominal pain again. Pelvic ultrasound indicated recurrence of enlarged ovaries with multiple large cysts, and its upper edge reached 20 mm above the umbilicus; both sides reached the midclavicular line, while the thickness of the endometrium was 17.4 mm. Biochemical evaluation demonstrated normal serum levels of LH, FSH,

progesterone (PROG), cortisol, Free T4 (FT4), thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), calcium, phosphate, and growth hormone (GH), and elevated levels of plasma CA125, estradiol, and prolactin (PRL). Brain magnetic resonance imaging (MRI) revealed the presence of a pituitary macroadenoma (17 mm × 27 mm × 19 mm), and visual field examination after brain MRI revealed bitemporal hemianopsia. Ultrasound showed a 48 mm × 30 mm × 23 mm mass in the right breast, and histopathology revealed breast fibroadenoma. Ultrasound imaging revealed no abnormalities in the thyroid, adrenal, or parathyroid glands. The female patient was then treated with oral bromocriptine (2.5 mg) three times a day.

History of past illness

The patient had no significant history of illness, medical history, drug allergy, transfusion, injury, pregnancy, or other complications.

Personal and family history

The patient had smoking history for over four years and had no remarkable personal or family history.

Menstrual history

The patient had menarche at age 12 years, and she had a regular menstrual cycle. In the past year, the menstrual cycle of the patient had extended to 2–3 months, accompanied by progressively increased dysmenorrhea.

Physical examination

The patient was 167 cm tall, weighed 68 kg, and had a body mass index of 24.38 kg/m^2. temperature was 36.7 °C, heart rate was 96 beats/min, respiratory rate was 20 breaths/min, and blood pressure was 98/68 mmHg.

Laboratory examinations

Biochemical evaluation showed that plasma estradiol and CA125 levels were elevated, while PRL, LH, FSH, PROG, cortisol, FT4, TSH, PTH, and GH levels were maintained at normal levels.

Imaging examinations

An ultrasonographic study of the pelvis revealed multicystic ovaries, similar to the typical signs of spontaneous ovarian hyperstimulation syndrome (OHSS). Computed tomography confirmed a large cystic mass in the abdominopelvic cavity (Figure 1A and B), with a range of 19.4 cm × 7.9 cm × 15.9 cm. A homogeneously enhancing 21 mm × 16 mm× 28 mm sellar mass imaged by Brain MRI was presented (Figure 2A-D).

MULTIDISCIPLINARY EXPERT CONSULTATION

In July 2020, the patient presented with abdominal pain and was transferred to our hospital. We invited neurosurgeons, pathologists, and radiologists to form a multidisciplinary team to discuss the diagnosis and treatment of the disease. Since the FSH levels of the patient were within normal ranges, one group of physicians suggested that ovarian cystectomy should be performed first, and then determined whether the histopathology is an estrogen-secreting tumor. However, different viewpoints expressed that pituitary adenomas should be treated first, and changes in the size of the ovarian cyst tumor should be observed after surgery.

FINAL DIAGNOSIS

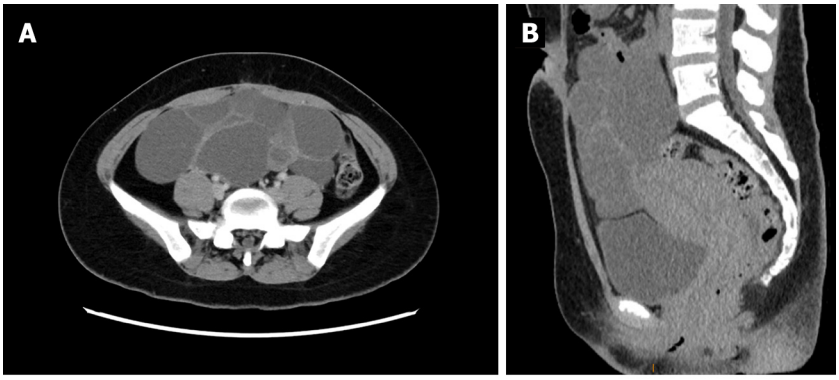
Functioning gonadotroph adenoma.

TREATMENT

The patient underwent transsphenoidal surgery.

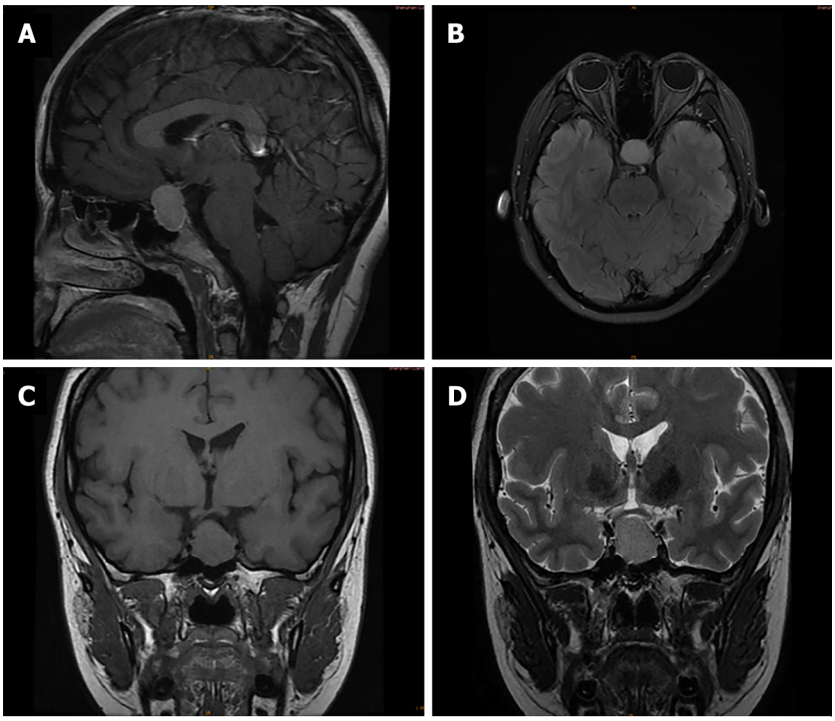
OUTCOME AND FOLLOW-UP

Tumor specimens demonstrated gonadotroph adenoma immunopositive for PIT-1(+), AE1/AE3 (+),



DOI: 10.12998/wjcc.v11.i6.1341

Figure 1 Preoperative computed tomography of the abdominal cavity showed multicystic ovaries in the abdominopelvic cavity. A: Axial image; B: Sagittal image.



DOI: 10.12998/wjcc.v11.i6.1341

Figure 2 Preoperative magnetic resonance imaging of the cranium. A: T1-weighted sagittal image; B: T2-weighted axial image; C: T1-weighted coronal image; D: T2-weighted coronal image. Magnetic resonance imaging pituitary showing a mass lesion within the pituitary gland.

SYN(+), and CgA(+), weakly positive for LH, FSH, PRL, TSH, and KI67, and absolute negativity for ACTH, GH, and P53. Immediate postoperative biochemical evaluation revealed a significant reduction in estradiol, and a normal range of PRL, LH, FSH, PROG, and GH levels remained. Postoperative pelvic ultrasound at one month showed an ovarian cyst measuring 2.4 cm × 2.0 cm in size, which was significantly smaller than before. One month after surgery, endocrine investigations were almost within normal laboratory limits. After three and six months, pelvic ultrasound confirmed normal size ovaries in the patient, the menstrual cycle returned to regular, and her endocrine investigations, including estradiol, PRL, LH, FSH, PROG, TSH, PTH, GH, ACTH, and CA125, were maintained within the normal range, but anti-Müllerian hormone (AMH) seemed slightly lower. The patient was then treated with bromocriptine 1.25 mg orally three times a day after surgery. As the prolactin level from one month to six months after surgery was within the normal range, the dosage was reduced gradually until the final stop. There was no evidence of tumor recurrence after two years of follow-up.

All the endocrine investigations are presented in Table 1. Informed consent was obtained from the patient.

Table 1 Biochemical investigations before and after pituitary surgery

Biochemicals	Normal values	Before surgery	After surgery 1 d	After surgery 1 mo	After surgery 3 mo
Estradiol (pg/mL)	FP:12.5-166, LP:43.8-211	6977	53.7	39.5	69.1
FSH (mIU/mL)	FP:3.5-12.5, LP:1.7-7.7	2.3	1.8	8.5	7.9
LH (mIU/mL)	FP:2.4-12.6, LP:1.0-11.4	3.8	0.6	3.8	3.2
PRL (uIU/mL)	102-496	65.87	33.26	550.3	59.28
PROG (ng/mL)	FP:0.057-0.893, LP:1.83-23.9	21.98	0.14	0.26	0.42
GH (pg/mL)	126-9880	463.1	438.1	158.7	336
Testosterone (ng/mL)		0.69	0.06	0.11	0.05
ACTH (pmol/L)	1.6-13.9	4.79			4.48
CA125 (U/mL)	< 35	41.6			14.2
AMH (ng/mL)	2.06-6.98	3.06			1.58
PTH (pmol/L)	1.27-9.33	3.55			3.82
FT4 (pmol/L)	6.44-18.02	10.34			13.32
TSH (μIU/mL)	0.35-5.1	1.46			2.126
Cortisol (nmol/L)	6-10 am:133-537	404			

FP: Follicular phase; LP: Luteal phase; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; PRL: Prolactin; PROG: Progesterone; GH: Growth hormone; ACTH: Adrenocorticotropic hormone; AMH: Anti-Müllerian hormone; PTH: Parathyroid hormone; FT4: Free T4; TSH: Thyroid-stimulating hormone; Pituitary surgery: transsphenoidal resection of pituitary macroadenoma.

DISCUSSION

The exact prevalence of clinical FGAs is unknown because of their rarity, non-specific clinical signs and symptoms, and a lack of understanding of their histopathology and pathogenesis. The FGAs can occur in premenopausal and postmenopausal females, males and children. Postmenopausal females may not manifest with a syndromic presentation because the ovaries are insensitive to FSH stimulation[7]. Testicular enlargement, sexual dysfunction, and elevated serum FSH have been reported in male patients with FGAs; most of them are macroadenomas[8]. FGAs rarely occure in children; symptoms caused by central precocious puberty have been reported in both boys and girls[9,10]. While FGAs are typically histologically benign, there are cases of patients with severe comorbidities (*via* endocrine effects and/or mass effect) that lead to a shortened lifespan, as well as cases of tumor regrowth and metastasis[11,12]. In this context, the female patient had irregular menstrual cycles for one year. Furthermore, the menstrual period was extended, the menstrual cycle was prolonged to every 2-3 months, and dysmenorrhea was aggravated in the past year. After surgery, the patient resumed regular menstruation, abdominal distention disappeared, and pelvic ultrasound confirmed normal-sized ovaries three months later. Due to compression of the macroadenoma, the patient also showed a partial visual field defect, and the visual field recovered gradually after transsphenoidal surgery.

OHSS usually occurs in women undergoing assisted reproductive techniques when applying hormone medications to stimulate ovulation and can develop severe symptoms such as discomfort, abdominal pain, nausea, vomiting, diarrhea, ascites, hypovolemia, hemoconcentration, and thromboembolism[13]. The patient exhibited a typical sign of spontaneous ovarian hyperstimulation syndrome with enlarged ovaries, multiple large cysts, and abdominal pain, but without ascites and hypercoagulability. The secretion of FSH stimulates the recruitment of multiple follicles and promotes the excessive secretion of estradiol, which in turn leads to the downregulation of FSH[14]. The histopathology revealed that FSH and LH were weakly positive, despite the levels of the serum FSH and LH being maintained in the normal range, suggesting that the secretion of FSH may increase the bioactivity of FSH and its isoforms[15]. The negative feedback control by estradiol may disappear, and it could not inhibit the secretion of FSH by the pituitary gland, even if its level was too high. It has also been proposed that the specificity of the intramolecular barrier to activate the FSH receptor would be lower in ovarian hyperstimulation mutants, thus allowing even low-affinity agonists, such as LH, HCG, or TSH, to become effective[16]. High concentrations of estradiol were observed in this case, and the estradiol level returned to the normal range after transsphenoidal surgery, which may indicate that FGAs were the cause of this phenomenon. Prolactin levels are elevated in female patients, probably due

to compression of the pituitary stalk and/or excessive estrogen secretion[16]. Anti-Müllerian hormone (AMH) levels may represent the quantity of the ovarian follicle pool and may be a useful marker of ovarian reserve[17]. Serum AMH levels decreased with age and were greatly reduced or undetectable in women with premature ovarian failure or in the postmenopausal period[18]. The decrease in AMH in this patient may have been caused by ovarian hyperstimulation due to the reduction in ovarian function. Preoperative cortisol, FT4, TSH, PTH, ACTH, and GH levels were normal, which helped differentiate them from other diseases and complications. Breast fibroadenoma is a common benign tumor in premenopausal women. Although the pathogenesis remains unclear, high levels of estrogen may promote disease development[19]. We also observed a reduction in the size of the fibroadenoma three months after the operation.

Functioning gonadotroph adenomas must be differentiated from polycystic ovarian syndrome (PCOS) and ovarian tumors, such as granulosa cell tumors. PCOS patients usually show mildly enlarged polycystic ovaries and menstrual irregularity, but they always have normal estradiol levels, increased LH relative to FSH, hyperandrogenism, insulin resistance, and obesity[20], which may help clinicians distinguish them from FGAs. The diameter of ovarian follicles in women with PCOS ranges from 2 to 9 mm, whereas those in women with gonadotroph adenomas are usually larger (> 2 cm). Ovarian granulosa cell tumors are often present in postmenopausal women and are characterized by a unilateral solid pelvic mass, abdominal pain, excessive estradiol secretion, endometrial hyperplasia, abnormal uterine bleeding, and low levels of LH and FSH[21]. Moreover, pathological examination and Brain MRI may help clinicians avoid misdiagnosis. Endocrine investigations, particularly estradiol levels, can provide an important reference for diagnosis. In previous reports of OHSS caused by functioning gonadotroph adenomas, estradiol levels were usually elevated, ranging from mild to markedly elevated[6,15,22,23]. In most cases of FGA, normal to high levels of serum FSH, decreased LH levels, and elevated PRL levels have also been reported[24]. Women with PCOS often have normal estradiol and increased AMH levels[18]. Ovarian granulosa cell tumors not only induced an increase in estradiol levels but also had a significant effect on elevating serum AMH and inhibin B concentrations [25]. Fully understanding the mechanism of the hypothalamic-pituitary-ovarian axis can facilitate correct diagnosis and treatment decisions.

Several studies have reported beneficial results following surgical treatment, adjuvant radiotherapy, and drug treatments. Due to the small number of cases, the optimal management of FGAs is based mainly on case reports or small systematic case series. Transsphenoidal surgery remains the primary choice, which not only relieves the mass effect symptoms and restores gonadotropin secretion, but also reduces the size of the ovaries, helps resume regular menses, resolves ovarian hyperstimulation syndrome, and enables the collection of tissue for histological analysis[5,15,16,23,26,27]. In cases where complete resection is difficult to achieve by surgery alone and tumor recurrence is detected during long-term follow-up, other treatments like adjuvant radiotherapy, radiosurgery, and drug treatments have been used to control the disease. Adjuvant radiotherapy has been reported to be helpful in several cases and is commonly used for managing residual tumors after surgery; nonetheless, the effectiveness of its routine usage remains controversial[6,26]. Gamma knife radiosurgery (GKRS) has recently been proposed for treating of residual or recurrent pituitary adenomas, which effectively and safely controls the tumor in the long term with minimal complications[28,29]. In studies of patients with pituitary adenoma after GKRS, hypopituitarism, visual decline, and tumor regrowth were reported during the follow-up[30,31]. GKRS is often employed in patients with NFGAs; long-term safety and efficacy data are still lacking for using GKRS in FGAs. Medical treatments of FGAs, including dopamine agonists (bromocriptine, cabergoline), somatostatin analogs (octreotide), and GnRH agonists and antagonists, temporarily suppress hormone production in a few cases. However, they are typically ineffective in controlling the growth of tumors or clinical syndromes[6,32,33,34,35].

CONCLUSION

In conclusion, we report a rare case of ovarian hyperstimulation due to a functional gonadotroph adenoma in a reproductive-aged woman. Early diagnosis of functioning gonadotroph adenomas should be considered in patients with hyperestrogenism, irregular menstruation, large or recurrent ovarian cysts, and visual field defects. Pituitary MRI should be performed, and transsphenoidal surgery is recommended for the management of this disease.

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FOOTNOTES

Author contributions: He Y contributed to manuscript writing, editing, and data collection; Gao YT contributed to manuscript editing; Sun L contributed to supervision; all authors have read and approved the final manuscript.

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CASE REPORT

Clinical manifestations of adult hereditary spherocytosis with novel *SPTB* gene mutations and hyperjaundice: A case report

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

Peer-review model: Single blind

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Abstract

BACKGROUND

The aim of the present study was to enhance understanding of the diagnosis and treatment of atypical hereditary spherocytosis (HS), and to broaden the diagnostic thoughts of physicians for patients with jaundice.

CASE SUMMARY

A 28-year-old male presented with jaundice, bile duct stone, and splenomegaly, but without anemia. Other causes of jaundice were excluded, and gene sequencing revealed a novel heterozygous variant of c.1801C>T (p.Q601X) in exon 14 of the SPTB (NM_01355436) gene on chromosome 14 (chr14: 65260580) in the patient's blood; the biological parents and child of the patient did not have similar variants. A splenectomy was performed on the patient and his bilirubin levels returned to normal after surgery. Thus, a novel gene variant causing HS was identified. This variant may result in the truncation of β-hemoglobin in the erythrocyte membrane, leading to loss of normal function, jaundice, and hemolytic anemia. The clinical manifestations of the patient were hyperjaundice and an absence of typical hemolysis during the course of the disease, which caused challenges for diagnosis by the clinicians.

CONCLUSION

Following a definitive diagnosis, genetic testing and response to treatment identified a gene variant site for a novel hemolytic anemia.

Key Words: Gall-stone; Jaundice; Hereditary spherocytosis; Gene mutations; Adult; Case report

Core Tip: A novel mutation in the SPTB gene was identified in a patient with hemolytic anemia, which caused the patient to present with extremely high jaundice without obvious hemolysis. At the same time, there was no similar mutation in the patient's family. Because medical treatment was ineffective, we finally performed splenectomy after communicating with the patient. After splenectomy, the patient's liver function recovered. The patient's liver function continued to be normal during follow-up.

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INTRODUCTION

Hereditary spherocytosis (HS) is a type of hemolytic anemia caused by congenital membrane defects of red blood cells. HS is an autosomal dominant inheritance disease that predominantly affects infants and children[1]. Here, a case of adult HS with a novel heterozygous variant of the *SPTB* gene (c.1801C>T) is reported. The patient had severe jaundice [total bilirubin (TBIL): 1625 μmol/L] without anemia. The final diagnosis was confirmed based on clinical observation, gene sequencing, and response to treatment and is summarized below.

CASE PRESENTATION

Chief complaints

A 28-year-old male was admitted to the First Hospital of Lanzhou University due to jaundice and stomachache on March 8, 2021.

History of present illness

The patient experienced intermittent right upper abdominal distension and pain after eating greasy food for 6 mo before admission, which could be relieved by taking medicine. Symptoms worsened 5 d before admission, including abdominal pain and white clay stools. The local hospital checked for elevated BIL, and an abdominal magnetic resonance imaging (MRI) showed cholecystolithiasis and bile duct dilation. Consequently, the patient was transferred to our hospital. The diagnosis was biliary calculi; therefore, endoscopic retrograde cholangiopancreatography with sphincterotomy + balloon exploration and lithotomy + biliary stent angioplasty was performed. Postoperative BIL remained high, so the patient was transferred to the Department of Infectious Diseases for further diagnosis and treatment.

History of past illness

The patient had no history of past illness.

Personal and family history

The patient was a cook without any notable unhealthy habits. He was not exposed to drugs or poisons and did not smoke or drink alcohol. The patient and his family members had no specific history of genetic diseases.

Physical examination

Body mass index 22.13 kg/m^2, waist circumference 90 cm and hip circumference 93 cm, severe yellow staining of skin and mucous membranes, abdominal tenderness, Murphy's sign positive, liver not palpable and spleen palpable three fingers under the costal.

Laboratory examinations

Hemoglobin (Hb) was 110 g/L, aspartate aminotransferase was 34 U/L, alanine aminotransferase was 70 U/L, TBIL was 1618 μmol/L, direct BIL (DBIL) was 998 μmol/L, and indirect BIL (IBIL) was 828 μmol/L. The cause of jaundice was actively investigated. The results of the infection index (hepatitis virus, non-heparophilic viruses, bacteria, fungi, and so on), immunological indicators, and iron and copper metabolism index were not obviously abnormal. Drugs, alcohol, parasites, and other factors were also excluded. Liver biopsy showed hepatic lobule structural disorder, widened portal area,

fibrous tissue hyperplasia, infiltration of inflammatory cells dominated by lymphocytes, bile duct hyperplasia, punctate necrosis of some hepatocytes, and biliary pigment deposition in the cytoplasm of some cells. Immunohistochemical and specific staining results included net staining (indicating fibrosis in portal area), CK19 (small bile ducts 2+), CD45 (inflammatory cells 2+), CD38 (individual cells 1+), ki67 (18%), GPC -3(-), Masson's trichrome stain (fibrosis in portal area), and CD34 (vascular 2+). The conclusion from the liver biopsy and staining was that the morphology was consistent with chronic inflammation with liver cholestasis and a tendency of liver cirrhosis (G2S2) (as shown in Figure 1).

In terms of hemolytic jaundice, the blood smear showed that the size of red blood cells was slightly different from normal, the filling was acceptable, no abnormal red blood cells were detected, and platelets were scattered and clustered; 39.0% of the blood cells were erythroid, predominantly middle and late immature erythrocytes, with no abnormal morphology, polychromatic erythrocytes were clearly visible and were basically the same size as mature erythrocytes, the filling was acceptable. These findings suggested that a diagnosis of proliferative anemia should be considered. Anemia screening assays (direct and indirect anti-human globules, anti-alkali Hb assay, Hb A2 assay, micro Hb electrophoresis, isopropanol, methemoglobin reduction test, G-6-PD fluorescent spot test, denatured globin body, H Inclusion bodies, and red blood cell osmotic fragility test) were negative. Bone marrow puncture considered hyperplastic anemia.

The patient was screened for hereditary liver disease. The detection was performed on an Illumina sequencing platform and the GATK software suite was used for sequencing data analysis. High-throughput sequencing of a liver panel showed that on chromosome 14 (chr14: 65260580), the *SPTB* gene in exon 14 had a mutation of cytosine to thymine at nucleotide 1801, resulting in a glutamine nonsense mutation at amino acid 601 to a stop codon [NM_001355436: exon14: c.1801C>T (p.Q601X)]. The variant that was identified in the high-throughput sequencing was validated by Sanger sequencing. This variant was suspected to cause HS. Parental genetic testing indicated that the variant was not found in the father or mother; in addition, the variant was not detected in the patient's daughter (Figure 2).

Imaging examinations

The spleen (length × thickness) was 192 mm × 63 mm. Abdominal MRI + magnetic resonance cholangiopancreatography + diffusion-weighted imaging and abdominal CTA were not obviously abnormal.

FINAL DIAGNOSIS

The patient was diagnosed with HS.

TREATMENT

While the cause of jaundice was investigated in the patient, he was given treatment for liver protection, BIL regression, and symptoms. As the treatment progressed, the liver function indexes of the patient improved; TBIL fluctuated between 250 and 400 μmol/L, DBIL was 140-300 μmol/L, and IBIL was 120-200 μmol/L. The spleen was progressively reduced to 167 mm × 60 mm. However, considering that the patient still had anemia and abnormal liver function, combined with the patient's genetic report and the trend of fibrosis in the liver, to make a clear diagnosis and effectively control the anemia and jaundice and combined with the wishes of the patient and his family, a splenectomy was performed on December 31, 2021. Intraoperative pathological examination showed spleen capsule thickening, splenic corpuscle atrophy, splenic sinus dilatation, and congestion.

OUTCOME AND FOLLOW-UP

Three days after surgery, the patient's BIL rapidly decreased to nearly normal levels. The patient's clinical and laboratory tests continue to be good (Table 1). Therefore, the patient was diagnosed with HS, and we believe that the CHR14:65260580 *SPTB* gene NM_001355436: exon14: c.1801C>T (p.Q601X) variant is the pathogenic gene of HS, which has not been reported previously in the literature.

DISCUSSION

HS is a rare genetic disorder with a global distribution but is the most common cause of hemolytic anemia caused by erythrocyte membrane defects. The incidence of HS in Northern Europe and North America is 1/5000 and 1/2000, respectively, while the predicted incidence of HS in China is (1.27-1.49)/

Table 1 Patient indicators during treatment

Indicator	Before ERCP	After ERCP	During medication	Before removal of biliary stent	After removal of biliary stent	Before splenectomy	After splenectomy	Recent results
TBIL (μmol/L)	1734.7	1618.1	442.9	83.5	96.4	105.1	31.5	22.5
DBIL (μmol/L)	1146.4	998.0	316.7	13.0	14.8	14.9	7.8	5.5
IBIL (μmol/L)	588.3	828.5	126.2	70.5	81.6	90.2	23.7	17.0
Hb (g/L)	122	110	94	76	72	109	122	139
MCH (pg)	33.1	32.1	34.5	32	35.0	32.0	31	
RDW-SD (fL)	66.2	66.4	51.9	64.4	57.2	58.6	55.3	52.7
RET# ($\times 10^{12}$/L)	0.235	0.254	0.260	0.368	0.249	0.231	0.026	0.043
AST (U/L)	37	34	34	14	12	31	47	22.5
ALT (U/L)	103	70	70	18	12	60	54	32.3
ALP (U/L)	359	299.9	299.9	102.0	105.0	169.4	171.7	214.5
GGT (U/L)	264.6	154.2	154.2	29.0	26.7	72.1	176.9	40.2
ALB (g/L)	43.2	39.0	39	45.7	71.7	57.1	47.0	50.1
Crea (μmol/L)	61	91.3	91.3	109.6	107.5	108.6	93.9	81.8
UA (μmol/L)	88	64	64	596	649	620	435	447
TG (mmol/L)	1.96	2.76	2.76	0.95	1.04	1.85	1.50	1.75
LDL-C (mmol/L)	1.91	1.83	1.83	0.94	1.16	1.21	2.21	2.18

Reference ranges: Total bilirubin 9.1-30.1 μmol/L, direct bilirubin 0-6.8 μmol/L, indirect bilirubin 0-19 μmol/L, hemoglobin 120-160 g/L, mean corpuscular hemoglobin 27-31 pg, red blood cell distribution width 39-46 fL, red blood cell distribution width (0.017-0.064) × 10^{12}/L, aspartate aminotransferase 1-49 U/L, alanine aminotransferase 1-49 U/L, alkaline phosphatase 20-125 U/L, gamma-glutamyl transpeptidase 3-69 U/L, albumin 32-55 g/L, Crea 44-108 μmol/L, uric acid 125-420 μmol/L, triglyceride 0.8-1.8 mmol/L, low-density lipoprotein 1.55-3.7 mmol/L. TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; Hb: Hemoglobin; MCH: Mean corpuscular hemoglobin; RDW-SD: Red blood cell distribution width; RET: Reticulocyte; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; ALB: Albumin; UA: Uric acid; TG: Triglyceride; LDL-C: Low-density lipoprotein.

100000[2].

The main pathogenesis of HS is the abnormality of the protein encoding the bilayer between the inner membrane skeleton and the outer lipid of erythrocytes, which leads to a decrease in the stability of the erythrocyte membrane. These defects damage the elasticity of erythrocytes so that they become spherical, and they can be destroyed by the spleen, resulting in hemolytic anemia. Simultaneously, erythrocytes are exposed to the adverse environment of a large spleen, including acidification and oxidation conditions, which aggravate hemolysis[3].

There is an obvious family history of HS and there are five common gene abnormalities that are known to cause HS: *SPTA1* gene encoding α spectrin, *SPTB* gene encoding β spectrin, *ANK1* gene encoding ankyrin, *SLC4A1* gene encoding band 3 protein, and *EPB42* gene encoding protein 4.2. HS mainly occurs through autosomal dominant inheritance, accounting for 75% of cases; the remaining cases are due to autosomal recessive inheritance, among which the *SPTA1* and *EPB42* genes are more common. New variants have also been reported, but their relative frequency has not yet been determined[4].

The clinical characteristics of HS include: (1) It can appear at any age, the onset time is usually early, and some patients have a positive family history of HS; (2) There are various clinical manifestations and severity. The main manifestations of patients with moderate and severe HS are anemia, jaundice, spleen enlargement, acute hemolysis, and biliary calculi. Once obstructive jaundice occurs, temporary liver obstruction can lead to dyslipidemia, the surface area of the erythrocyte membrane increases, and hemolysis can be alleviated in a short time; and (3) The anti-human globulin test is negative in HS patients. Most patients with HS have high mean Hb levels and spherical erythrocytes on peripheral blood smears[5]. Genetic testing has marked advantages over biochemistry and cell morphology in the diagnosis of HS, especially when the clinical symptoms are atypical, the family history is negative, or routine laboratory tests cannot confirm the diagnosis[6].

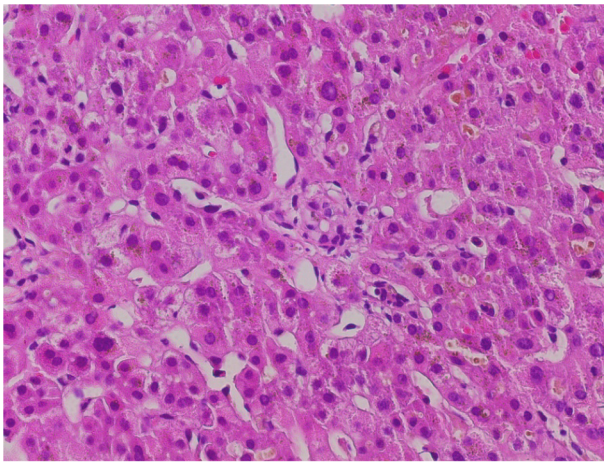

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Figure 1 Pathology following liver puncture (hematoxylin-eosin staining, × 400 magnification).

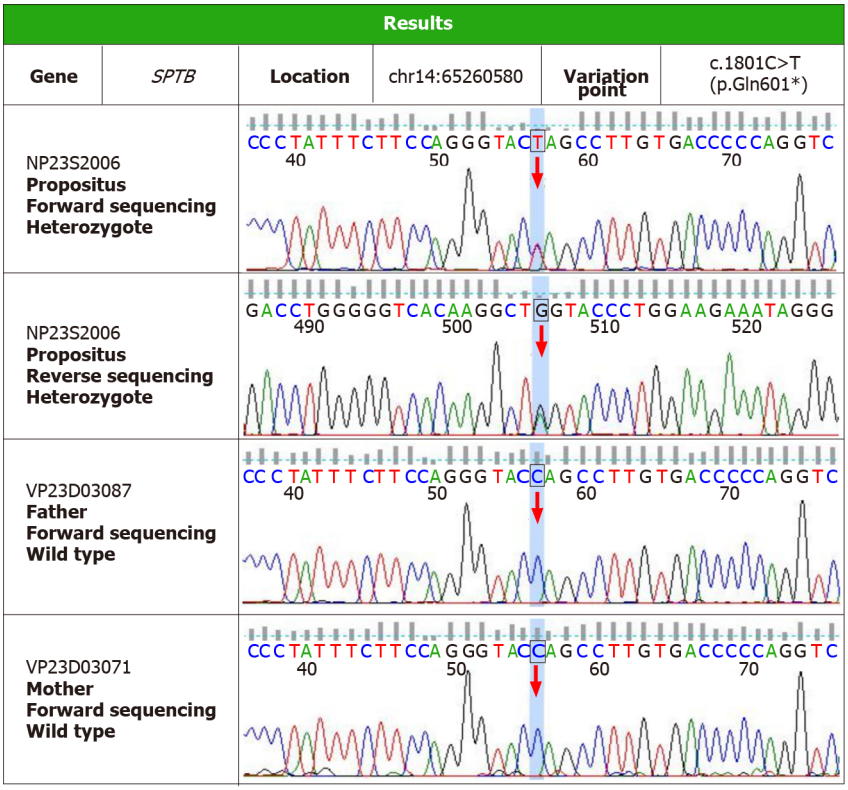

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Figure 2 Results of high-throughput sequencing of the liver panel.

In the current study, the patient was monitored for mutation of cytosine to thymine at nucleotide 1801 of exon 14 of the *SPTB* gene on chromosome 14. The *SPTB* gene has a crucial role in maintaining cell membrane organization and stability and is a major component of the cytoskeletal network beneath the red blood cell plasma membrane. The spectrin protein encoded by *SPTB* interacts with other proteins through a specific binding domain to maintain the biconcave shape of human erythrocytes[7]. Variants of this gene may cause red blood cells to fail to form their normal shape, leading to spherocytosis and elliptocytosis[8].

HS is treated to reduce hemolysis and anemia, and other complications. The decision to perform a splenectomy should consider the severity of hemolysis, the patient's age, and surgical complications[9]. Splenectomy is feasible in the following cases: (1) Children over 6 years old who have transfusion dependence, severe anemia, or related severe symptoms; (2) Patients with severe hemolysis and/or severe symptoms (*e.g.*, abdominal symptoms related to splenomegaly, discomfort related to jaundice), or delayed growth or extramedullary hematopoietic; and (3) When HS patients have severe and

recurrent cholelithiasis (splenectomy can be used to reduce cholelithiasis). Some studies suggest that splenectomy and cholecystectomy can significantly improve the quality of life and prolong the survival time for HS patients with cholelithiasis[10]. After splenectomy in patients with HS, Hb and serum BIL levels can return to normal within a few days. Splenectomy is reported to be more effective in reducing hemolysis in HS patients with variants of *SPTA1* and *SPTB* genes compared with other genes. This may be due to the varying degrees of reticuloendothelial clearance in the blood machinery of different individuals, related to the opsonization (natural antibody binding) of blood protein/protein albumin/protein monomeric erythrocytes[10].

The patient in the current study had no family history of HS and had acute onset as an adult. The patient's clinical symptoms were severe jaundice and gallstones. However, when the stones were removed, the jaundice did not improve. In the early stage of the disease, the patient's Hb was normal, the leucocytic screening was negative, and there were no spherical red blood cells on the peripheral blood smear. However, during the course of the disease, there were sufficient hematopoietic raw materials, no obvious blood loss, and Hb was repeatedly reduced; consequently, hemolytic disease could not be excluded. Full-exome sequencing for genetic diseases was conducted in the patient and indicated that *SPTB* gene NM_001355436: exon14: c.1801C>T (p.Q601X) of CHR14:65260580 was suspected as a pathogenic gene. The proband's parents and daughter did not have this gene abnormality. The patient's postoperative indicators rapidly returned to normal after splenectomy. Therefore, combined with the above characteristics, it is considered that the modified gene locus is mutated into a HS pathogenic gene. Furthermore, there are no previous case reports of this variant.

CONCLUSION

In conclusion, when HS is considered in patients without typical clinical symptoms, molecular detection of genes can be used to facilitate diagnosis, and clinical characteristics and response to treatment can be combined to clarify diagnosis.

FOOTNOTES

Author contributions: Jiang N conducted data curation and wrote the manuscript; Mao WY revised and approved the final manuscript; and all authors contributed to the article and approved the submitted version.

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CASE REPORT

Post-traumatic cauda equina nerve calcification: A case report

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Abstract

BACKGROUND

Post-traumatic cauda equina nerve calcification is extremely rare in clinical practice, and its etiology, pathogenesis, treatment and prognosis are unclear. There are few studies and reports on Post-traumatic cauda equina nerve calcification, and this review reports a case of Post-traumatic cauda equina nerve calcification for reference.

CASE SUMMARY

A 52-year-old patient presented to our hospital with a history of lumbar spinal stenosis and a lumbar vertebral fracture caused by trauma. The patient's right lower limb had weakness in hip flexion, knee extension and plantarflexion with muscle strength grade 3, right ankle dorsiflexion and thumb dorsiflexion with muscle strength grade 0. The patient's skin sensation below the right knee plane disappeared. The patient's Computed tomography (CT) data showed signs of cauda equina nerve calcification and the terminal filaments in the plane of the third to fifth lumbar vertebrae. After treatment the patient's symptoms were slightly relieved.

CONCLUSION

We provide an extremely rare case of Post-traumatic cauda equina nerve calcification and offer a conservative treatment plan. However, the etiology, mechanism and treatment of Post-traumatic cauda equina nerve calcification are

still unclear. This requires scholars to conduct more research and exploration in this area.

Key Words: Post-traumatic; Calcification; Cauda equina nerve; Spinal Cord Injury; Case report

Core Tip: We report an extremely rare case of Post-traumatic cauda equina nerve calcification and speculate on its etiology and mechanism, providing material for scholars to study the etiology, mechanism and treatment of post-traumatic cauda equina nerve calcification.

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INTRODUCTION

Post-traumatic cauda equina nerve calcification refers to the deposition of calcium in ten pairs of lumbosacral nerve roots below the conus medullaris, resulting in various clinical symptoms[1]. The cauda equina nerve is the bridge between the spinal cord and the peripheral nerve, connecting the pseudounipolar neurons of the dorsal root ganglion and the spinal cord neurons. Because of its special anatomical structure (only a layer of nerve inner membrane, lack of corresponding protective tissue), it is vulnerable to mechanical injury. The nutrition of cauda equina nerve comes from cerebrospinal fluid and blood, and there is a relatively anemia area in the anastomosis between the spinal artery and the root artery supplying the cauda equina nerve, so the cauda equina nerve is more prone to decompensation due to mechanical compression[2]. Post-traumatic cauda equina nerve calcification is extremely rare clinically, and its etiology, pathogenesis, treatment, and prognosis are unclear. No studies or reports on Post-traumatic cauda equina nerve calcification have been inquired, and a case of Post-traumatic cauda equina nerve calcification is reported here for reference.

CASE PRESENTATION

Chief complaints

On May 13, 2022, a 53 years female community worker with 35 years of progressive lumbar kyphosis was admitted to our hospital with symptoms worsening over 7 mo, claudication and right knee retroflexion.

History of present illness

The patient complained of lumbar spine fracture and bilateral lower limb paralysis due to injury from fall more than 35 years ago, and underwent emergency surgery in other hospitals. Two years after the surgery, the motor and sensory functions of the left lower limb gradually recovered, while the right lower limb had weakness in hip flexion, knee extension and plantarflexion, with muscle strength of about grade 3. He was admitted to the hospital 7 mo ago after a fall during a walk in the park, resulting in right knee retroflexion and right ankle sprain. In the last week, the patient's symptoms were aggravated without any obvious cause, and the right hip was accompanied by radiating pain and numbness in the right lower limb, especially in the lateral and posterior side of the right lower limb. During the pain attack, the patient took metamizole sodium tablets (0.5g po st). After taking metamizole sodium tablets, the patient's pain was slightly relieved. The patient complained of numbness and trapped pain in the lumbosacral region with radiating pain and numbness in the right lower extremity, especially the lateral and posterior sides of the right lower limb. The patient has difficulty squatting down, and the pain increases when bending down. The patient had no symptoms such as chills, high fever, spontaneous sweating, night sweating, dizziness, nausea and vomiting. The patient's sleep and urination were normal. Since the patient's stool is dry, laxatives are used to help him defecate for 3 days.

History of past illness

The patient had a history of hypertension for more than 3 years, with blood pressure up to 150/100 mmHg. Patients regularly take nifedipine sustained-release tablets to control their blood pressure, which has been controlled at present. The patient underwent internal fixation of the lumbar spine at an

another hospital 35 years ago and had no adverse blood transfusion reactions during the operation. Had a cesarean section in another hospital more than 30 years ago.

Personal and family history

The patient had no relevant personal or family history.

Physical examination

The patient's Lumbar kyphosis and right knee retroflexion. The patient had limited anterior flexion and posterior extension of the lumbar region with percussion pain and pressure pain at the spinous process and paraspinal process of the third lumbar vertebra - fifth lumbar vertebra (L3-5). The patient's right lower limb was positive for lasegue sign and supine abdominal sticking test. Patient's muscle strength: iliopsoas (Second lumbar vertebra /fourth lumbar vertebra) (L2/4) muscle strength, quadriceps (L2/4) muscle strength, gluteus maximus Fifth lumbar vertebra/second sacral vertebra (L5/S2) muscle strength: right: grade 3, left: grade 4+. biceps femoris (L5/S2) muscle strength, tibialis anterior L4/5 muscle strength, thumb extension (L4/S1) muscle strength: right: grade 0, left: grade 4+. gastrocnemius, hallux valgus (L5/S2) muscle strength: right: grade 3, left: grade 4+. The patient's right Achilles tendon reflex disappeared, the skin sensation below the knee joint plane of the right lower limb disappeared, and the skin sensation below the knee joint plane of the left knee decreased. The patient's pathological reflex was not elicited.

Laboratory examinations

Erythrocyte Sedimentation Rate: 24 mm/h. Complete biochemistry: Apolipoprotein A1: 0.77 g/L, High density lipoprotein-C: 0.84 mmol/L, Albumin ratio (A/G): 1.18, Triglycerides (TG): 2. 78 mmol/L, Homocysteine (HCY): 21 μmol/L, Glutamyl transpeptidase (γ-GT): 218 U/L, Creatinine (CREA): 34 μmol/L, Rheumatoid factor (RF):42.26, C-reactive protein (CRP): 11.12 mg/L. Bone densitometry suggested decreased bone mass.

Imaging examinations

Lumbar spine Computed tomography (CT) showed: L5 plane end filament and cauda equina nerve calcification signs (Figure 1). The X-ray film of lumbar vertebrae shows that the sequence of lumbar vertebrae is abnormal, L3 vertebral body is diseased and shifted backward, L2-3 intervertebral space disappears, L2-3, L3-4, L4-5, L5-S1 intervertebral space narrows, and all vertebrae and vertebral facet joints have hyperosteogeny (Figure 2). The X-ray film of the right knee joint showed that the right knee joint space was narrow inside and wide outside, the articular surface was sclerotic, and the lower edge of the articular surface was spotted with low density. Hyperosteogeny appeared on the upper edge of patella, tibial plateau, tibial intercondylar crest and femoral condyle. The density of the suprapatellar bursa is increased and the surrounding soft tissue is swollen (Figure 3). The X-ray film of the full length of the spine shows that L3-4 vertebral body is diseased and shifted backward, the lumbar spine protrudes backward at the L2-3 plane, the intervertebral space at the L2-3 segment is narrowed, and the L3 vertebral body is wedge-shaped and flattened (Figure 4). The lumbar spine Magnetic Resonance Imaging (MRI) showed: Lumbar vertebrae protrude backward, L3 vertebrae show wedge-shaped changes, spinal canal stenosis on the same level of L3, intervertebral space narrowing on the same level of L2-3, endplate inflammation in the L3-4 intervertebral space, Schmorl node formation near T10-11 vertebral body, degeneration and bulge of L3-4 and L4-5 intervertebral discs, and many abnormal strip signals in the filum terminale (Figure 5). The right knee MRI showed: The cartilage of the medial femoral condyle and tibial plateau is worn, the cartilage is denatured, the posterior cruciate ligament of the right knee is torn, the medial collateral ligament is injured, the anterior and posterior corners of the medial and lateral meniscus of the right knee are worn, the right knee joint has effusion, and the medial head bursa of the gastrocnemius has effusion (Figure 6). Lumbar vertebral body (plain scan + 3D reconstruction) CT showed: Lumbar vertebral body (plain scan + 3D reconstruction) CT showed: L2-3 plane lumbar lordosis, L2-3 vertebral space narrowing, L3 vertebral body wedge-shaped flattening, L3, 4 vertebral body adjacent edge patchy high density. There are some bone defects in the lamina and spinous process of L3 and L4 vertebrae, and the vertebral canal at the same plane is deformed (Figure 7).

Neurological examination

Motor nerve conduction velocity measurement (both lower extremities), sensory nerve conduction velocity measurement (both lower extremities), neuroelectrogram, needle electrode electromyography results showed: Neurogenic damage in both lower extremities.

FINAL DIAGNOSIS

Based on this patient's imaging data and his symptoms, we diagnosed this patient with Post-traumatic cauda equina nerve calcification.

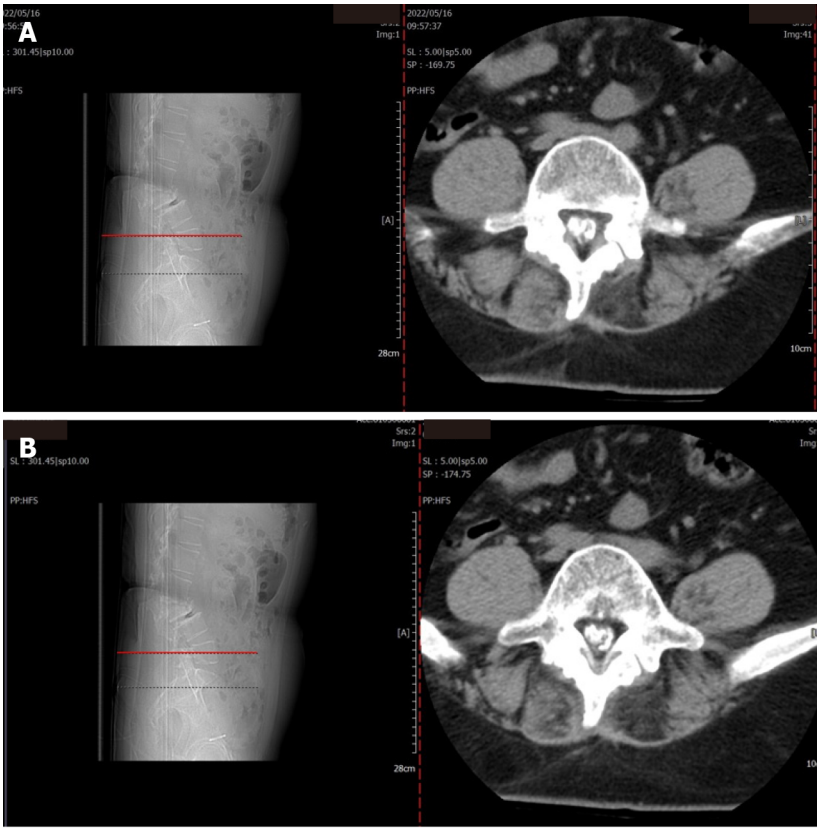

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Figure 1 Lumbar spine computed tomography. L5 plane end filament and cauda equina nerve calcification signs. A: L5 upper edge of vertebral body; B: L5 center of vertebral body.

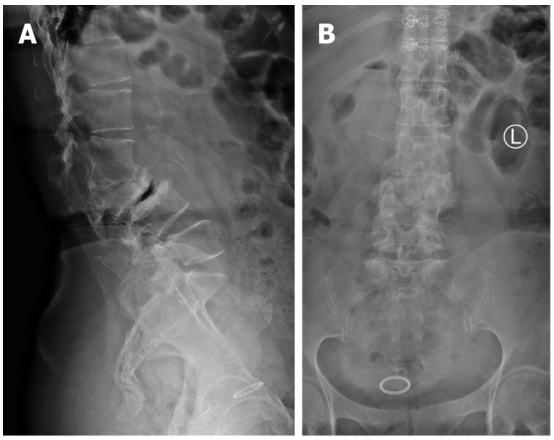

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Figure 2 The X-ray film of lumbar vertebrae. The sequence of lumbar vertebrae is abnormal, L3 vertebral body is diseased and shifted backward, L2-3 intervertebral space disappears, L2-3, L3-4, L4-5, L5-S1 intervertebral space narrows, and all vertebrae and vertebral facet joints have hyperosteogeny. A: Orthostatic lumbar X-ray film; B: Lateral lumbar X-ray film.

TREATMENT

We use the combination of traditional Chinese and western medicine to treat the patient's clinical symptoms symptomatically. Use mannitol injection, dexamethasone sodium phosphate injection, pregabalin capsules, etocoxib, mecobalamin tablets, sodium glutamate injection, and compound betamethasone injection according to scientific drug use rules to dehydrate and detumescence, nourish nerves, diminish inflammation and pain. In addition, we also use radio frequency electrotherapy, traditional Chinese medicine directional penetration, intracutaneous acupuncture, radioactive shock wave and other physical therapy methods to activate blood circulation and remove blood stasis, warm meridians and relieve pain.

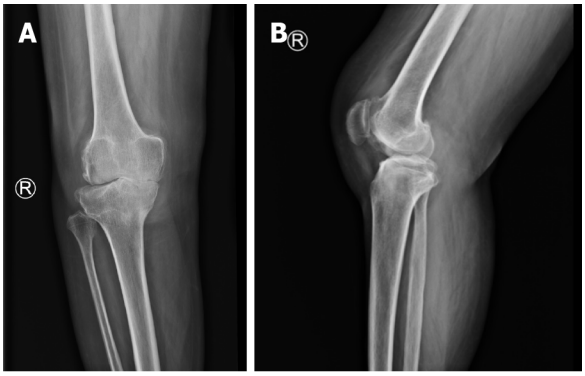

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Figure 3 The X-ray film of the right knee joint. The right knee joint space was narrow inside and wide outside, the articular surface was sclerotic, and the lower edge of the articular surface was spotted with low density. Hyperosteogeny appeared on the upper edge of patella, tibial plateau, tibial intercondylar crest and femoral condyle. The density of the suprapatellar bursa is increased and the surrounding soft tissue is swollen. A: Orthostatic Knee joint X-ray film; B: Lateral Knee joint X-ray film.

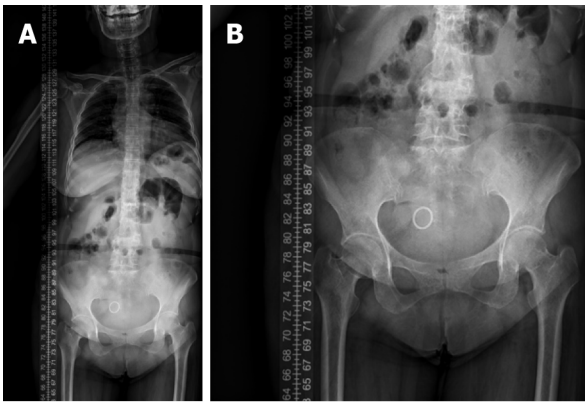

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Figure 4 The X-ray film of the full length of the spine. L3-4 vertebral body is diseased and shifted backward, the lumbar spine protrudes backward at the L2-3 plane, the intervertebral space at the L2-3 segment is narrowed, and the L3 vertebral body is wedge-shaped and flattened. A: The Orthostatic X-ray film of the full length of the spine; B: The Orthostatic X-ray film of lumbar spine and pelvis.

OUTCOME AND FOLLOW-UP

We advise patients to maintain a light diet and recommend active functional exercise. Continue to take etoricoxib tablets, methylcobalamin tablets, and pregabalin capsules. The patient was also advised to carry out a variety of blood-activating and stasis-removing types of physical therapy. After completing regular follow-up (1st, 2nd, 3rd and months after discharge), the patient's limb muscle strength changed to grade II and limb sensation appeared. The patient had good compliance.

DISCUSSION

Nerve calcification usually occurs in the cranial nerve and the dental nerve. It is generally accepted that nerve calcification is divided into two main types: Physiological and pathological calcification. Physiological calcification is due to the natural formation of calcified spots on the nerve with age. Pathological calcification is caused by degenerative diseases, parasitic infections, ischemic necrosis of the surrounding tissue of the nerve, oxidative stress, and apoptosis[3]. However, pathological calcification of cauda equina nerve is extremely rare.We speculate that cauda equina nerve calcification in this patient may be secondary to acute trauma and surgical scar, thus stimulating local lesions. In addition, lumbar spinal stenosis, lumbar disc herniation, spinal tumors and spinal infection are also possible causes of cauda equina nerve calcification[4]. L2-5, S1-5 and the 10 pairs of nerve roots emanating from their caudal segments together form the cauda equine nerve. The cauda equina nerve, in the usual sense, is the nerve root below L2 that innervates the pelvis as well as the perineum. It is a very important nerve in the human body[5]. Once the cauda equina nerve undergoes pathological changes, it will lead to dysfunction of sensory nerve, motor nerve, autonomic nerve, *etc.*, thus causing

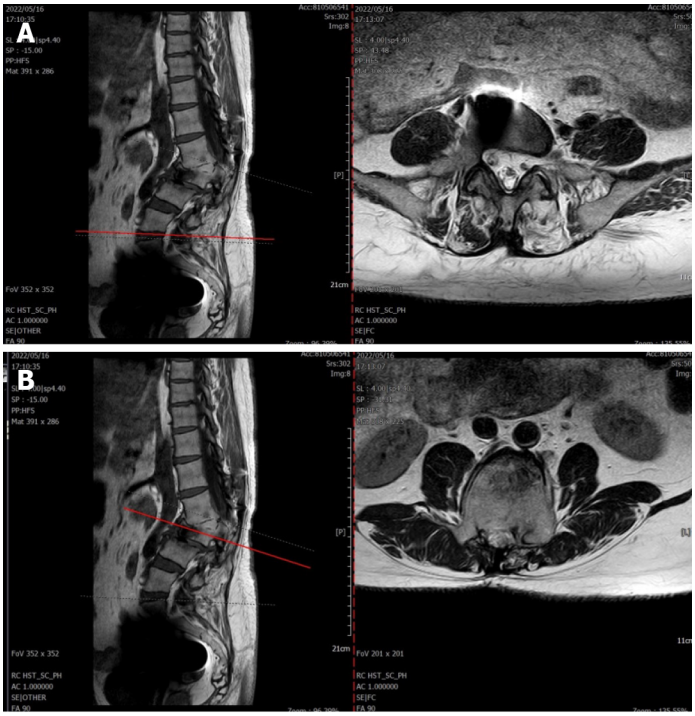

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Figure 5 The lumbar spine magnetic resonance imaging. Lumbar vertebrae protrude backward, L3 vertebrae show wedge-shaped changes, spinal canal stenosis on the same level of L3, intervertebral space narrowing on the same level of L2-3, endplate inflammation in the L3-4 intervertebral space, Schmorl node formation near T10-11 vertebral body, degeneration and bulge of L3-4, L4-5 and L5-S1 intervertebral discs, and many abnormal strip signals in the filum terminale. A: L5-S1 Plain magnetic resonance imaging (MRI) scan of L5-S1 intervertebral disc; B: L3 MRI plain scan.

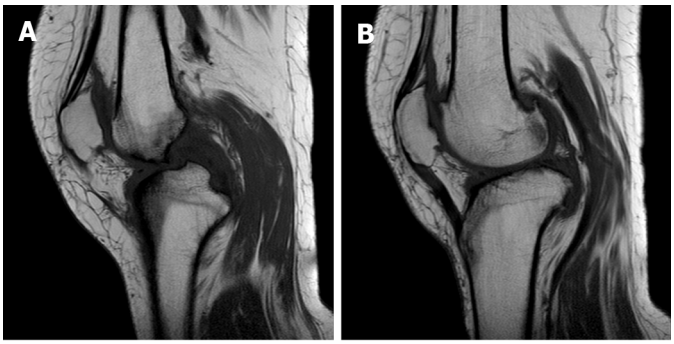

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Figure 6 The right knee magnetic resonance imaging. The cartilage of the medial femoral condyle and tibial plateau is worn, the cartilage is denatured, the posterior cruciate ligament of the right knee is torn, the medial collateral ligament is injured, the anterior and posterior corners of the medial and lateral meniscus of the right knee are worn, the right knee joint has effusion, and the medial head bursa of the gastrocnemius has effusion. A: Lateral magnetic resonance imaging (MRI) of knee; B: Oblique MRI of knee.

other body dysfunction. as opposed to the cauda equina nerve calcification, Cauda equina injury is relatively common in clinical practice[6]. The clinical symptoms of cauda equina compression were first reported by Verbiest in 1949 and were named Cauda Equine Syndrome (CES). The clinical symptoms of cauda equina nerve injury mainly include Low back pain, numbness of one or both lower limbs, weakness of lower limbs, weakness or disappearance of tendon reflex, sensory abnormalities in the sellar region, sphincter dysfunction, urinary incontinence, and sexual dysfunction. The cauda equina nerve is easy to be damaged (for example, the free nucleus pulposus and epidural hematoma will cause the cauda equina nerve to be compressed), because the cauda equina nerve has no protective sheath of connective tissue and is particularly sensitive to compression. The recovery after peripheral nerve injury is very slow, which may be due to the lack of blood supply. The nutrition of cauda equina nerve also comes from cerebrospinal fluid and blood, and the recovery of cauda equina nerve after injury is slower than that of peripheral nerve. Therefore, we can boldly speculate that the mechanism of cauda equina nerve calcification may be that the surrounding tissues of cauda equina nerve suffer from mechanical compression or tissue necrosis, which affects the blood supply of cauda equina nerve. Due to long-term

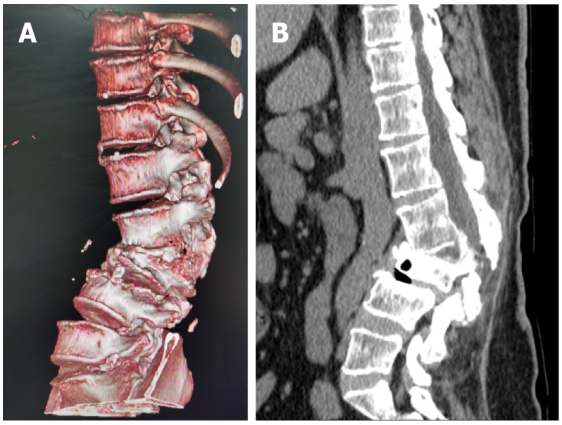

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Figure 7 Lumbar vertebral body (plain scan + 3D reconstruction) computed tomography. Lumbar vertebral body (plain scan + 3D reconstruction) computed tomography (CT) showed: L2-3 plane lumbar lordosis, L2-3 vertebral space narrowing, L3 vertebral body wedge-shaped flattening, L3, 4 vertebral body adjacent edge patchy high density. There are some bone defects in the lamina and spinous process of L3 and L4 vertebrae, and the vertebral canal at the same plane is deformed. A: Lumbar vertebral body CT (3D reconstruction); B: Lumbar vertebral body CT (plain scan).

poor blood supply, nerve dehydration and poor calcium and phosphorus metabolism lead to calcium salt deposition, which eventually leads to cauda equina nerve calcification[7,8].

There are many reports on Idiopathic Basal Ganglia Calcification (IBGC) in the existing literature, but the specific cause is still unclear, and scholars believe that it is related to the following factors: (1) Genetic studies show that IBCG patients have autosomal recessive or dominant inheritance; (2) Vitrification during atherosclerosis can lead to calcium deposition, so some scholars believe that local calcium accumulation is related to changes in vascular osmotic pressure; (3) The abnormal level metabolism of iron and calcium phosphate, especially the decrease of serum ferritin level and iron binding capacity, will also lead to IBGC; (4) Exogenous toxic substances continuously stimulate and activate glutamate receptor, thus producing neurotoxin effect, leading to calcium ion deposition; (5) It has been reported in the literature that during brain biopsy of patients with IBGC, there are immune inflammatory cells infiltrating around calcification points and ESR is accelerated, while C-reactive protein, rheumatoid factor (RF) and antinuclear antibody (ANA) are significantly increased. So the occurrence of IBGC is also related to the immune system. It is worth noting here that the ESR, C-reactive protein, RF and ANA of the cases reported by us are higher than the normal values. This is consistent with the study of IBCG; and (6) The IBCG has also been suggested to be associated with carbonic anhydrase II deficiency. Regrettably, the epidemiological characteristics and specific treatment methods of basal ganglia calcification have not been studied[9,10,11].

The benign tumor of the cauda equina nerve may also lead to the calcification of the cauda equina nerve. We call this benign tumor the neurilemmoma of the cauda equina nerve. spinal cord neurilemmoma often occur in the spinal cord nerve roots, but only a few occur in the cauda equina nerve. Because the neurilemmoma of the cauda equina nerve has good activity and broad intradural space, it usually has no obvious pain symptoms. The report of neurilemmoma calcification is extremely rare. In 2012, Dr. Seung Jae Hyun and others from South Korea reported that a 21 year old patient with dystrophic neurilemmoma of cauda equina had calcification, and the neurilemmoma was completely removed by surgery. However, this report does not explain the relationship between trauma and calcification of cauda equina neurilemmoma[12]. Paraganglioma is a neuroendocrine tumor located outside the adrenal gland. Paragangliomas originating from filum terminale or cauda equina nerve are rare (accounting for 1% of all paragangliomas and 3%-4% of all tumors in the lower lumbar spine). Calcification of cauda equina nerve paraganglioma is very rare. It is noteworthy that Professor M Vural once reported cauda equina paraganglioma with obvious calcification characteristics, but did not clarify its cause and pathogenesis[13]. Professor J Rot é s Querol once reported a case of cauda equina syndrome caused by ankylosing spondylitis, which caused calcification of lumbosacral meninges. However, the CT images of the cases reported by Professor J Rot é s Querol showed perispinal calcification rather than central calcification[14]. Intradural lumbar disc herniation is another important cause of intraspinal calcification and even cauda equina nerve calcification. Intradural lumbar disc herniation means that the free nucleus pulposus punctures the fibrous ring, posterior longitudinal ligament and dura mater, and directly compresses the spinal cord or nerve after entering the subdural cavity, resulting in acute spinal cord or cauda equina nerve injury. Intradural disc herniation is a rare type of disc herniation, with a incidence rate of 0.26%-0.3%. The most common location of the disease was the lumbar spine, accounting for 92%[15]. Surgical exploration is the only standard for the diagnosis of intradural lumbar disc herniation. Although it is difficult to make a definite diagnosis of intradural lumbar disc herniation through imaging and symptoms, some special signal signs shown by

imaging data can well indicate the existence of free intradural nucleus pulposus. For example, the Y sign refers to the prominent nucleus pulposus separating the dura and arachnoid membranes into two lines in a "Y" shape. Over time, the free nucleus pulposus entering the dura will directly compress the cauda equina nerve and calcification will occur to some extent[16]. We speculate that the calcification of the free nucleus pulposus will probably cause the calcification of the cauda equina nerve compressed by it.

Since cauda equina nerve calcification in this patient is secondary to trauma stress, it is necessary to discuss arachnoiditis during injury. There are also some literatures that study the problems related to cauda equina nerve calcification from this perspective. In 1999, I. G. Bilgen reported a case of cauda equina syndrome caused by ankylosing spondylitis, a patient with adhesive arachnoiditis. CT data of the patient showed signs of dural calcification.His MRI data showed that the cauda equina had adhesions with the dorsal arachnoid membrane. They believe that arachnoiditis is responsible for cauda equina syndrome and curvilinear dural calcification[17]. In 2021, Brunner A *et al*[18] introduced a case of intradural calcification caused by chronic adhesive arachnoiditis and performed a dural incision exploration, and found nerve calcification structures in the dural sac. Brunner A *et al*[18] believed that the main cause of calcification was the inflammation of arachnoid membrane. Arachnoid inflammation leads to excessive proliferation of arachnoid cells, which leads to excessive production of collagen tissue and rapid formation of intradural scars. Subsequently, osteoblasts are generated, leading to progressive intradural ossification. However, the pathogenesis of ossifying arachnoiditis has not been completely clarified. El Asri AC *et al*[19] reported a rare case of post-traumatic Arachnoiditis ossifi cans of the cauda equina nerve. El Asri AC *et al*[19] clearly proposed that trauma, surgery, infection and subarachnoid hemorrhage are the main causes of post traumatic arachnoiditis ossifi cans of the cauda equina nerve.

Since cases of Post-traumatic cauda equina nerve calcification are extremely rare in clinical practice, our research on this disease has not been carried out and the literature that we have been able to study is very scarce. Therefore, it is necessary that we carry out studies on the etiology, mechanisms, treatment and prognosis of this disease.

CONCLUSION

We provide a rare case of Post-traumatic cauda equina nerve calcification. This case reports the symptoms, imaging data and treatment of a patient with Post-traumatic cauda equina nerve calcification, and analyzes the etiology and mechanism of Post-traumatic cauda equina nerve calcification.

FOOTNOTES

Author contributions: Liu YD, Deng Q, Li JJ, Zhang KD contributed to conceptualization; Liu YD, Li JJ, Peng RD contributed to data curation and investigation; Deng Q conducted the project administration; Liu YD, Han XF, Yang HY and Xiang QQ wrote the original draft, and reviewed and edited the manuscript; all authors issued final approval for the version to be submitted.

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CASE REPORT

Endometriosis-associated endometrioid adenocarcinoma of the fallopian tube synchronized with endometrial adenocarcinoma: A case report

Jian-Yang Feng, Qing-Ping Jiang, Hong He

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Abstract

BACKGROUND

Endometriosis is a common gynecological disorder that affects women of reproductive age. It is characterized by a cancer-like invasion of the extra-uterine endometrium and exhibits a strong association with ovarian clear cell cancer and endometrioid cancer. Endometriosis-associated fallopian tube endometrioid adenocarcinoma synchronized with endometrial adenocarcinoma was rarely reported.

CASE SUMMARY

A 49-year-old woman was referred to our hospital complaining about abnormal vaginal bleeding for three years following unsatisfactory medication. Intraoperative frozen sections unexpectedly unveiled an endometrioid cancer of the left fallopian tube with superficial invasion surrounded by diffuse endometriosis synchronized with endometrioid endometrial cancer.

CONCLUSION

It was difficult to make a differential diagnosis when confronted with incidental findings of fallopian tube cancer lesions synchronized with endometrial cancer. The key differential diagnosis of primary endometriosis-associated endometrioid adenocarcinoma of the fallopian tube from endometrial adenocarcinoma involvement relies on the pathological identification of malignant transformation in fallopian tube endometriosis disease.

Key Words: Endometriosis-associated cancer; Fallopian tube neoplasms; Endometrial neoplasms; Case report

Core Tip: The key to distinguishing primary endometriosis-associated fallopian tube cancer from fallopian tube involvement in endometrial cancer was the pathological identification of malignant transformation in endometriosis-associated fallopian tube tumors.

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INTRODUCTION

Endometriosis is a common gynecologic, estrogen-dependent, and benign chronic inflammatory disease caused by ectopic endometrial-tissue infiltration with three heterogeneous phenotypes (superficial endometriosis, ovarian endometrioma, and deep infiltrating endometriosis)[1]. Possible causes for endometriosis involve retrograde menstruation, pre-existing endometrial abnormalities, and inflammatory factors[1,2]. There is evidence for endometriosis exhibiting a potential for malignant transformation, and that this change can constitute a precursor lesion of ovarian clear cell cancer and endometrioid cancer[3,4]. However, the mechanism(s) underlying the carcinogenesis of endometriosis requires further elucidation. According to the most recent staging system of the International Federation of Gynecology and Obstetrics (FIGO), fallopian tube involvement of endometrial cancer should be staged as FIGO IIIa, while synchronized primary endometrial cancer and primary fallopian cancer should be staged respectively. Under some circumstances, however, it is difficult to make a differential diagnosis, *e.g.*, when confronted with incidental findings of fallopian tube cancer lesions synchronized with endometrial cancer. It was therefore critical to our case to identify the origin of the cancerous lesion, and thus contribute to the determination of cancer stage and post-operative therapeutic options. This report was approved by the hospital ethics committee (approval number: 2022-009).

CASE PRESENTATION

Chief complaints

A 49-year-old woman, gravida 1 and para 0, complained about abnormal vaginal bleeding for three years.

History of present illness

Her last menstrual period had been 2019-2-19, and her bleeding during it was slight, irregular, and intermittent. Bleeding began during the menstrual interval and lasted for a short period without other concomitant symptoms. She was prescribed 10 mg of dydrogesterone twice a day for 10–14 days to relieve symptoms for a few months, but the results were unsatisfactory. Transvaginal sonography indicated a 22.0-mm thick endometrium with a non-homogeneous echo pattern, and further diagnostic curettage was then performed. The pathology report ultimately identified local, atypical complex hyperplasia of the endometrium.

History of past illness

There was no other illness in previous medical history.

Personal and family history

We noted no exceptional other personal and family history.

Physical examination

Physical examination showed that her BMI was 27.89 kg/m^2 (weight, 67 kg; height, 155 cm), and bimanual palpation showed an active and painless mass of approximately 40.0 mm at the left adnexa with no other positive findings.

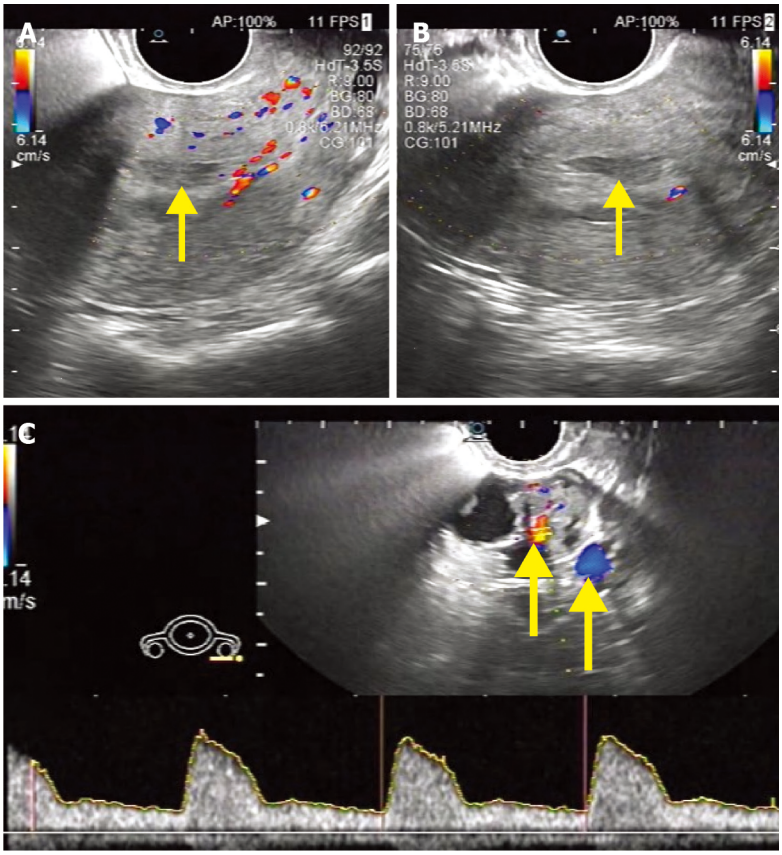

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Figure 1 Transvaginal ultrasonographic examination of the uterine cavity and fallopian tube. A and B: Transvaginal sonography indicates a mixed lesion (A–B) with a non-homogeneous echo (yellow arrow) in the uterine cavity and a solid cyst (yellow arrow) (C) of the left adnexa; both lesions are accompanied by a rich blood flow. A low resistance index (RI, 0.78) and high arterial spectrum (Vmax, 26 cm/s) of the left adnexal mass (yellow arrow) are also detected.

Laboratory examinations

Laboratory tests indicated a hemoglobin level of 117 g/L (range, 115–150), and some serum tumor markers were unremarkable: CA125 of 17.0 u/mL (range, 0–47), CA153 of 7.2 U/mL (range, 0–20), CA199 of 15.51 U/mL (range, 0–43); however, HE4 (110.4 pmol/L; range, 29.3–68.5) was slightly increased. Liver, kidney, and coagulation functions were negative, and the liquid-based cytology and high-risk HPV tests were negative.

Imaging examinations

Transvaginal ultrasonography revealed a uterine volume of 63.0 mm × 51.0 mm × 58.0 mm, a mixed lesion (33.0 mm × 14.0 mm) with a non-homogeneous echo in the uterine cavity, and a solid cystic mass (50.0 mm × 29.0 mm) of the left adnexa (Figure 1A-C).

A pathological review at our hospital suggested that the mass of the uterine cavity was a local, atypical, and complex endometrial hyperplastic lesion.

FURTHER DIAGNOSTIC WORK-UP

The patient had no desire to preserve her uterus and a malignant endometrial lesion had not been completely excluded within the context of a local, atypical, and complex endometrial hyperplastic lesion. After completing the preoperative examination to exclude operative contraindications, laparoscopic surgery was scheduled with full informed consent. Surgical exploration displayed a distorted and thickened left hydrosalpinx (50.0 mm × 40.0 mm) with a blocked end (Figure 2A). When we viewed the serous-membrane surface of the left fallopian tube we observed no suspected lesions, and we also suspected there were none in the left ovary, right adnexa, or the surface of the uterine body. Total hysterectomy and bilateral salpingo-oophorectomy were then performed. We thus uncovered incidental cauliflower lesions and fish-like exogenous lesions filled with a feculent liquid in the left tube by sectioning the lesions intraoperatively (Figure 2B) and found an ulcerous lesion of the endometrium (20.0 mm × 10.0 mm) in the left uterine horn (Figure 2C). Frozen sections unexpectedly unveiled a left fallopian tube endometrioid cancer with superficial myometrial invasion surrounded by diffuse

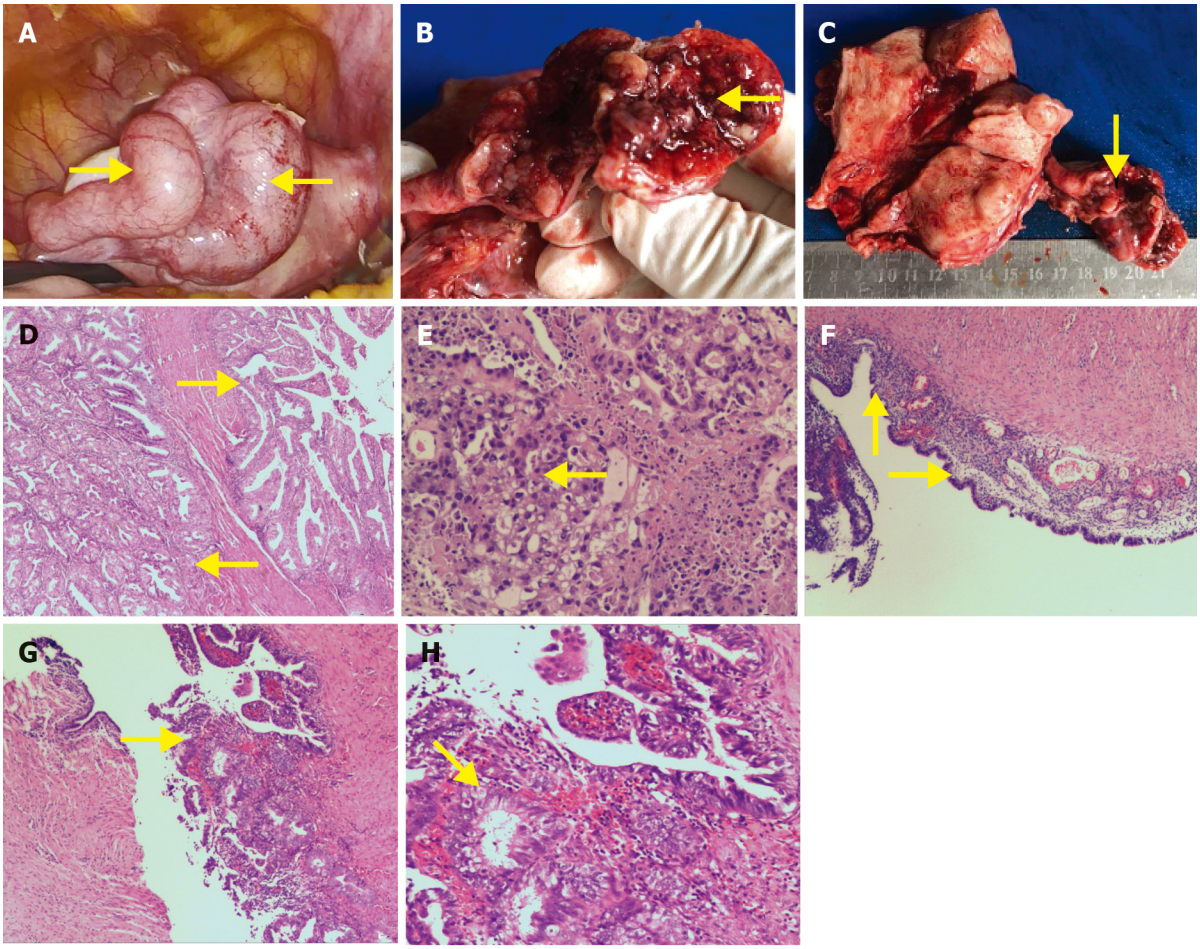

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Figure 2 Fallopian tube endometrioid adenocarcinoma arising from endometriosis synchronized with endometrial endometrioid adenocarcinoma. A: A distorted and thickened left hydrosalpinx (50.0 mm × 40.0 mm) with a blocked end (yellow arrow) was seen during laparoscopic exploration; B: Diffuse, cauliflower, and fish-like exogenous cancerous lesions (yellow arrow) were filled with feculent liquid in the left fallopian tube; C and D: The endometrioid adenocarcinoma in the uterus was grade 1, with a myometrial invasion of less than 50% (Hematoxylin-eosin Staining, HE, ×100, yellow arrow); E: Endometrioid adenocarcinoma of the fallopian tube (HE, ×100, yellow arrow); F: The endometriotic area in the mucosa of the left fallopian tube (HE, ×100, yellow arrow); G and H: The transitional area from endometriosis to atypical hyperplasia in the left fallopian tube (G, HE, ×100; H, HE, ×200, yellow arrow).

endometriosis synchronized with endometrioid endometrial cancer. We then implemented complete staging surgery, including bilateral pelvic and para-aortic lymphadenectomy.

Final paraffin pathology confirmed a well-differentiated endometrial endometrioid adenocarcinoma (EEA) derived from the uterine fundus with myometrial invasion of less than 50% (Figure 2D), positive left parametrial metastasis, and negative lymphovascular space involvement or pelvic and para-aortic lymphadenopathy. We also simultaneously diagnosed an endometriosis-associated endometrioid adenocarcinoma of the left fallopian tube (Figure 2E) and detected a transitional area from the endometriosis to the atypical hyperplasia to endometrioid adenocarcinoma in the left fallopian tube (shown in Figure 2F, 2G, and 2H). These two cancerous lesions also shared similar expression patterns for ER-α, PR, P53, Ki-67, PTEN (Figure 3A and 3C), PAX2 (Figure 3B and 3D), WT-1, MLH1, MSH2, MSH6, and PMS2 upon immunohistochemical examination.

FINAL DIAGNOSIS

After discussion by a multi-disciplinary team, we concluded it was a simultaneous FIGO I stage endometriosis-associated fallopian tube endometrioid adenocarcinoma and FIGO IIIb stage EEA.

TREATMENT

Since a high-risk clinicopathological factor–positive left parametrial metastasis was identified,

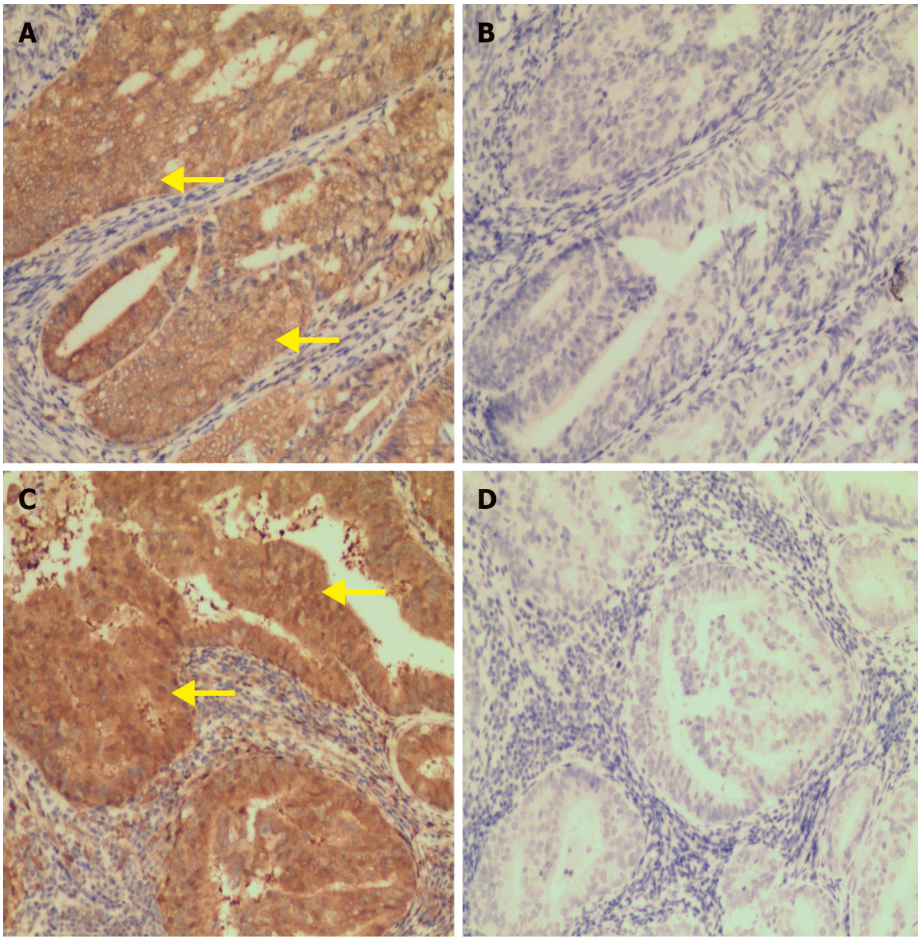

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Figure 3 PTEN and PAX2 expression patterns in endometrial and fallopian tube endometrioid adenocarcinoma. Both endometrial- and fallopian-tube endometrioid adenocarcinoma showed the same model for positive expression of PTEN (A and C, IHC, ×100, yellow arrow) and loss of expression of PAX2 (B and D, IHC, ×100).

postoperative adjuvant pelvic external beam radiotherapy and brachytherapy were prescribed.

OUTCOME AND FOLLOW-UP

Postoperative routine follow-up was performed. The results of postoperative dynamic HE-4 examination, vaginal stump cytology, and pelvic and abdominal sonography were negative. There was no evidence of recurrence in the subsequent three years.

DISCUSSION

Endometriosis is a condition in which functional endometrial tissue is present outside the uterus, and it is associated with an increased risk of ovarian and endometrial cancer[5]. Endometriosis is often confined to the pelvic cavity and principally involves the ovary, ovarian ligaments, cul-de-sac, and uterovesicular peritoneum; however, with a preoperative diagnosis of endometriosis in patients undergoing laparoscopic surgery, the incidence of fallopian tube endometriosis was 3.8%–12% macroscopically and 37.4–42.5% microscopically[6]. The most common histological subtype of malignant transformation in endometriosis is clear cell cancer, followed by endometrioid adenocarcinoma[7], with age-adjusted incidence ratios of 2.29 [95% confidence interval (CI): 1.24–4.20] for ovarian clear-cell cancer and 2.56 (95%CI: 1.47–4.47) for endometrioid ovarian cancer[8]. Importantly, the incidence of microscopic fallopian tube endometriosis among patients with histologically diagnosed endometriosis was significantly higher than in those manifesting macroscopic disease (42% *vs* 11%–12%, respectively)[6]. Ectopic endometriotic lesions are, in theory, estrogen-dependent and can invade the stroma, demonstrating their potential for malignant transformation. However, the prognostic impact of endometriosis on endometriosis-associated cancers is elusive[7,9,10].

In this case, we first noted the marked evolutionary malignant transformation from fallopian tube endometriosis to atypical hyperplasia to endometrioid adenocarcinoma. We hypothesized that the stimuli required to promote the malignant transformation were non-ovarian-derived estrogen biosynthesized from adipose tissue *via* the steroid hormone metabolic pathway within an overweight background in our patient. The ectopic endometriotic lesions in the fallopian tube were obstructed by the blocked end of the fimbriae to be disseminated into the pelvic cavity, then they invaded the tubal myometrium, and were ultimately stimulated by estrogen to promote tumorigenesis. The endometrium was also similarly and persistently induced by estrogen to ultimately initialize carcinogenesis.

Second, according to the algorithms of Scully *et al*[11], the fallopian tube endometrioid adenocarcinoma with superficial myometrial infiltration was surrounded by atypical hyperplasia upon an endometriotic background, while the EEA showed less than 50% myometrial invasion without lymphovascular invasion or distant metastasis. Third, tumor biomarkers such as CA125, CA153, and CA199 were unremarkable, while only HE4 was slightly elevated, which was inconsistent with endometrial cancer accompanied by fallopian tube metastasis. These pathological and clinical characteristics supported both fallopian tube and endometrial cancer occurring independently. We consequently proposed that the tumorigenesis in both the fallopian tube and endometrium was contemporaneous.

CONCLUSION

In clinical practice, making a differential diagnosis of concurrent primary cancer of the fallopian tube and endometrium from fallopian metastasis of endometrial cancer, which involves post-adjuvant treatment decisions and oncologic outcomes, is challenging. Using Scully algorithms, we might be able to make a proper differential diagnosis when confronted with concurrent cancers derived from multiple sites of the female genital tract. In this case report, we demonstrated a concurrent endometriosis-associated endometrioid cancer of the fallopian tube and primary endometrial cancer in a premenopausal woman. Fortunately, the pathological identification of malignant transformation in the fallopian endometriosis lesion led to distinct differentiation from primary endometrial cancer dissemination.

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CASE REPORT

Gemcitabine-induced peripheral vascular disease and prolonged response in a patient with metastatic pancreatic adenocarcinoma: A case report

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Abstract

BACKGROUND

Gemcitabine is an antimetabolite used in the treatment of pancreatic cancer. One of the side effects of gemcitabine is vascular toxicity. Here, we report the case of a patient treated with gemcitabine who had peripheral vascular disease concomitant with a prolonged antitumor response.

CASE SUMMARY

A 75-year-old man was diagnosed with locally recurrent pancreatic cancer. Partial response was achieved after 9 mo of gemcitabine. At the same time, the patient reported peripheral vascular disease without necrosis. Chemotherapy was suspended, and after one month the Positron Emission Tomography (PET) scan showed locoregional tumor recurrence. Gemcitabine was resumed and partial response was obtained, but peripheral vascular disease occurred.

CONCLUSION

Our results suggest that the appearance of peripheral vascular disease may be related to a prolonged response to gemcitabine.

Key Words: Gemcitabine; Pancreatic cancer; Peripheral vascular disease; Prolonged tumor response; Case report

Core Tip: Gemcitabine is known for vascular side effect. In this case, we report a vascular acrosyndrome that occurred during first-line with Gemcitabine for pancreatic adenocarcinoma. In this case, the patient experienced prolonged tumor response. Immunological phenomena could be responsible for this double effect.

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INTRODUCTION

Gemcitabine is a nucleoside metabolic inhibitor. This antimetabolite drug has displayed significant antitumor activity in pancreatic adenocarcinoma[1]. Gemcitabine causes often myelosuppression, influenza-like syndrome and vascular toxicity[2]. Among toxic vascular effects of gemcitabine, we find venous and arterial events, digital ischemia and necrosis, vascular inflammation, and thrombotic microangiopathy. We report a case of locoregional recurrent pancreatic adenocarcinoma in a patient treated with gemcitabine who experienced severe peripheral vascular disease and prolonged antitumor response.

CASE PRESENTATION

Chief complaints

A 75-year-old man presented with a diagnosis of borderline adenocarcinoma of the pancreatic body in April 2019.

History of present illness

In July 2021, during Gemcitabine, the patient reported the appearance of Raynaud's phenomenon-like symptoms.

History of past illness

For borderline adenocarcinoma of the pancreatic body, he underwent neoadjuvant chemotherapy by FOLFIRINOX (12 cycles) with stable disease. He underwent pancreaticoduodenectomy in January 2020 (ypT2N2R1). A PET scan showed locoregional recurrence during a follow-up in August 2020 (Figure 1). In accordance with ESMO guidelines, chemotherapy with gemcitabine was initiated. Partial objective response was observed after 9 mo and gemcitabine was continued as maintenance therapy (Figure 1).

Personal and family history

A 75-year-old man had a history of smoking (15 pack-year), and stopped in 1976. He was treated with verapamil for hypertension and with tinzaparine for a deep vein thrombosis of the lower left extremity since 2019.

Physical examination

The symptoms consisting of loss of sensitivity and cold-induced cyanosis of the left middle finger matching with a typical syncopal phase of the Raynaud's phenomenon. Other arguments in favor of this phenomenon were sparing of the thumb and absence of digital pulp ulceration. Allen's test showed pathological results at the radial and ulnar levels. There were no megacapillaries or flame hemorrhage, cupuliform ulceration, or rectangular telangiectasia. There was no toe involvement.

Laboratory examinations

Laboratory analyses showed normal hemogram, electrolytes, creatinine, liver function, and hemostasis. C3- and C4-complement, cryoglobulin, ANCA and CPK did not show any abnormality. Anti-extractable nuclear antigen antibodies and antinuclear antibody (ANA) were negative. The specific absence of anti-Scl70 or anti-centromere antibodies was noted. Other antiphospholipid antibodies were not detected either.

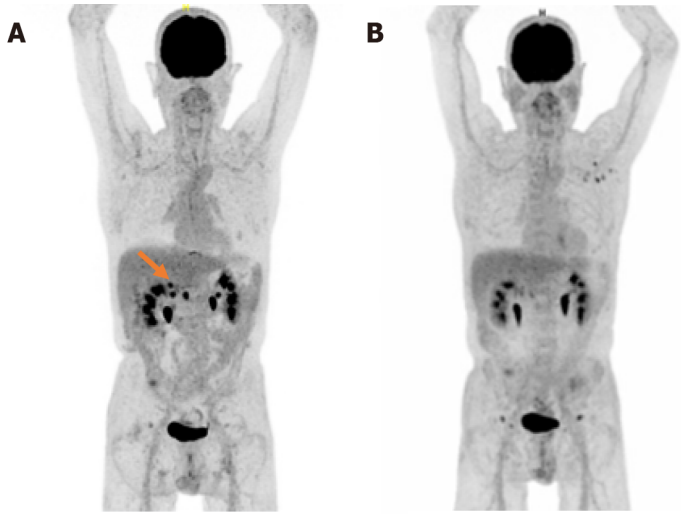

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Figure 1 A positron emission tomography scan with fluorodeoxyglucose F 18. A: Locoregional recurrence in August 2020; B: Partial response in May 2021.

Imaging examinations

An arterial and venous Doppler ultrasound found no abnormality.

FINAL DIAGNOSIS

At the patient's request, chemotherapy was suspended for 4 wk after the onset of symptoms. Paraneoplastic syndrome was initially suspected. PET scan in August 2021 showed locoregional tumor recurrence coincident with an elevation of CA 19-9 blood level at 893 ng/mL. Weekly gemcitabine chemotherapy was consequently resumed, and partial response was obtained after 3 mo of chemotherapy. CA 19-9 blood levels gradually decreased to 380 ng/mL. Gemcitabine was eventually interrupted in December 2021 after 13 cycles because of resurgence of the vascular acrosyndrome (permanent cyanosis and pain) then affecting the distal phalanx of both left and right 2nd and 3rd fingers (Figure 2) and causing great repercussions on daily activities. Symptoms showed little to no improvement after 2 mo with the appearance of ulceration of the 3rd digits (Figure 3). A Doppler echocardiography showed no macrovascular abnormalities but capillary microscopy revealed impaired microcirculation.

TREATMENT

The patient was then referred to the cardiovascular department where a treatment with iloprost (prostacyclin analog) was introduced for a duration of 28 days.

OUTCOME AND FOLLOW-UP

We noticed clinical improvement after 1 mo of treatment, and the disappearance of the ulceration (Figure 3). Gemcitabine was not resumed and disease progression was observed on the March 2022 CT scan. The patient died in June 2022.

DISCUSSION

In the present study, we report a case of metastatic pancreatic adenocarcinoma in a patient presenting with peripheral vascular disease that occurred during first-line chemotherapy. The vascular symptoms improved after discontinuation of gemcitabine. In this case, the patient experienced prolonged tumor response. The median survival time was 5.6 mo in historical studies using gemcitabine. Here, the patient showed no sign of progressive disease 17 mo after treatment initiation. Cases of Raynaud's

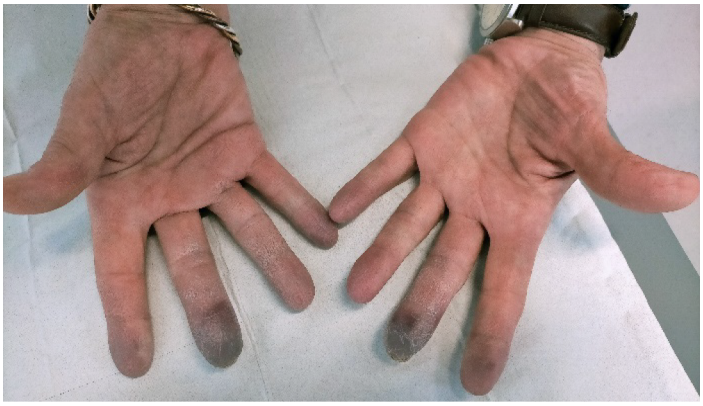

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Figure 2 Peripheral vascular disease affecting distal phalanx of both left and right, second and third fingers.

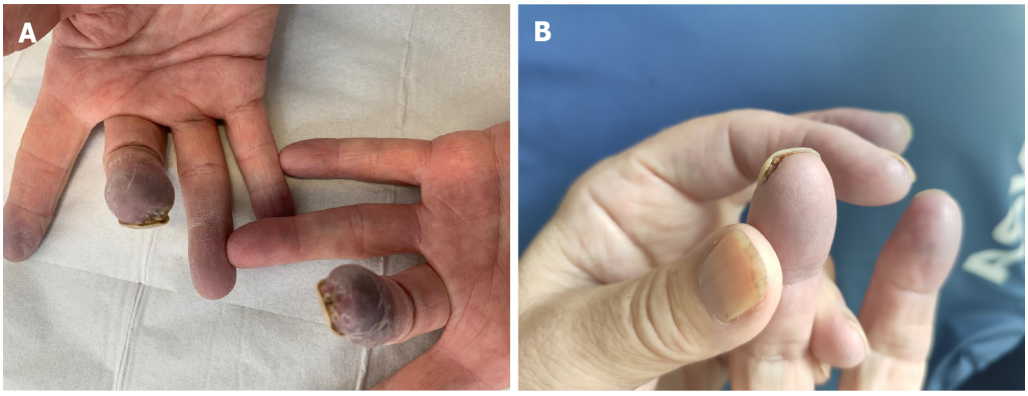

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Figure 3 Evolution of ulcerations with treatment. A: Ulceration of the third digits on both hands; B: Clinical improvement after treatment with iloprost.

phenomenon and digital necrosis after receiving gemcitabine for bladder cancer and lung cancer have been reported[3-6]. Three cases of Raynaud's phenomenon and/or digital ischemia have also been described in patients with pancreatic cancer[6-8]. Peripheral vascular disease is a rare and painful condition that impairs the patient quality of life. The most frequent etiologies are connective diseases, vasculopathies, hematological diseases, paraneoplastic syndromes, drugs, infectious diseases, and embolic diseases. They can all be complicated by secondary vasospasm[9]. In this case, we discuss the multifactorial mechanisms underlying peripheral vascular disease, aggravated by the administration of antimetabolites, and the relationship to the associated better outcomes.

Antimetabolites can have cumulative toxicity leading to endothelial dysfunction and hypercoagulability. Several chemotherapies can induce endothelial lesions or cause thromboembolic events[10-15].

Many vascular side effects have been reported in the literature as related to gemcitabine treatment. We note venous and arterial events, vasculitis with necrosis, thrombotic microangiopathy, severe capillary leak syndrome, and digital necrosis[5,6,16,17]. Here, chemotherapy was stopped, resulting in the improvement of symptoms despite cancer progression. The occurrence of peripheral vascular disease in patients with cancer can also be considered a paraneoplastic disorder, natably in the case of adenocarcinoma, squamous cell carcinoma or hematological diseases[18]. Several mechanisms have been proposed to explain peripheral vascular disease associated with cancer. It is suggested hypothesis a peripheral vasospasm or larger production of vasoconstrictor substances by tumor cells following neoplastic involvement of the cervical sympathetic trunk[19]. A thromboembolic mechanism with either migration of tumor fragments or hyperviscosity, hypercoagulability and spontaneous platelet aggregation has also been suggested[20]. In many case-report of patients with paraneoplastic peripheral vascular disease, vasospastic complications improve after initiation of suitable anticancer treatment[21]. For our patient, this etiology was unlikely to be the cause of the patient's digital manifestations, as he had an radiologic response at the time of symptoms worsening.

The hypothesis immunological's mechanism has also been suggested. In fact, cancer diseases can promote autoimmunity by generating autoantibodies against different autoantigens, leading to the activation of the complement upon contact with the arterial wall[22].

The association between toxicity and treatment efficacy has long been a concern in cancer patients. Better outcomes associated with immune-related adverse events is well described in cancer patients treated with immunotherapy. For example, vitiligo is significantly correlated with a better outcome to ICI in melanoma[23].

The restoration of antitumor immunity during treatment with immunotherapy leads to multiples manifestations, including vasculitis of the medium and large vessels but rarely of the small vessels[24]. Several recent studies have described the development of acral vascular necrosis with immunotherapy, without history of autoimmune disease[25,26]. The mechanism of action of immunotherapy could lead to a disturbance of immune tolerance with stimulation of T population of lymphocytes or to the formation of autoantibodies against many antigens such as endothelial cells and be at the origin of the disorder's vascularization. Additionally, an autoimmune etiology of digital ischemic symptoms during treatment of immunotherapy is supported, as a steroids treatment might improve acral necrosis[27,28].

One study postulated that antimetabolites induced both vascular and immunological adverse effects and prolonged response as shown with ICI[29]. Gemcitabine has the capacity to activate the immune system and create an inflammatory tumor microenvironment[30,31]. In particular, it depletes regulatory T lymphocytes and selectively kills immunosuppresive cells, thereby alleviating immunosuppression and enhancing cytotoxic T-cell-dependent anti-cancer immune responses[32].

CONCLUSION

Peripheral vascular disease is a rare complication of antimetabolite chemotherapeutic drugs. This is the second study to report the case of peripheral vascular disease and prolonged response with gemcitabine. Immunological phenomena could be responsible for this double effect.

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FOOTNOTES

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CASE REPORT

Epidemic Japanese B encephalitis combined with contactin-associated protein-like 2 antibody-positive autoimmune encephalitis: A case report

Pan Huang

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Abstract

BACKGROUND

It is not uncommon to develop viral encephalitis. Epidemic Japanese B encephalitis infection combined with contactin-associated protein-like 2 (CASPR-2) antibody-positive autoimmune encephalitis has not been reported at present. In clinical work, we need to consider more options.

CASE SUMMARY

A 32-year-old male worker presented with headache, fever and call-unresponsive presentation. Complete cranial magnetic resonance image showed symmetrical abnormal signals in bilateral medial temporal lobe, bilateral thalamus and basal ganglia. Improved lumbar puncture showed that cerebrospinal fluid protein and cell count increased significantly. Viral encephalitis was considered, and the patient's consciousness still increased rapidly after antiviral treatment. Further detection of Cerebrospinal fluid Japanese B encephalitis virus Polymerase Chain Reaction positive, serum autoimmune encephalitis antibody showed CASPR-2 antibody positive (1:320), the patient's condition gradually improved after plasma exchange treatment. 3 mo later, the serum CASPR-2 antibody was negative and the patient's condition was stable.

CONCLUSION

This article reports the world's first case of Epidemic Japanese B encephalitis infection combined with CASPR-2 antibody-positive autoimmune encephalitis, with a view to raising awareness.

Key Words: Epidemic Japanese B encephalitis; Contactin-associated protein-like 2 antibody; Autoimmune encephalitis

Core Tip: For viral encephalitis in summer, there is no significant improvement after antiviral treatment, so the possibility of Japanese B encephalitis and autoimmune encephalitis should be considered.

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INTRODUCTION

Epidemic Japanese B encephalitis is a disease of the central nervous system caused by Japanese encephalitis virus. Due to the birth of a vaccine, this disease is relatively rare. Autoimmune encephalitis is a type of encephalitis caused by an immune response directed against central nervous system antigens mediated by autoimmune mechanisms. contactin-associated protein-like 2 (CASPR-2) antibody-positive autoimmune encephalitis is currently clinically rare and only a few cases have been reported. This article reports the world's first case of Epidemic Japanese B encephalitis infection combined with CASPR-2 antibody-positive autoimmune encephalitis, with a view to raising awareness.

CASE PRESENTATION

Chief complaints

A male patient, 32 years old, a worker, was admitted to the hospital due to headache, fever for 7 d and unconsciousness for 1 d.

History of present illness

7 d before admission, the patient developed headache and fever after cold (the patient was poorly conscious at the time of admission and could not describe the nature and location of the headache), with a maximum body temperature of 42 degree Celsius, accompanied by chills, no nausea and vomiting, abdominal pain, diarrhea, incontinence, and limb The convulsions were treated at the local hospital but no significant improvement was seen. The patient's condition worsened 1 d before admission, and began to grab clothes and sheets, and gradually developed to be unresponsive. The body temperature continued to exceed 39 degree Celsius. Considering the possibility of encephalitis, in order to further confirm the diagnosis "Infection" income department.

History of past illness

In the past, he suffered from asthma and improved after hormone therapy.

Personal and family history

The patient had no relevant personal or family history.

Physical examination

Body temperature 38.8 degree Celsius, pulse 84 times/min, breathing 22 times/min, blood pressure 137/50 mmHg. Sleepy, uncooperative physical examination, no autonomous speech, advanced intelligent activity examination cannot be performed. Double pupils and other large round shapes, about 3mm in diameter, light reflection is dull, conjunctival congestion and edema. No facial tongue paralysis, pharyngeal reflex exists. The muscle tension of the extremities increased, and there was avoidance during pain stimulation. The tendon reflexes of the extremities were normal (++), and the bilateral pathological signs were negative. Neck resistance was positive, 5 transverse fingers, and Glasgow Coma Scale was 8 points.

Laboratory examinations

At admission, C reactive protein was 52.68 mg/L, and the white blood cells were normal. Admitted to consider viral encephalitis, given acyclovir antiviral, dehydration and intracranial pressure treatment, the next day after admission, oxygen saturation decreased, consciousness deepened to coma, weak spontaneous breathing, bilateral pupils 4mm, light reflection disappeared, limb The cyanosis is cold and immediately transferred to intensive care unit (ICU) for tracheal intubation. A complete lumbar puncture examination during ICU treatment revealed cerebrospinal fluid protein 0.87 g/L, white blood cell counts 0.071 x 10^9/L, glucose 4.31 mmol/L, chloride 117.9 mmol/L, negative test for herpes simplex virus DNA and fungus, and deliver Cerebrospinal fluid and plasma autoimmune encephalitis antibody

profile. During the period of waiting for the results of autoimmune encephalitis, after receiving communication with the patient, he was given methylprednisolone 1000 mg qd intravenous drip shock combined with gamma globulin 25 g qd treatment. On the 8th day of admission, the patient's level of consciousness was reduced to lethargy, spontaneous eye-opening, and body temperature gradually decreased too normal. On the same day, the patient's delivery of autoimmune encephalitis antibody showed positive plasma CASPR-2 antibody (1:320), The cerebrospinal fluid was negative for CASPR-2 antibody (Figure 1A and B). At this point, the patient was considered to have CASPR-2 antibody encephalitis, and then plasma exchange was performed (the plasma volume was calculated according to 40 m/kg). A total of 4 plasma exchanges were performed on the next 7 d. After the above treatment, the patient's condition gradually improved and the ventilator treatment was discontinued.

Imaging examinations

After the patient's condition was stable, a head magnetic resonance image (MRI) examination revealed mild brain atrophy and abnormal symmetry signals in the medial temporal lobe, bilateral thalamus, and basal ganglia (Figure 2A-D).

FINAL DIAGNOSIS

Epidemic Japanese B encephalitis combined with CASPR-2 antibody-positive autoimmune encephalitis.

TREATMENT

Combined with the patient's head MRI image results and the onset time is summer, it is highly suspected to be Epidemic Japanese B encephalitis, Cerebrospinal fluid is sent to the disease control center, and after 5 d, the report is Japanese encephalitis. At this point, the diagnosis of Epidemic Japanese B encephalitis combined with CASPR-2 antibody-positive autoimmune encephalitis was clear. After the above comprehensive treatment, the patient's condition improved 42 d after admission and was discharged. The patient's consciousness and speech were clear when discharged, but the senior Knowing functional decline, limb strength is 5 grades, bilateral pathological signs are negative, and meningeal irritation signs are negative.

OUTCOME AND FOLLOW-UP

After discharge from the hospital, he was followed up in the outpatient clinic every month, and there were no fluctuations in his condition. After 3 mo, the serum and cerebrospinal fluid autoimmune encephalitis antibody CASPR-2 antibody turned negative (Figure 1C and D).

DISCUSSION

In recent years, autoimmune encephalitis has gradually attracted people's attention[1] . CASPR-2 is the main target antigen for the autoantibody of the voltage-gated potassium channel complex of neurons in and around the central nervous system The nervous system is expressed, so its clinical manifestations are central and peripheral nerve symptoms[2,3]. Peripheral nerve symptoms are due to neurological and muscle rigidity, muscle convulsions caused by overexcitation of peripheral nerves, such as Morvan syndrome and Isaacs syndrome[4,5], The central symptoms are often due to cognitive decline and seizures caused by the limbic system. The imaging findings of CASPR-2 antibody-positive autoimmune encephalitis are mainly manifested as abnormalities of the limbic system, accounting for about one-third of patients with positive findings on the head MRI. Compared with other types of encephalitis, the incidence of CASPR-2 antibody-positive autoimmune encephalitis is not high, about 3%, but the treatment effect is relatively significant[6,7]. The diagnostic criteria for CASPR-2 antibody-positive autoimmune encephalitis are as follows[8]: (1) Have anti-CASPR2 antibody positive; and (2) Rule out other possible causes such as: Morvan syndrome, primary central nervous system vasculitis, Rasmussen encephalitis, *etc.* In treatment, anti-CASPR2 antibody-positive autoimmunity is treated with high-dose corticosteroids (oral or intravenous), immunoglobulin, and/or plasma exchange as first-line treatment, while cyclophosphamide and rituximab are refractory cases's choice[9].

Epidemic Japanese B encephalitis is an acute zoonotic disease caused by Japanese encephalitis virus (JE virus). Epidemiology shows that there are currently 67900 new cases worldwide each year, of which about 50% occur in China, and the mortality rate is 25%-30%[10,11]. JE virus infection expands in peripheral tissues and enters the central nervous system, causing extensive central nervous system

A

Antibody Project (CSF)	Result
Anti-AMPA1 receptor antibody	Negative
Anti-AMPA2 receptor antibody	Negative
Anti-CASPR-2 antibody	Negative
Anti-GABAB receptor antibody	Negative
Anti-LGI1 antibody	Negative
Anti-NMDA receptor antibody	Negative
Anti-LgLON5 antibody	Negative
Anti-DPPX antibody	Negative
Anti-Gly1 receptor antibody	Negative
Anti-DRD2 receptor antibody	Negative
Anti-GAD65 antibody	Negative

B

Antibody Project (Serum)	Result
Anti-AMPA1 receptor antibody	Negative
Anti-AMPA2 receptor antibody	Negative
Anti-CASPR-2 antibody	Positive(1:320)
Anti-GABAB receptor antibody	Negative
Anti-LGI1 antibody	Negative
Anti-NMDA receptor antibody	Negative
Anti-LgLON5 antibody	Negative
Anti-DPPX antibody	Negative
Anti-Gly1 receptor antibody	Negative
Anti-DRD2 receptor antibody	Negative
Anti-GAD65 antibody	Negative

C

Antibody Project (CSF)	Result
Anti-AMPA1 receptor antibody	Negative
Anti-AMPA2 receptor antibody	Negative
Anti-CASPR-2 antibody	Negative
Anti-GABAB receptor antibody	Negative
Anti-LGI1 antibody	Negative
Anti-NMDA receptor antibody	Negative
Anti-LgLON5 antibody	Negative
Anti-DPPX antibody	Negative
Anti-Gly1 receptor antibody	Negative
Anti-DRD2 receptor antibody	Negative
Anti-GAD65 antibody	Negative

D

Antibody Project (Serum)	Result
Anti-AMPA1 receptor antibody	Negative
Anti-AMPA2 receptor antibody	Negative
Anti-CASPR-2 antibody	Negative
Anti-GABAB receptor antibody	Negative
Anti-LGI1 antibody	Negative
Anti-NMDA receptor antibody	Negative
Anti-LgLON5 antibody	Negative
Anti-DPPX antibody	Negative
Anti-Gly1 receptor antibody	Negative
Anti-DRD2 receptor antibody	Negative
Anti-GAD65 antibody	Negative

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Figure 1 Serum and cerebrospinal fluid antibodies to autoimmune encephalitis. A: Cerebrospinal fluid autoimmune encephalitis antibodies; B: Serum autoimmune encephalitis antibodies; C: Cerebrospinal fluid autoimmune encephalitis antibodies recheck after 3 mo; D: Serum autoimmune encephalitis antibodies recheck after 3 mo.

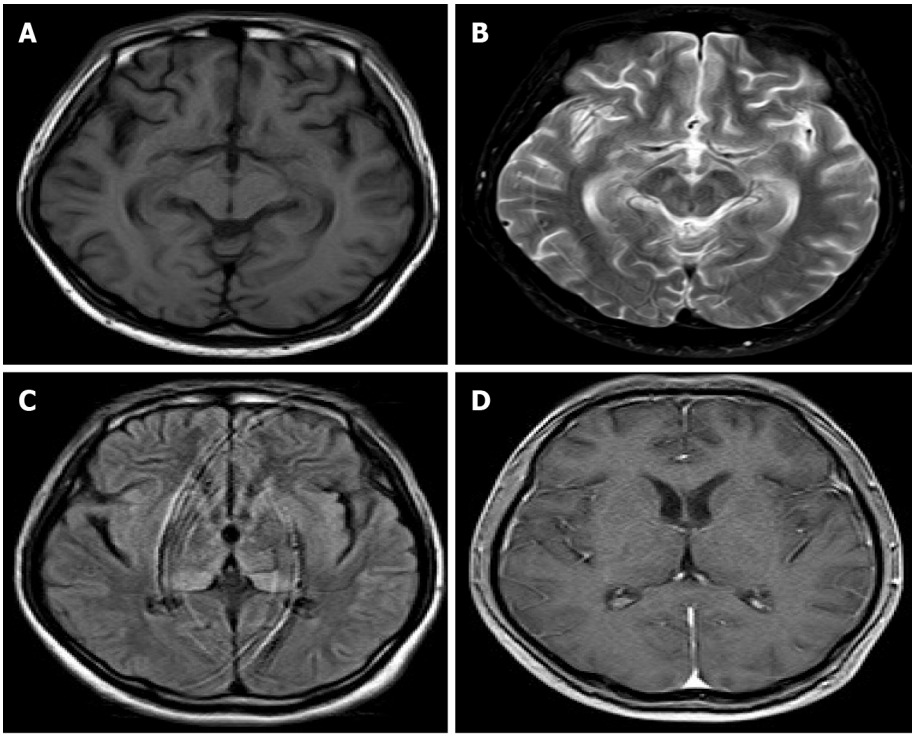

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Figure 2 Head magnetic resonance image. A: T1 image: No obvious abnormalities; B: T2 image: Bilateral medial temporal lobe high signal; C: T2 Flair image: High signal in both basal ganglia and thalamus; D: T1 enhanced image.

inflammation and destruction of the blood-brain barrier, thereby triggering central nervous system symptoms. Its typical clinical manifestations include recurrent seizures, paralysis and Knowledge barrier[12]. The imaging findings are mainly manifested as abnormal signals involving the thalamus and limbic system. The magnetic resonance T2-Flair and diffusion weighted imaging images are more likely to detect the lesion. In terms of treatment, vaccine immunoprevention is the main measure against Japanese encephalitis. Intravenous administration of methylprednisolone combined with human immunoglobulin can also improve the clinical symptoms and long-term recovery of some Japanese encephalitis patients. The diagnosis of Japanese B encephalitis in this case was based on the following:

The patient's onset of illness was in the summer, the favourable season for Japanese B encephalitis, with the typical clinical presentation of high fever/impaired consciousness/convulsions and, most importantly, a polymerase chain reaction test of the patient's cerebrospinal fluid by the Centre for Disease Control that found positive for Japanese B encephalitis virus.

There have been reports of Herpes simplex encephalitis combined with autoimmune encephalitis, and Epidemic Japanese B encephalitis combined with autoimmune encephalitis has only been reported in a few cases, but Epidemic Japanese B encephalitis combined with CASPR-2 antibody-positive autoimmunity No related reports of encephalitis. From the diagnostic criteria, the patient not only met the diagnostic criteria for Epidemic Japanese B encephalitis, but also met the diagnostic criteria for CASPR-2 antibody-positive autoimmune encephalitis, However, the relationship between the two in this patient needs further study. By consulting the literature, we preliminarily speculated that this patient may be secondary to CASPR-2 antibody-positive autoimmune encephalitis after Japanese encephalitis infection: The first is a molecular simulation mechanism, that is, the JE virus protein that infects the central nervous system has the same or similar antigen structure cluster as CASPR-2[13]. The second is that after infection of the central nervous system JE virus leads to destruction of brain tissue, a large number of CASPR-2 antigen structure clusters are exposed, thereby inducing the body to produce autoantibodies against CASPR-2 and secondary autoimmune reactions[14].

CONCLUSION

In summary, this article reports a case of Epidemic Japanese B encephalitis combined with CASPR-2 antibody-positive autoimmune encephalitis.

FOOTNOTES

Author contributions: Huang P was the patient's surgeon and drafted the manuscript.

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

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CASE REPORT

Acute pancreatitis as initial presentation of acute myeloid leukemia-M2 subtype: A case report

Wen-Xin Yang, Kang An, Gai-Fang Liu, Heng-Yu Zhou, Jun-Cha Gao

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Abstract

BACKGROUND

Direct infiltration of the pancreas by acute myeloid leukemia (AML) with acute pancreatitis (AP) as an initial symptom is extremely rare. Only once in the literature, the leukemia cells in AML have been implicated as the cause of AP. Pancreatitis caused by a rare predisposing factor is often misdiagnosed as idiopathic pancreatitis or pancreatitis of other common causes. Severe AP (SAP) progresses rapidly with a high fatality rate. Therefore, it is important to identify the predisposing factors in the early stage of SAP, evaluate the condition, determine prognosis, formulate treatment plans, and prevent a recurrence. Here, we describe a case of SAP due to AML.

CASE SUMMARY

A 61-year-old man presented to the hospital with fever and persistent abdominal pain. Blood analysis presented significantly elevated serum amylase and severe thrombocytopenia. Computed tomography examination of the abdomen revealed peripancreatic inflammatory effusion. The patient had no common etiologies and risk factors for AP, but the concurrent severe thrombocytopenia could not be explained by pancreatitis. Finally, the bone marrow aspirate and biopsy inspection revealed the underlying reason for pancreatitis, AML (M2 type based on the French-American-British classifications system).

CONCLUSION

Direct infiltration of the pancrease by acute leukemia, particularly AML cells, is an infrequent cause of AP. Therefore, although AP is a rare extramedullary infiltration characteristic for AML patients, it should be considered when determining

the etiology of AP.

Key Words: Acute pancreatitis; Acute myeloid leukemia; Abdominal pain; Extramedullary infiltration; Etiology; Case report

Core Tip: Although acute pancreatitis (AP) is a rare extramedullary infiltration characteristic for acute myeloid leukemia patients, it should be considered when determining the etiology of AP. Early diagnosis and etiological management can help avoid ineffective treatments and improve the outcomes. To better diagnose and treat such patients, we review the literature available on leukemia complicated by AP and analyze its mechanisms and clinical symptoms.

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INTRODUCTION

Acute pancreatitis (AP) is caused by the premature activation of pancreatic enzymes, which leads to inflammatory disorders of the pancreatic system and pancreatic cell auto-digestion[1]. AP patients often present to the emergency department with the complaint of persistent abdominal pain. The common etiologies of AP include gallstones, alcohol abuse, medication, and metabolic disorders such as hyperlipidemia, hypercalcemia, and endoscopic retrograde cholangiopancreatography. Severe AP (SAP) progresses rapidly with a high fatality rate. Therefore, physicians must identify the inducing factors early to evaluate the condition and devise treatment plans.

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults. It is characterized by abnormal proliferation of undifferentiated hematopoietic stem cells in bone marrow with damage to the normal blood cells. Its clinical features and prognosis show significant variation. Primarily due to poor prognosis and high mortality, it reduces the quality of life of patients. According to a recent study on AML in the United States, the M2 subtype was the most common (25%) of AML based on the French-American-British (FAB) classification, and the five-year survival rate for patients with AML is 28.3%[2]. The percentage of deaths increases with age.

Current literature concentrates pancreatitis associated with acute leukemia more on the use of chemotherapeutic drugs, and mainly in children with acute lymphoblastic leukemia (ALL). Direct infiltration of the pancreas by acute leukemia, particularly AML cells, is an infrequent cause of AP. Therefore, a better understanding of the extramedullary infiltration characteristic for AML is urgently needed. And when determining the etiology of AP, the possibility of acute leukemia should be considered.

Herein, we present a case of pancreas infiltration in a 61-year-old male AML patient, and through a literature review of previous cases, we analyze and summarize the features and potential mechanism for the extramedullary infiltration of AML.

CASE PRESENTATION

Chief complaints

A 61-year-old Chinese man was admitted to the emergency department with acute pain in the left upper abdomen with progressive worsening for 3 h.

History of present illness

Symptoms started 3 h before presentation with persistent epigastric pain initially, and then it gradually developed to diffuse abdominal tenderness with nausea, emesis, and lumbar-back radiating pain.

History of past illness

This patient had no history of chronic diseases, such as hypertension, hyperuricemia, hyperlipidemia, and coronary heart disease.

Personal and family history

The patient was a non-smoker and there was no history of alcohol consumption. The patient denied receiving chemotherapy or undergoing recent trauma. His family history was also not significant.

Physical examination

Vital monitoring at admission showed a pulse rate of 111 bpm, blood pressure of 161/111 mmHg, body temperature of 38.4 °C, and respiratory rate of 21 breaths/min.

There was no jaundice detected on the skin and sclera. During chest auscultation, decreased breath sounds were heard in bilateral lungs. Abdominal examination disclosed diffuse abdomen tenderness, abdominal muscle tension, and slightly decreased bowel sounds. Cullen's, Gray-Turner's, and Murphy signs were absent.

Laboratory examinations

Initial laboratory testing indicated that the white blood cell (WBC) count was 7.63 × 10^9/L (reference range: 3.5-9.5 × 10^9/L), with a monocyte percentage of 18.10%, low platelet count 12 × 10^9/L (reference range: 150-400 × 10^9/L), hemoglobin 12.2 g/dL (reference range: 12-16 g/dL), C-reactive protein 0.13 mg/dL (reference range: 0-0.33 mg/dL), elevated level of serum amylase (4288 U/L, reference range: 35-135 U/L), and normal bilirubin, triglycerides, and serum calcium. The laboratory examination revealed severe thrombocytopenia, mild anemia, increased monocyte count, and significantly increased serum amylase.

The significant decrease in platelet count could not be explained based on pancreatitis and infection, thus, blood system diseases must be considered. Bone marrow cell morphology (Figure 1A) revealed active bone marrow hyperplasia with increased myeloblasts (approximately 41%). The size of myeloblasts varied, and most of them were nearly round. There was medium cytoplasmic volume, stained blue, dark edge color. The nuclei were slightly irregular, pitted, and folded, and the nucleolus was fine-granular, with mostly 2-4 nucleolus. The proportion of red blood cells was normal, mainly polychromatic normoblasts and metarubricytes, and the size of mature red blood cells was different. The proportion of lymphocytes was normal, and they were mature lymphocytes. There were rare platelets. Myeloperoxidase staining was strongly positive (Figure 1B). Peripheral blood film depicted no significant increase in WBC count. Myeloblasts were more common, with a similar morphology as bone marrow (Figure 1C). FAB AML-M2 type seemed more likely, taking acute leukemia into account. Cytogenetic analysis of the bone marrow showed a 46 XY karyotype (Figure 1D). On flow cytometry, myeloblasts (68.93%) were positive for CD34, CD117, CD38, CD64, CD11c, CD33, CD13, and CD7 and negative for CD15, CD36, CD14, CD16, CD19, CD3, CD20, CD56, and CD 10. Monoblasts (19.36%) were positive for CD14, CD15, CD38, CD7, CD64, CD36, CD11c, CD33, and CD13 and negative for CD20, CD19, CD3, CD56, CD7, CD9, and CD10. The gene mutation tests about the myeloid malignancies showed *CEBPA* double mutations, *CSF3R* mutation, and *STAG2* mutation. *CEBPA* and *CSF3R* mutations were associated with negative prognostic factors in AML. Gene tests were also performed with probes specific for more than 50 genes, including *RUNX-1* fusion and *JAK2* fusion genes, and the results of these studies were normal.

Imaging examinations

Computed tomography (CT) of the abdomen demonstrated pancreatitis with diffuse edema of the pancreas, peripancreatic effusion, and gallbladder stones (Figure 2A).

Contrast-enhanced CT of the thorax and abdomen in the next day suggested: (1) Bilateral pleural effusion and adjacent atelectasis; (2) Pancreatitis accompanied by peripheral inflammatory exudation and uneven enhancement of pancreatic parenchyma. There were also hypodense lesions infiltrating the pancreas and a slightly thicker adjacent duodenal wall; and (3) Ascites (Figure 2B).

FINAL DIAGNOSIS

Based on the patient's medical history, clinical characteristics, and diagnostic test results, the final diagnosis was AML with SAP (extramedullary infiltration).

TREATMENT

After infection control, fluid resuscitation, blood component transfusion, and symptomatic antipyretic treatment, the inflammatory indicators decreased, and abdominal pain and bloating were alleviated, with the resumption of oral intake. However, the patient still had intermittent fever with the onset of dyspnea, shortness of breath, and wheezing. Arterial blood gas analysis indicated respiratory failure (PO_2 = 6.44 kPa, PCO_2 = 5.84 kPa, and oxygenation index = 230 mmHg). After non-invasive ventilator support, the patient's oxygenation index was above 200 mmHg, and his shortness of breath and

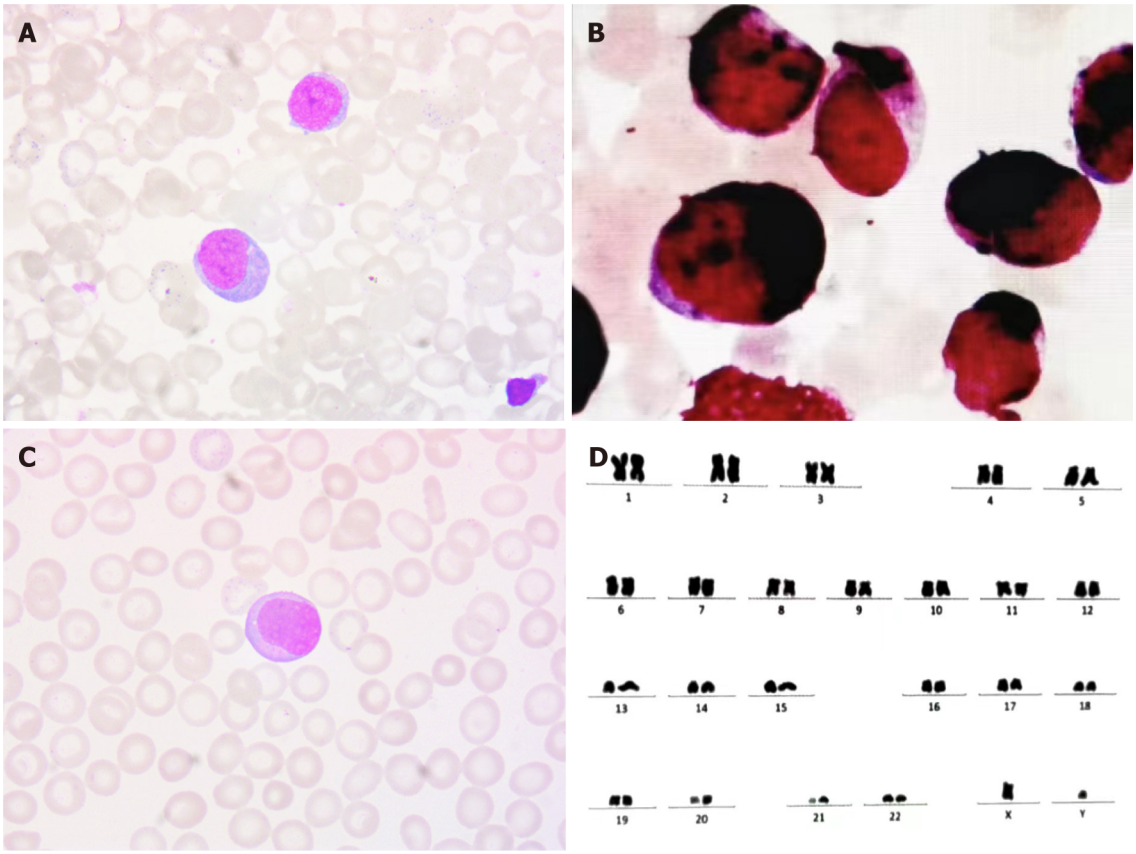

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Figure 1 Chromosomal karyotyping analysis and immunohistochemical examination of the peripheral blood and bone marrow. A: Bone marrow cell morphology revealed increased myeloblasts; B: Further immunohistochemical staining revealed an increase in myeloblasts staining strongly and weakly positively for myeloperoxidase; C: Peripheral blood imaging; D: The patient's karyotype is 46, XY.

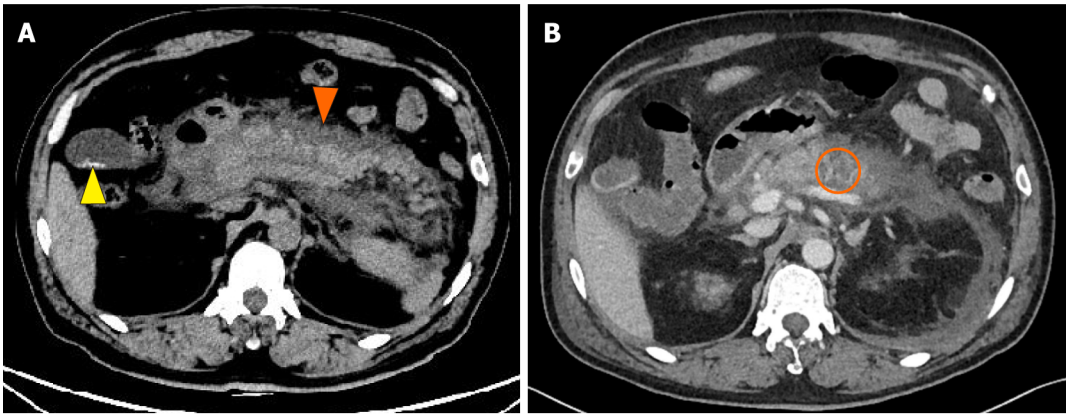

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Figure 2 Imaging of infiltration of the pancreas and acute pancreatitis. A: Abdominal computed tomography (CT) showed diffuse edema of the pancreas and peripancreatic effusion splenomegaly (orange arrow) with gallbladder stones (yellow arrow); B: Abdominal contrast-enhanced CT showed uneven density of the pancrea and no clear enhancement in the arterial phase, with hypodense lesions in the pancreas (orange circle).

wheezing were improved. Pancreatitis remained relatively stable. The patient was hospitalized for 9 d and continued to undergo treatment of AML at another hospital. He received chemotherapy with the idamycin and cytarabine regimen in the hospital.

OUTCOME AND FOLLOW-UP

Leukemia and pancreatitis both improved after chemotherapy. After two cycles of chemotherapy, the

lesions in his pancreas disappeared (Figure 3). The patient achieved a full recovery and complete remission (Figure 4) with platelet recovery. The patient has been alive for 1 year since the initial development of AML. Pancreatic walled-off necrosis developed in the healed pancreas after the treatment of pancreatitis. There was no significant increase in amylase, no obvious abdominal pain or distension, and no recurrence of pancreatitis.

DISCUSSION

Pancreatitis associated with acute leukemia has been reported mainly in children with ALL, most of which were linked with the use of asparaginase as a chemotherapeutic drug. Pancreatitis has also been reported in AML patients using cytarabine[3,4] or *all-trans* retinoic acid[5-7] and other combined chemotherapy regimens[8]. Pancreatitis caused by chemotherapy medications, on the other hand, is usually mild and can be improved if the chemotherapeutic drugs are suspended. In addition, bone marrow transplantation has also been a risk factor for pancreatitis[9-11]. A few cases of AP with adult T-cell leukemia were induced by hypercalcemia[12]. There were cases of AP with direct infiltration of leukemia cells in ALL[13-15], one of which confirmed atypical lymphocytic infiltration at the pathological level using fine-needle aspiration biopsy[13]. Although the other reports were not supported by pathological evidence, with the progress of induction therapy, regression of leukemic infiltration was seen in the pancreas. Acute leukemia, whether direct infiltration or in combination with chemotherapeutic drugs, can result in AP. But in AML, the pancreas is a rare organ for extramedullary infiltration. Only once in the literature, the leukemia cells in AML have been implicated as the cause of AP. In Japan, a patient with AML developed AP mimicking autoimmune pancreatitis[16].

In a previous case report, a patient with AML-M2 type was complicated with extramedullary manifestations[17]. Our patient was initially thought to have biliary pancreatitis because of the gallstone found by abdominal CT, but the patient had no bile duct stones. Serum bilirubin, γ-glutamyltransferase, and alkaline phosphatase were normal, and there was no evidence of cholangitis; therefore, the occurrence was unlikely to be caused by the stone. The patient's blood lipids were not elevated, and he had no prior drinking history; thus, alcohol or hyperlipidemia was ruled out. Then, after a follow-up inspection, he was diagnosed with AML, revealing the underlying reason for pancreatitis. Serum calcium levels at admission were within the normal range; the patient had no history of chemotherapy, so chemotherapy-related adverse reactions were also excluded. On the top of that, after chemotherapy for leukemia, there was no recurrence of pancreatitis. Based on the above details, it was presumable that the leukemic infiltration of the pancreas resulted in pancreatitis in this patient.

The extramedullary manifestations of leukemia can affect any organ, resulting in diversified early manifestations of leukemia, with separate organ damage or prominent local manifestation as the initial symptoms. AP caused by leukemic cell infiltration to the pancreas is rare in AML, and the mechanism is still unclear. Studies have shown that AML cells can accelerate the progression of leukemia by reshaping a supportive malignant microenvironment[18], which results in an invasion of the pancreas and other extramedullary organs. Studies focused maily on *CXCR4/CXCL12* signaling axis, matrix metalloproteinases (MMPs), and urokinase-type plasminogen activator system (uPAs) while investigating malignant tumor microenvironment in AML. Higher *CXCR4* expression in hematopoietic stem cells suggests an increase in recurrence rate and significantly poor prognosis[19,20]. The bone marrow plasma MMP-9 level is significantly higher in AML patients with extramedullary infiltration, showing that the premature production of MMP-9 may contribute to leukemic cells infiltration to extramedullary organs[21]. The uPAs induces plasminogen activation, which plays a vital role in tissue remodeling, proteolysis, invasion, and metastasis. Lanza *et al*[22] demonstrated that urokinase plasminogen activator receptor expression increased in patients with AML with invasive manifestations.

There was a high risk of hemorrhage after needle biopsy because of the low platelet count, so typical pathological changes such as leukemic cell infiltration to the pancreas could not be confirmed. But AP should be considered in AML patients with acute, persistent epigastric pain, regardless of whether or not there was amylase elevation. In the absence of fine-needle aspiration biopsy, the highly plausible possibility of direct infiltration by leukemia cells should be sought if other causes were excluded, as early detection and timely treatment of leukemia could improve the outcome of pancreatitis. If not handled properly, pancreatitis caused by a rare cause can develop into severe pancreatitis with systemic inflammatory response syndrome and organ dysfunction with rapid progression, poor prognosis, and high risk of death. It is harmful and difficult to diagnose, so clinicians must pay greater attention to this.

Although extramedullary infiltration of AML is generally regarded as an indicator of poor prognosis, this conclusion is still debatable[23-25]. Due to limited data available, it is difficult to determine the prognostic significance of pancreatic involvement in patients with AML. Therefore, for leukemia patients with extramedullary invasion of uncommon sites such as the pancreas, this may not indicate a more aggressive disease than other common sites, but treatment and diagnosis can be delayed. Especially in the said case, the rare AP as the first extramedullary infiltration manifestation led to misdiagnosis or missed diagnosis.

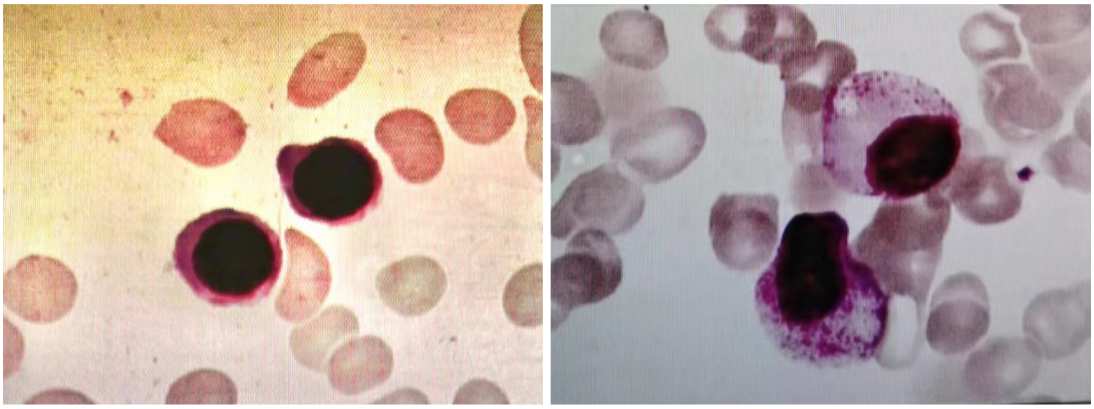

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Figure 3 Bone marrow aspirate and biopsy examination. Still active bone marrow hyperplasia and no myeloblasts indicated that hematological remission was achieved.

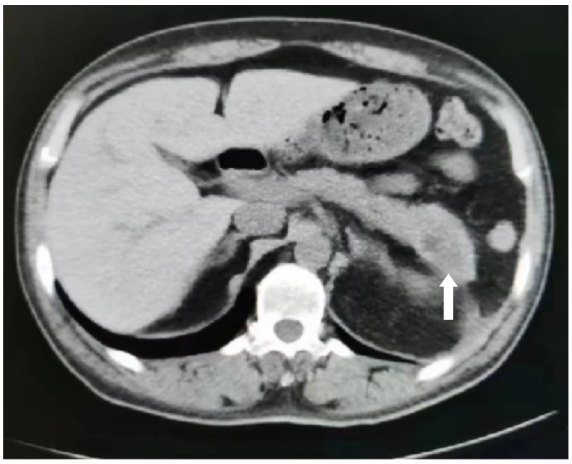

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Figure 4 Imaging of the healed pancreas. Abdominal computed tomography showed that the abnormal pancreas findings disappeared after the second course of consolidation chemotherapy, and walled-off necrosis of the pancreatic tail (white arrow).

CONCLUSION

This case report suggested that AP may be related to AML and highlighted a rare but significant etiology of AP. Many advancements have been made in diagnostic techniques and clinician awareness to identify rare predisposing factors of AP. Early diagnosis and etiological management can help avoid ineffective treatments and improve the outcomes.

FOOTNOTES

Author contributions: Yang WX and An K contributed to manuscript writing and editing, and data collection; Liu GF and Zhou HY contributed to data analysis; Gao JC contributed to conceptualization and supervision; All authors have read and approved the final manuscript.

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CASE REPORT

Postoperative jaundice related to *UGT1A1* and *ABCB11* gene mutations: A case report and literature review

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Abstract

BACKGROUND

Patients with obstructive jaundice caused by intrahepatic bile duct stones can be effectively managed by surgery. However, some patients may develop postoperative complications, liver failure, and other life-threatening situations. Here, we report a patient with mutations in the uridine 5'-diphospho-glucuronosyltransferase 1A1 (*UGT1A1*) and bile salt export pump (adenosine triphosphate-binding cassette subfamily B member 11, *ABCB11*) genes who presented multiple intrahepatic bile duct stones and cholestasis, and the jaundice of the patient increased after partial hepatectomy.

CASE SUMMARY

A 52-year-old male patient admitted to the hospital on October 23, 2021, with a progressive exacerbation of jaundice, was found to have multiple intrahepatic bile duct stones with the diagnoses of obstructive jaundice and acute cholecystitis. Subsequently, the patient underwent left hepatectomy with biliary exploration, stone extraction, T-tube drainage, and cholecystectomy without developing any intraoperative complications. The patient had a dark urine color with worsening jaundice postoperatively and did not respond well to plasma exchange and other symptomatic and supportive treatments. Since the progressive increase in postoperative bilirubin could not be clinically explained with any potential

reason, including, if not at all, viral infection, cholangitis, autoimmune liver disease, and other causes, the patient underwent whole-exon screening for any genetic diseases, which surprisingly identified *UGT1A1* and *ABCB11* gene mutations related to glucuronidation of indirect bilirubin as well as bile acid transport in hepatocytes, respectively. Thus, we hypothesized that postoperative refractory cholestasis might result from *UGT1A1* and *ABCB11* gene mutations and further recommended liver transplantation to the patient, who eventually declined it and died from liver failure six months later.

CONCLUSION

Surgery may aggravate cholestasis in patients with multiple intrahepatic bile duct stones and cholestasis associated with *UGT1A1* and *ABCB11* gene mutations. A liver transplant may be the best option if active medical treatment fails.

Key Words: Cholestasis; Intrahepatic bile duct stones; Postoperative jaundice; adenosine triphosphate-binding cassette subfamily B member 11; Uridine 5'-diphospho-glucuronosyltransferase 1A1; Case report

Core Tip: We presented a case of multiple intrahepatic bile duct stones, cholestasis, and progressive jaundice after surgical treatment, which was diagnosed upon the finding of adenosine triphosphate-binding cassette subfamily B member 11 (*ABCB11*) and uridine 5'-diphospho-glucuronosyltransferase 1A1 (*UGT1A1*) gene mutation from the genetic study. Since the patient refused to undergo liver transplantation, his postoperative aggravating jaundice was medically managed, but he soon died due to liver failure. The *UGT1A1* gene is related to the glucuronidation of indirect bilirubin. Its mutation leads to increased indirect bilirubin, while the *ABCB11* gene is involved in bile transport, and its mutation may lead to disturbance of bile acid transport, changes in bile composition, cholestasis, and the formation of intrahepatic bile duct stones. Surgical treatment in such patients may induce exacerbation of cholestasis, and liver transplantation should be the preferred treatment if medical management fails.

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INTRODUCTION

Obstructive jaundice caused by intrahepatic bile duct stones is relatively common, and its chief symptoms entail progressive, painless jaundice, occasionally accompanied by right upper quadrant pain, anorexia and greasy skin, itchy skin, dark yellow urine, and clay-colored stool. Primary intrahepatic stone disease (PIS) tends to occur regionally with familial aggregation[1] and carries a higher incidence in Southeast Asia than in Western countries[2,3]. Recurrent episodes and continued progression to advanced stages of PIS may lead to biliary cirrhosis or intrahepatic cholangiocarcinoma [4], two of which account for the most important causes of death from benign biliary tract disease.

PIS requires complex management with multiple surgical interventions, and hepatectomy has been the primary choice. However, less than 1% of patients may experience increased postoperative jaundice, liver failure, and even life-threatening conditions, which are related to various factors, including the underlying liver disease, the number of liver segments removed, intraoperative liver ischemia time, intraoperative continuous blood transfusion, postoperative hematoma, parenteral nutrition, anesthetics and drugs (such as antibiotics, analgesics), and sepsis and oxidative stress[5-7]. Moreover, although the PIS pathogenesis remains undefined, the disease possesses distinct ethnic and regional characteristics. Therefore, genetic factors may also be involved in the pathogenesis of PIS. Currently, gene mutation-related multiple intrahepatic bile duct stones, cholestasis, and postoperative jaundice aggravation have not received much clinical attention. We report a case of uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) and adenosine triphosphate- binding cassette subfamily B member 11 (*ABCB11*) gene mutations with multiple intrahepatic bile duct stones, cholestasis, and progressive jaundice after surgical treatment. Furthermore, we present a literature review on the potential effect, mechanism, and prognosis of *UGT1A1* and *ABCB11* gene mutations on intrahepatic bile duct stones and postoperative jaundice.

CASE PRESENTATION

Chief complaints

A 52-year-old male was admitted to the hospital on October 23, 2021, with yellowish skin and sclera for three months and a progressive exacerbation of postoperative jaundice for one month.

History of present illness

Three months ago, the patient noticed yellowish skin/sclera and dark-brown urine without any apparent predisposition, which had worsened with abdominal pain a month later, so he was admitted to a local hospital for further management. The post-admission examination of liver function test revealed normal transaminases but elevated levels of direct bilirubin, indirect bilirubin, gamma-glutamyl transpeptidase (GGT), and total bile acid (Table 1). Upper abdominal computed tomography (CT) examination showed multiple intrahepatic and extrahepatic bile duct stones and obstructions, cholestasis, and gallbladder enlargement. The patient was diagnosed with obstructive jaundice having multiple intrahepatic bile duct stones with acute cholecystitis, so he underwent left external hepatectomy with bile duct exploration, stone extraction, T-tube drainage, and cholecystectomy on September 9, 2021. The abdominal pain was significantly relieved postoperatively without fever, nausea, vomiting, or any sign of abdominal distension, but the urine color had been persistently getting darker with aggravation of jaundice of skin and sclera. Liver function re-examination showed a progressive increase in the bilirubin level compared to before the operation. Thus, the patient was further managed with plasma exchange and symptomatic and supportive treatments. However, the effect was not good, and he was admitted to our service for further diagnosis and treatment.

History of past illness

He reported a history of hypertension for ten years and did not take medication regularly. However, he denied a history of long-term heavy drinking, exposure to poisons and traditional Chinese medicines, and trauma.

Personal and family history

The patient denied any family history of malignancy and other hereditary disorders.

Physical examination

The patient had a Body Mass Index of 23.44, and his vital signs were stable, with clear consciousness. Moreover, the patient presented with the face of chronic liver disease and severe jaundice of the skin and sclera but did not have liver palm and spider nevus. Heart and lung examinations did not find any obvious abnormality, while the abdominal physical localized a T-tube drainage tube in place at the right abdomen with palpable tenderness at the right upper quadrant in the absence of rebound pain, muscle tension, and shifting dullness.

Laboratory examinations

Dynamic changes in biochemical indicators of liver function tests were listed as follows (Table 1): On Sep 6, 2021, preoperative LFTs were triglyceride (TG) as 3.62 mmol/L (Ref: < 1.7 mmol/L), total cholesterol (TC) as 4.46 mmol/L (Ref: < 5.2 mmol/L), high density lipoprotein cholesterol (HDL-C) as 0.17 mmol/L (Ref:0.91-1.55 mmol/L), and low density lipoprotein cholesterol(LDL-C): 3.14 mmol/L(Ref: < 3.12 mmol/L).

On October 23, 2021, postoperative LFTs showed TG as 3.46 mmol/L, TC as 5.16 mmol/L, HDL-C as 0.64 mmol/L, and LDL-C as 3.23 mmol/L.

On October 23, 2021, C-reactive protein and coagulation function were checked with normal findings, hepatitis B and viral infection were ruled out with negative antigen in the serum antibody tests, and a negative autoimmune antibody panel ruled out autoimmune hepatitis. Other tests were in the normal ranges, including thyroid function tests, ceruloplasmin, total iron binding capacity, and unsaturated iron binding capacity.

On October 23, 2021, bile drainage fluid was sent for culture, which came back with positive *Pseudomonas putida*, being sensitive to antibiotics such as piperacillin, ceftriaxone, and ceftazidime.

On November 17, 2021, the culture came back with negative gram-negative bacilli lipopolysaccharide and fungal (1-3)-B-D glucan.

On November 19, 2021, metagenomics next-generation sequencing (mNGS) on peripheral blood was reported back without detections of bacteria, mycobacteria, fungi, viruses, mycoplasma, Chlamydia, rickettsia, and parasites.

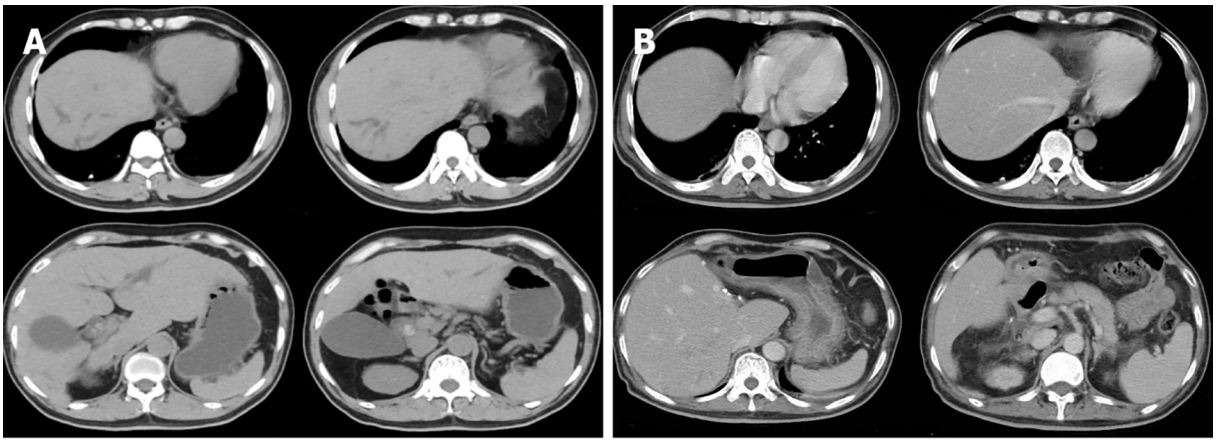
Imaging examinations

A preoperative non-contrast CT scan of the upper abdomen unveiled left intrahepatic and multiple bile duct stones with dilated intra-and extrahepatic bile ducts and an enlarged gallbladder (Figure 1A). Postoperative non-contrast CT scan and magnetic resonance imaging of the upper abdomen illustrated

Table 1 Dynamic changes of biochemical indexes of liver function in patients

Date	ALT, U/L	AST, U/L	TBIL, μmol/L	DBIL, μmol/L	IBIL, μmol/L	GGT, U/L	ALP, U/L	TBA, U/L
	Ref: 0-40	Ref: 0-34	Ref: 5.1-19.0	Ref: 1.7-6.8	Ref: 1.7-13.2	Ref: 10-60	Ref: 45-120	Ref: 0-50
2021-09-06 (Pre-operative)	33.0	28.0	135.1↑	84.1↑	51.0↑	77.0↑	105.0	208.0↑
2021-09-10 (Post-operative)	311↑	545↑	167.6↑	106.9↑	60.7↑	48.0	126.0↑	120.8↑
2021-09-22	39.0	23.0	187.1↑	109.4↑	77.7↑	32.0	78.0	53.0↑
2021-09-28 (Before discharge)	47.0↑	32.0	286.2↑	166.2↑	120.0↑	34.0	97.0	80.9↑
2021-10-23 (On readmission)	43.0↑	32.0	593.3↑	285.9↑	307.4↑	36.0	109.0	131.4↑
2021-10-30 (After drug treatment)	30.0	27.0	602.2↑	283.2↑	319.0↑	23.0	97.0	213.6↑
2021-11-14 (After plasma exchange)	22.0	33.0	230.6↑	141.1↑	89.5↑	28.0	76.0	151.9↑
2021-11-17 (Before discharge)	29.0	44.0↑	336.7↑	193.5↑	143.2↑	34.0	88.0	183.0↑

ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate aminotransferase; DBIL: Direct bilirubin; GGT: Gamma-glutamyl transpeptidase; IBIL: Indirect bilirubin; TBIL: Total bilirubin; TBA: Total bile acids.



DOI: 10.12998/wjcc.v11.i6.1393

Figure 1 Computed tomography image. A: The preoperative computed tomography (CT) image of the upper abdomen of the patient: Normal liver parenchyma with dilated intrahepatic as well as common bile duct (about 18 mm) and enlarged gallbladder without wall-thickening; B: Postoperative CT image of the upper abdomen: the enlarged and deformed remnant liver with dilated intrahepatic bile duct in the upper segment of the right posterior; the portal vein is widened, the widest diameter is about 1.4 cm. The spleen was normal in size and shape.

signs of liver cirrhosis with multiple intrahepatic bile duct stones in the upper right posterior lobe of the liver with cholangitis, peri-cholangitis, and portal hypertension (Figure 1B) and (Figure 2). Besides, postoperative magnetic resonance cholangiopancreatography further confirmed multiple intrahepatic bile duct stones with mild dilatation in the upper right posterior lobe of the liver (Figure 3A), and T-tube angiography could not visualize the right and left hepatic duct but the lower end of the common bile duct (Figure 3B). Postoperative histopathologic examination exhibited cholestatic liver disease and intrahepatic bile duct dilatation with chronic inflammation (Figure 4). Furthermore, sequential immunohistochemical staining unveiled mild and delicate hyperplasia along biliary ducts, then Alpha-Smooth Muscle Actin staining spotted a few activated hepatic stellate cells, Masson and Sirius red staining revealed fibrous tissue hyperplasia in the portal area with an interlobular short fibrous septum, Periodic Acid Schiff Diastase Stain displayed a little waxy substance in Kupffer cells, and Prussian blue signified a little iron granules deposition in hepatocytes and Kupffer cells. Besides, copper staining was negative.

Intra-hospital management

During hospitalization, the patient was managed on the diagnoses of cholestatic hepatitis, biliary tract infection, and decompensated liver cirrhosis with piperacillin-tazobactam sodium, dexamethasone, and supportive medications for protecting the liver and eliminating jaundice. After the treatments, re-examining white blood cells and C-reactive protein did not confirm any ongoing infection. However, the bilirubin was significantly higher than before. Afterward, intermittent plasma exchange replacement

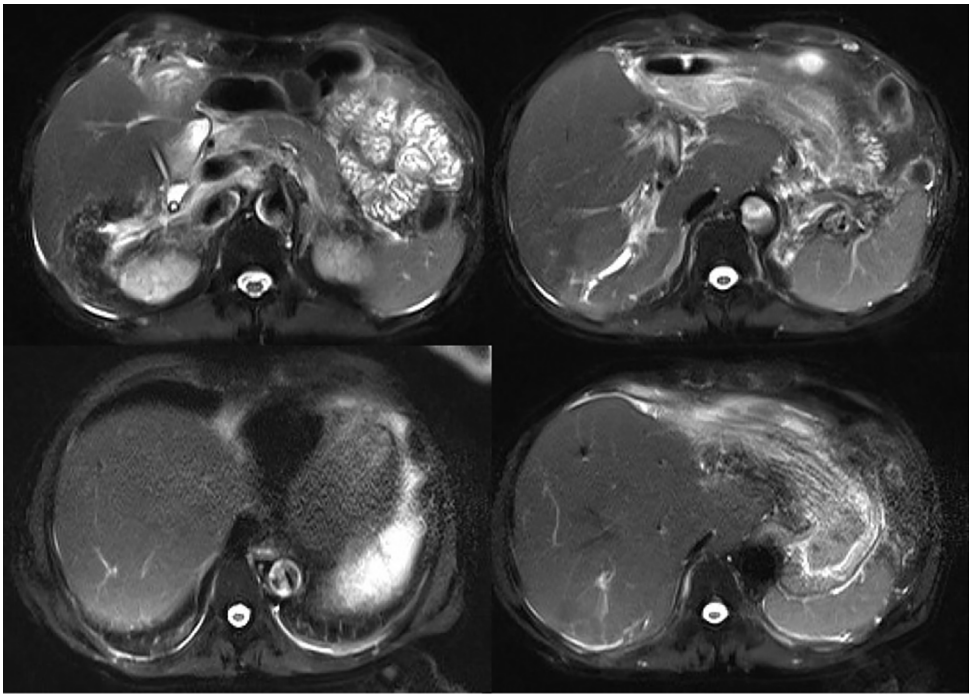


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Figure 2 Postoperative magnetic resonance imaging of the upper abdomen. Enlarged and deformed liver with uneven signals in the liver parenchyma and dilated intrahepatic bile duct in the upper right posterior lobe of the liver. Multiple nodular short T2 signal in the dilated and rigid bile duct with increased T2 weighted imaging signal in the surrounding liver parenchyma. The portal vein is widened with a size of 1.4 cm.

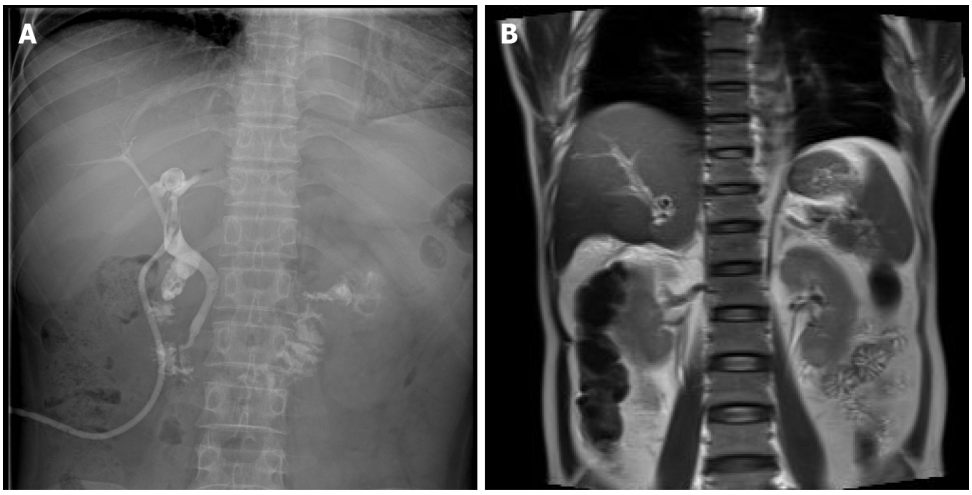

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Figure 3 T-tube and magnetic resonance cholangiopancreatography images. A: T-tube angiography: the left and right hepatic ducts were not visualized, the bile duct was rigid, and the lower end of the common bile duct was unobstructed; B: Magnetic resonance cholangiopancreatography: The intrahepatic bile duct in the upper right posterior lobe of the liver was dilated, and multiple nodular short T2 signals were seen in the lumen. Gallbladder not shown.

therapy with double plasma molecular absorption system (DPMAS) was administered to the patient four times to control progressive jaundice but failed to stop the progression.

CT examination was repeated after this admission to unveil the signs of cirrhosis, which was paradoxical to the preoperative finding of normal liver. Further pathological examination of the resected liver tissue revealed fibrous tissue hyperplasia in the hepatic portal area, suggesting that the patient only possessed early hepatic fibrosis before surgery. Taken together, we advised the patient of whole-exon screening to fish out any genetic disorder to search for the cause of cirrhosis, which surprisingly revealed *UGT1A1* and *ABCB11* gene mutations (Table 2 and Figure 5).

Table 2 Results of whole-exon genetic testing for the genetic disorders

Gene	Chromosomal position	Basic variation information	Zygote type	Inheritance patterns
UGT1A1	chr2:234669144	NM_000463.3:c.211G>A (p.Gly71Arg)	Hom	AR
	chr2:234681059	NM_000463.3:c.1456T>G (p.Tyr486Asp)	Het	AR
ABCB11	chr2:169787353	NM_003742.4:c.3233T>C (p.Ile1078Thr)	Het	AR
	chr2:169869837	NM_003742.4:c.334A>G (p.Ile112Val)	Het	AR

AR: Autosomal recessive; Hom: Homozygous; Het: Heterozygous.

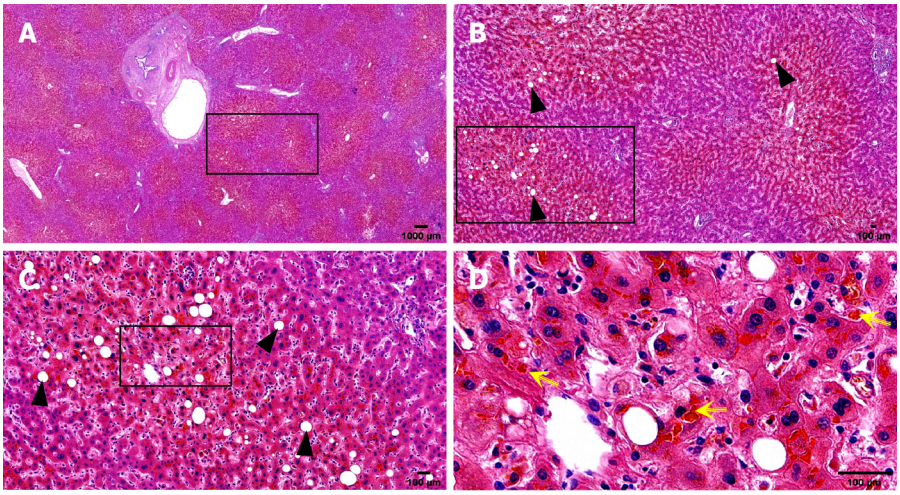

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Figure 4 Histopathological biopsy of the liver. The portal area was enlarged to varying degrees, with hyperplasia of fibrous tissue, infiltration of a moderate amount of lymphocytes and a small number of plasma cells, minor bile duct damage, fibrosis around a small number of small bile ducts, and mild bile duct hyperplasia, mild edema of hepatocytes, a few balloon-like degenerated hepatocytes, a few glycogenuclear hepatocytes, bulicular and microbulicular steatosis of hepatocytes (hepatic steatosis cells < 5%), irregular distribution, rare punctate necrosis. Some hepatocytes cholestatic pigment granules can be seen, and some bile ducts are dilated and cholestatic. Yellow arrow: Cholestatic pigment particles; Black triangle: Hepatocyte adipose change. A: Hematoxylin-eosin (HE) (× 1); B: HE (× 4); C: HE (× 10); D: HE (× 40).

FINAL DIAGNOSIS

Based on the clinical, pathological, and genetic findings, the patient was diagnosed with intrahepatic bile duct stones with cholestasis associated with *UGT1A1* and *ABCB11* gene mutations, biliary tract infection, and decompensated liver cirrhosis.

TREATMENT

Piperacillin and tazobactam sodium were first given to prevent infection, dexamethasone to reduce inflammation, compound glycyrrhizic acid monoamine S, adenosine methionine and ursodeoxycholic acid to protect the liver and eliminate jaundice, and plasma exchange therapy DPMAS was given later, but the effect was poor. Liver transplantation was recommended, but the patient and his family refused for financial reasons.

OUTCOME AND FOLLOW-UP

Since the patient and his family refused liver transplantation, his condition quickly deteriorated after discharge, and he died of liver failure six months later.

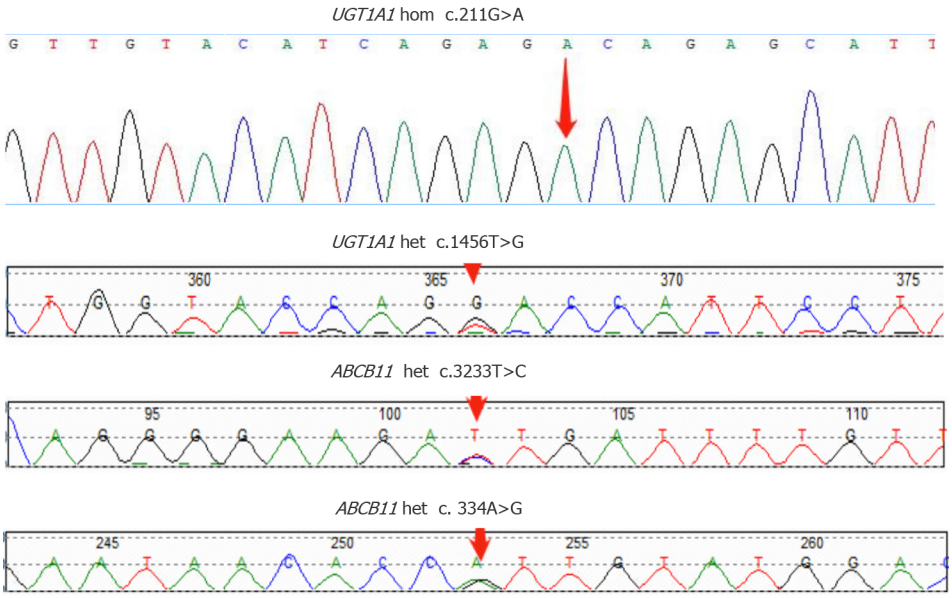

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Figure 5 Sanger sequencing map of the patient's *ABCB11* and *UGT1A1* genes with designated mutation sites.

DISCUSSION

The patient, diagnosed with obstructive jaundice from multiple intrahepatic bile duct stones, underwent left hepatectomy combined with biliary exploration, T-tube drainage, and cholecystectomy. However, he developed aggravation of postoperative jaundice, featured as the progressive increase of bilirubin, imaging signs of liver cirrhosis without blatant biliary obstruction, and ineffective medical therapy, including plasma exchange DPMAS. This postoperative jaundice with significant cellular injuries was pathologically characterized by cholestasis on the resected left liver, which was further examined with the whole-exon examination, identifying hereditary disease genes that showed *UGT1A1* and *ABCB11* gene mutations. The *UGT1A1* gene encodes the enzyme to glucuronidate indirect bilirubin for its removal from the body. Hence, its mutation causes indirect bilirubin elevation as the main feature. *ABCB11* gene encodes the bile salt export pump (BSEP), and its mutation leads to bile acid transport disorder, changes in bile composition, cholestasis, and the formation of cholesterol stones with the elevation of direct bilirubin. In this case, both direct and indirect bilirubin were significantly elevated. Therefore, by comprehensive analysis, multiple intrahepatic bile duct stones and cholestasis, in this case, may be related to *UGT1A1* and *ABCB11* gene mutations.

The *UGT1A1* gene is located at 2q37 of the human genome and encodes uridine 5'-diphosphate-glucuronidase, the only enzyme to glucuronidate bilirubin in the liver[8,9]. *UGT1A1* gene mutations cause unconjugated hyperbilirubinemia in both Crigler-Najjar syndrome (CN) and Gilbert syndrome (GS)[10]. Crigler-Najjar syndrome is classified as type I and type II variants, which reduce UGT1A1 enzymatic activity to 0% and 10%, respectively, while the enzyme in GS can only release 30% of its activity[10]. The *ABCB11* gene is located at locus 2q24 in the human genome and contains 28 exons[11], which can be translated into BSEP with a molecular weight of approximately 150–170 kDa. The BSEP proteins, which can be found along the canalicular membrane of hepatocytes, consist of two tandem homologous moieties to harbor an intracellular nucleotide-binding domain (NBD) and six transmembrane domains, which can be energized for transporting bile acids out of the cells upon hydrolysis of ATP by NBD. Mutations in the *ABCB11* gene result in the accumulation of primary bile acids in the intercellular space of the liver, thereby increasing the levels of bilirubin in serum and bile salts in the liver and blood. Studies have shown that mutations in the *ABCB11* gene are closely associated with cholestasis, including benign recurrent intrahepatic cholestasis[12,13], progressive familial intrahepatic cholestasis[14,15] and intrahepatic cholestasis of pregnancy[16,17]. In addition, beyond its transporting capacity, BSEP can facilitate cholesterol solubilization and inhibit its supersaturated crystallization[18,19]. Taken together, decreased bile salt secretion due to the BSEP alteration from the mutation of the *ABCB11* gene subsequently superimposes the formation of cholesterol gallstones along with abnormal bile metabolism and composition changes, which contribute to the pathogenesis of PIS[20]. Furthermore, cholestasis assists in depositing bile components to form intrahepatic bile duct stones and accumulates toxic bile acids, which lead to biliary wall injury and inflammation[21]. Long-term inflammation can lead to the thickening and stenosis of the biliary wall, thereby exacerbating cholestasis and promoting the formation of intrahepatic bile duct stones, further exacerbating cholestasis. This vicious cycle thus leads to disease progression[22,23]. In our patient, the

point mutation of c.211G>A (p.Gly71Arg) and c.1456T>G (p.Tyr486Asp) was found in exon 1 and exon 5 of the *UGT1A1* gene, respectively, which are most frequently seen in CN-II[24,25]. Along with the *ABCB11* gene mutation, both genes cooperatively aggravate intrahepatic cholestasis and hepatocellular injury before and after the surgery.

Intrahepatic bile duct stones and cholestasis can be managed with hepatic lobectomy, cholangiojejunostomy, Roux-Y anastomosis, simple choledocholithotomy, T-tube drainage, or liver transplantation according to the different intra- and extrahepatic biliary stones and clinical manifestations of each patient. After the obstructive pathologies in most patients with obstructive jaundice are removed surgically, the bilirubin levels drop, and the liver function gradually improves. However, in a few patients, bilirubin levels do not decrease but increase after surgery with the aggravation of jaundice and persistent intrahepatic cholestasis[26]. Postoperative cholestasis has many predisposing factors, including ischemia-reperfusion injury, the basis of liver cirrhosis, biliary tract infection, and the down-regulation of the expression level of bile acid efflux transporter in liver tissue. Long-term intrahepatic and extrahepatic biliary stones complicated by repeated suppurative cholangitis along the intrahepatic bile duct cause hepatic parenchyma fibrosis, hyperplasia, and pseudolobular formation, subsequently leading to the development of cholestatic liver cirrhosis[27,28], which dysfunctions hepatic uptake, transport, esterification and absorption of bilirubin and further elevates bilirubin level to make the pathogenesis fall into a vicious circle. Although the factors of biliary obstruction can be relieved by the operation, the hepatic injury from the persistent obstruction was deteriorated by anesthesia, ischemia, and inflammatory reactions. In addition to liver cirrhosis, sepsis with endotoxemia can also contribute to postoperative intrahepatic cholestasis by breaching the bile excretion function of hepatocytes[29,30], impairing the ability of hepatocytes to uptake bile salts, affecting the permeability of the cell membrane, and de-functioning bile transport. Furthermore, post-hepatectomy hyperbilirubinemia may be associated with hepatic mitochondrial dysfunction or impaired expression of bile excretion pumps on hepatocyte canalicular membranes[31-33].

In this report, our patient did not exhibit any evidence of liver cirrhosis in the preoperative upper abdominal imaging studies but had the feature of liver cirrhosis in the upper abdominal CT and magnetic resonance imaging one month after the operation. Normally, cirrhosis cannot develop in such a short time unless we might preoperatively omit the existence of this disease entity so that the patient underwent the inappropriate liver resection without classifying the patient according to Child's criteria. Otherwise, another hidden pathology was blinded until the postoperative stage. The postoperative pathological examination of the specimen from the surgery showed signs of early hepatic fibrosis, and the postoperative molecular pathology identified *UGT1A1* and *ABCB11* gene mutations, thereby giving us another perspective on the underlying causes of postoperative developments of cholestasis and cirrhosis. While managing the postoperative cholestasis of this patient, we not only performed T-tube angiography, which showed no obvious intra- and extrahepatic biliary obstruction but also treated the patient with antibiotics according to the drug sensitivity results to the infection and hormone therapy to reduce inflammation. However, since his bilirubin had progressively increased and was not controlled even with plasma exchange DPMAS replacement therapy, we sent the patient to receive genetic testing to identify the underlying causes, which showed the genetic defects in *UGT1A1* and *ABCB11*, thus singling out liver transplantation as the only effective method to the patient.

Interestingly, during the postoperative management, the coagulation function of the patient was always in the normal range, suggesting that the synthesis function of his lever was never perturbed. Such clinical uniqueness could be explained by the fact that his *UGT1A1* and *ABCB11* genes affect bilirubin metabolism and bile transport rather than significantly damaging liver cells and obstructing intra- and extrahepatic bile ducts for postoperative liver decompensation and lack of efficacy in the given treatment. Another issue related to our patient was low serum GGT levels that were paradoxical to its elevation in patients with biliary obstruction. Low GGT could be considered a potential laboratory indicator for non-obstruction caused while working up the patients with cholestasis.

CONCLUSION

UGT1A1 and *ABCB11* gene mutations associated with multiple intrahepatic bile duct stones and cholestasis are rare, so they are easy to ignore in clinical practice. Such patients have poor surgical treatment effects, which may induce aggravation of cholestasis, a progressive increase in bilirubin, and rapid progression of liver fibrosis. Therefore, liver transplantation may be the first choice for patients with multiple intrahepatic bile duct stones and cholestasis related to *UGT1A1* and *ABCB11* gene mutations after active medical treatments are ineffective. Patients with clinically found cholestasis should pay attention to whether the GGT level is elevated, which is more valuable for the preliminary judgment of hereditary metabolic intrahepatic cholestasis.

FOOTNOTES

Author contributions: Jiang JL and Liu X contributed equally to this work; Jiang JL, Liu X, Jiang XL, and Yi Y collected medical history; Chen Y and Zhong WW summarized and analyzed the medical history data; He YH and Jiang JL conceived and designed the content of the article; Jiang JL and Liu X wrote the initial paper; He YH, Liu KY, Shi JH, and Pan ZQ revised the paper; He YH had primary responsibility for final content; All authors read and approved the final manuscript.

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CASE REPORT

Hidrotic ectodermal dysplasia in a Chinese pedigree: A case report

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Abstract

BACKGROUND

We report on a large family of Chinese Han individuals with hidrotic ectodermal dysplasia (HED) with a variation in *GJB6* (c.31G>A). The patients in the family had a triad of clinical manifestations of varying degrees. Although the same variation locus have been reported, the clinical manifestations of this family were difficult to distinguish from those of congenital thick nail disorder, palmoplantar keratosis, and congenital hypotrichosis.

CASE SUMMARY

This investigation involved a large Chinese family of 46 members across five generations and included 12 patients with HED. The proband (IV4) was a male patient with normal sweat gland function and dental development, no skeletal dysplasia, no cognitive disability, and no hearing impairments. His parents were not consanguineously married. Physical examination of the proband revealed thinning hair and thickened grayish-yellow nails and toenails with some longitudinal ridges, in addition to mild bilateral palmoplantar hyperkeratosis. *GJB6*, *GJB2*, and *GJA1* have been reported to be the causative genes of HED; therefore, we subjected the patient's samples to Sanger sequencing of these three genes. In this family, the variation locus was at *GJB6* (c.31G>A, p.Gly11Arg). Overexpression vectors of wild-type *GJB6* and its variants were established and transfected into HaCaT cell models, and the related mRNA and protein expression changes were determined using real-time reverse transcriptase-polymerase chain reaction and Western blot, respectively.

CONCLUSION

We report another HED phenotype associated with *GJB6* variations, which can help clinicians to diagnose HED despite its varying presentations.

Key Words: Hidrotic ectodermal dysplasia; *GJB6*; Connexin; Gene sequencing; Cell transfection; Case report

Core Tip: We report on a Chinese family with hidrotic ectodermal dysplasia (HED), with patients in the family presenting varying degrees of hair dysplasia, nail dysplasia, and palmoplantar hyperkeratosis. In addition, we performed a literature review of other reported HED genotypes and their corresponding phenotypes, which lays a foundation for subsequent studies on these associations. Overexpression vectors of the *GJB6* gene and its variants (variation sites: c.31G>A, c.263C>T, c.110T>A) were established and transfected into a HaCaT cell model. The expression changes of related mRNA and proteins before and after gene editing were obtained by real-time reverse transcriptase-polymerase chain reaction and Western blot, respectively, to provide clues for subsequent pathogenesis studies.

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INTRODUCTION

To date, four variations in *GJB6* (G11R, A88V, V37E, and D50N), a *GJA1* (V41L) variation combined with a *GJB2* (R127H) variation, and an independent *GJB2* (V27I) variation have been found to trigger hidrotic ectodermal dysplasia (HED)[1]. The typical clinical presentation of HED is a triad of symptoms: Hair development disorders, palmoplantar hyperkeratosis, and finger/toenail dysplasia[2]. The variant locus of the investigated case has been reported previously; however, the clinical presentation characteristics of the investigated family differed from those previously reported. Each patient in the family exhibited a triad of symptoms, with varying degrees of severity; when a patient is characterized by one of the clinical manifestations of hyperkeratosis of the palm and toes, sparse hair, or hypoplasia of the finger (toe) nails, it is difficult to distinguish the disease from congenital thick nail disease, palmoplantar keratosis, or congenital oligodactyly based on clinical symptoms.

CASE PRESENTATION

Chief complaints

A 32-year-old Chinese man presented with sparse hair, grayish-yellow thickened nails, and hyperkeratosis of the palmoplantar from birth.

History of present illness

The patient had normal sweat gland function and dental development, no cognitive disability, no hearing impairments, and no skeletal dysplasia. His parents were not consanguineously married.

Personal and family history

In the five generations of the 46 members of the proband's family, 12 HED patients (nine males and three females) were included (Figure 1A). The proband (IV4) and his affected family members had varying degrees of hair dysplasia, nail dysplasia, and palmoplantar hyperkeratosis from birth (Table 1).

Physical examination

Physical examination revealed thinning hair, thickened grayish-yellow nails and toenails with some longitudinal ridges visible (Figure 1B and C), and mild bilateral palmoplantar hyperkeratosis (Figure 1D and E). The 11 surviving patients from the family had hair deficiency of varying severity and presentation, including sparse hair, slow growth, and/or easy breakage (Table 1). All 11 patients had thickened and brittle finger/toenails, with some patients having grayish-yellow finger/toenails and slow growth. All patients had varying degrees of palmoplantar keratinization, which decreased in severity in later generations (Figure 1F).

Laboratory examinations

Target genes were extracted using a DNA Blood Mini Kit (CWBIO, Beijing, China) and amplified *via*

Table 1 Clinical findings of 11 cases of hidrotic ectodermal dysplasia

No.	Age	Sex	Nail lesion	Alopecia	Keratoderma
II1	72	F	+++	++	+++
III2	52	F	++	++	+++
III4	56	M	+++	+++	+++
III6	48	M	+++	+	++
IV1	28	F	++	+	++
IV3	23	F	++	+	++
IV4	32	F	+++	+	++
IV6	29	F	+++	+	+++
IV10	27	F	++	+++	++
V2	4	F	++	+	+
V3	2	F	+	+++	+

No.: Patient No. in the pedigree; F: Female; M: Male; +: Mild lesion; ++: Moderately severe lesion; +++: Severe lesion.

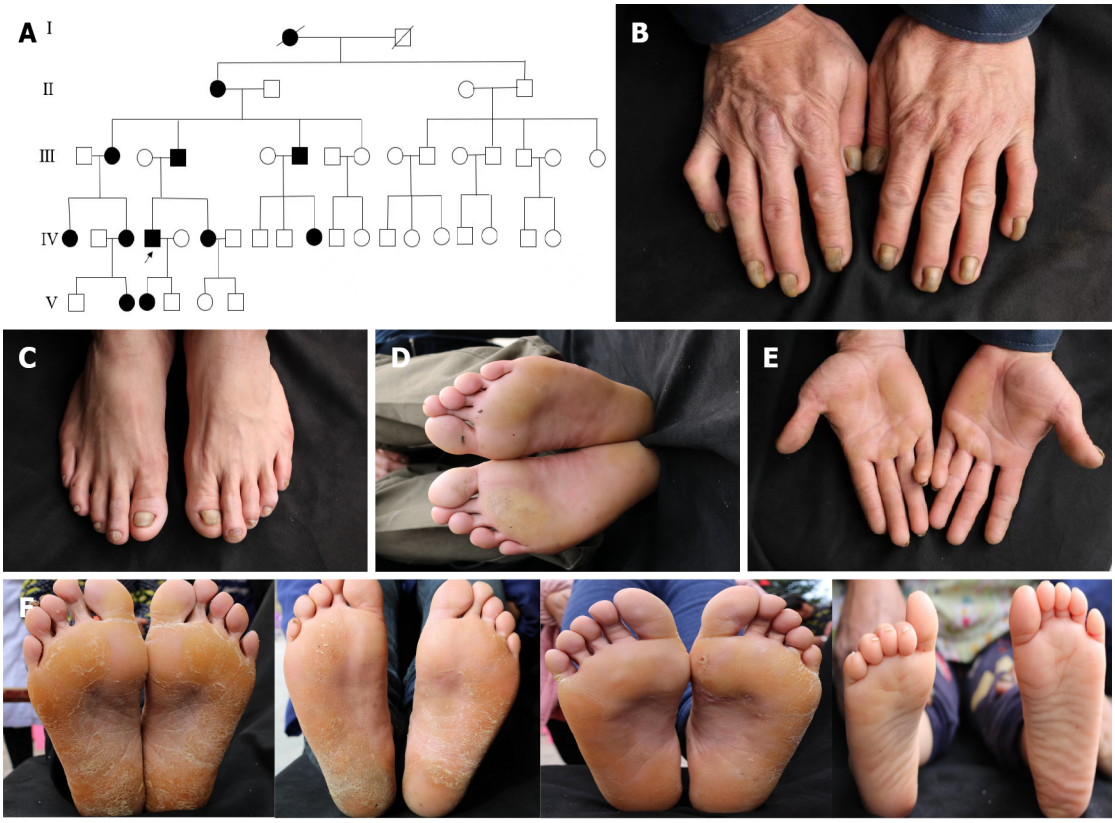

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Figure 1 The proband. A: Genealogical analysis of a Chinese family with hidrotic ectodermal dysplasia. Normal individuals are shown as clear circles (females) or squares (males), and affected individuals are shown as solid symbols. Deceased individuals are shown with a slash. The arrow indicates the proband; B: The proband (IV4) had thickening and yellowing of all fingernails; C: The proband had thickening and yellowing of all toenails; D: The proband had yellow patches visible on the soles of the feet; E: The proband had mild keratinization visible on the palm of the hand; F: The degree of palmar toe keratinization decreased in severity in the subsequent generations.

polymerase chain reaction, and mutated genes were detected *via* Sanger sequencing. A known heterozygous variation (c.31G>A) in *GJB6* was found in all 11 patients with HED (Figure 2A and B) but not detected in any of the nine healthy individuals of the family.

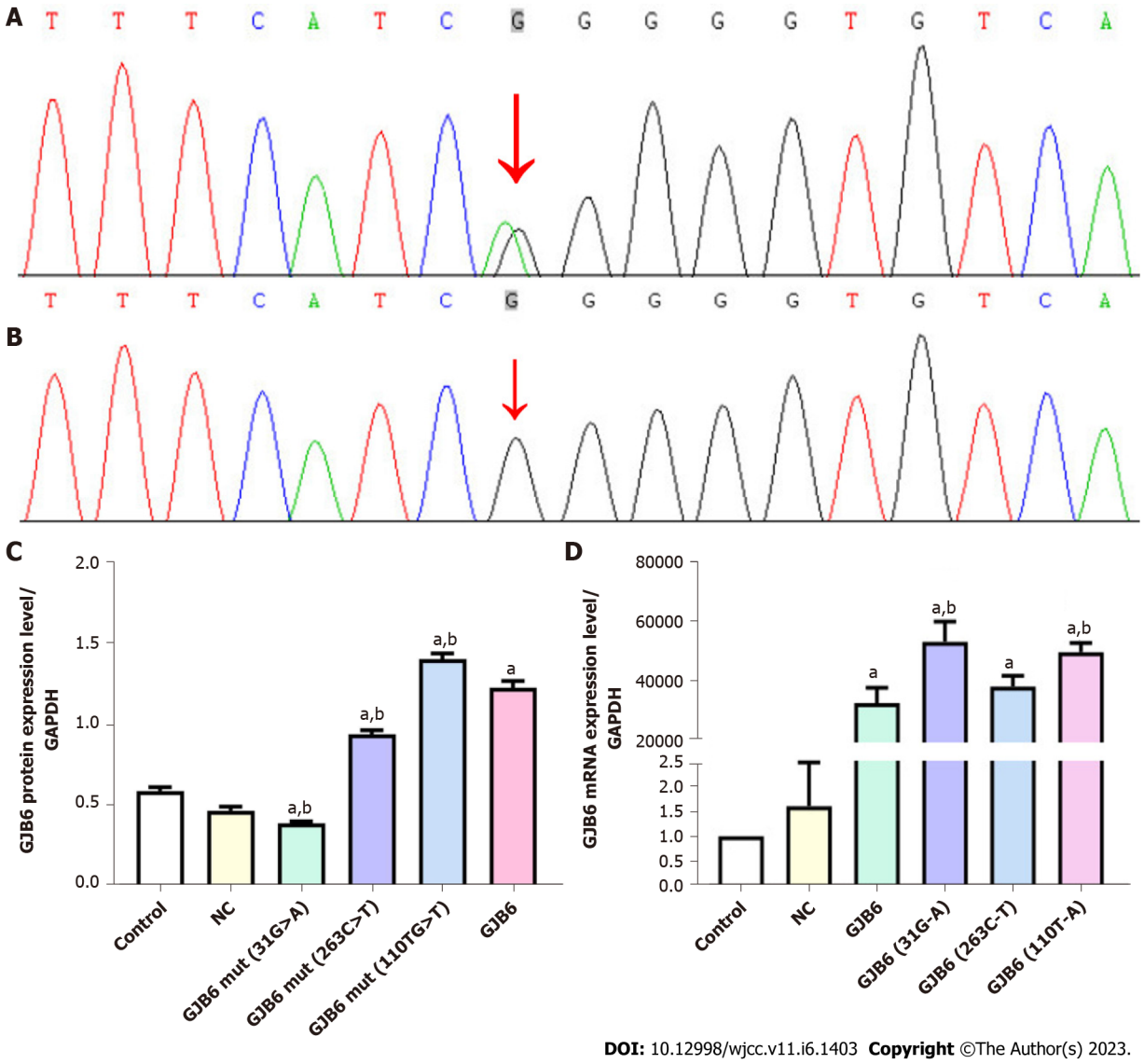

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Figure 2 Region of *GJB6*. A: Region of *GJB6* derived from the proband showing a heterozygous missense mutation 263G→A (arrow) in *GJB6*; B: Sequence analysis of the same region of *GJB6* from a normal individual; C: Real-time reverse transcriptase-polymerase chain reaction results of the expression level of *GJB6* mRNA ($^aP < 0.01$ compared with the blank control and NC control groups; $^bP < 0.01$ compared with the *GJB6* overexpression group); D: Western blot results of the protein expression level of GJB6 ($^aP < 0.01$ compared with the blank control and NC control groups; $^bP < 0.01$ compared with the *GJB6* overexpression group).

FINAL DIAGNOSIS

Based on the current findings combined with the patient's medical history, the final diagnosis was HED.

TREATMENT

Because there is no effective treatment for this disease, the pedigree of patients was not treated after diagnosis.

OUTCOME AND FOLLOW-UP

Overexpression vectors of *GJB6* and its variants (c.31G>A, c.263C>T, and c.110T>A) were constructed. The empty vector was used as a normal control (NC) group, and cells grown in normal culture were used as a blank control group. Overexpression vectors of *GJB6* and its variants were transfected into HaCaT cells. After 24 h of cell transfection, the expression levels of *GJB6* mRNA and protein were detected *via* real-time reverse transcriptase-polymerase chain reaction and Western blot, respectively. The data were statistically analyzed using SPSS Statistics 19, GraphPad Prism 7, and Quantityone

Table 2 Clinical phenotypes corresponding to *GJB6* mutations in previously reported families with hereditary hidrotic ectodermal dysplasia

Location (GRCh38)	NM accession number	Mutation locus	Ethnic group	Sex	Hair loss/sparse hair	Nail dysplasia	Palmoplantar hyperkeratosis	Supplementary	Ref.
chr13:20223450	NM_001110219.3	c.31G>A	American	2M/4F	4/6	6/6	1/6	Precedent with eccrine syringofibroadenoma	Poonawalla *et al*[3], 2009
		c.31G>A	Chinese	4M/4F	8/8	8/8	0/8	/	Chen *et al* [4], 2010
		c.31G>A	Polish	4M/1F	5/5	5/5	5/5	Inherent immune deficiency combined with skeletal abnormalities	Pietrzak *et al* [5], 2016
		c.31G>A	Polish	4M/3F	7/7	7/7	7/7	Some patients had hypotonia and delayed motor development	Kutkowska *et al*[6], 2015
		c.31G>A	Taiwan, Chinese	10M/9F	2/19	19/19	/	Patients presented with rolled nails without nail thickening	Hu *et al*[7], 2015
		c.31G>A	Chinese	3M/9F	12/12	12/12	12/12	/	Present case, 2022
chr13:20223218	NM_001110219.3	c.263C>T	French	2M/3F	5/5	5/5	5/5	/	Lamartine *et al*[8], 2000
		c.263C>T	Russians	2M/2F	4/4	4/4	4/4	Precedent with progressive corneal dystrophy	Marakhonov *et al*[9], 2012
		c.263C>T	Chinese	26M/19F	44/45	42/45	33/45	/	Yang *et al* [10], 2016
		c.263C>T	Chinese	3M/2F	5/5	5/5	4/5	Two patients with *GJB2* (c. 109G>A) mutations	Shi *et al*[1], 2019
		c.263C>T	Chinese	16M/17F	33/33	33/33	33/33	Proband and her father had hearing impairment	Zhan *et al* [11], 2020
chr13:20223371	NM_001110219.3	c.110T>A	Scottish	1F	1/1	1/1	/	/	Smith *et al* [12], 2002

F: Female; M: Male.

software. Significant differences between groups were analyzed *via* one-way ANOVA, and statistical significance was set at $P < 0.05$. The mRNA and protein expression levels of *GJB6* and its variant loci (c.31G>A, c.263C>T, and c.110T>A) are shown in Figure 2C and D.

Six months later, 11 patients from this pedigree were still alive.

DISCUSSION

In the reported family, the variation locus was at c.31G>A in *GJB6*, and although this variation locus has been reported previously, the clinical presentations of the patients of this family differed from those of other cases (Table 2). Table 2 shows that different variant loci lead to different clinical phenotypes and that the same variant locus can correspond to different clinical phenotypes, even in the same family. No one-to-one correspondence could be formed between the genotype and clinical phenotype of patients with HED.

Connexin 30 (Cx30) is the protein product of *GJB6* and is primarily utilized in the human cochlea and skin; therefore, deafness and skin problems may occur when there is a variation in *GJB6*. In this study, the conversion of guanine (G) at position 31 of *GJB6* to adenine (A) in patients of the family was detected using Sanger sequencing. This nucleotide base change results in the replacement of a normal glycine (Gly) with arginine (Arg), leading to an altered Cx30 product. This change affects the conforma-

tional and structural flexibility of the N-terminus of Cx30, which regulates the selectivity and gating polarity of the linker protein[3]. This leads to an abnormal transport activity through the skin gap junctions, which causes the phenotypic characteristics of HED. In addition, we performed a literature review of other reported genotypes of HED and their corresponding phenotypes, which may help clinicians diagnose the disease despite its varied presentations (Table 2). However, further study is required to determine how the pathogenesis of HED is affected by aberrant mRNA and protein expression because of *GJB6* variation.

CONCLUSION

There is no standard, effective treatment for HED, which can only be treated palliatively by wearing wigs, applying topical moisturizers, and following special nail care. Although HED is generally not life-threatening, it has serious physical and psychological effects on patients because of its effect on appearance. Sensorineural deafness, cataracts, oral mucosal leukoplakia, mental retardation, impaired immune system, skeletal malformations, and pestle finger have also been reported in HED patients. Therefore, prenatal genetic counseling and genetic testing remain effective methods to reduce the transmission of this hereditary disease.

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FOOTNOTES

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CASE REPORT

Hepatitis A virus-associated acute acalculous cholecystitis in an adult-onset Still's disease patient: A case report and review of the literature

Chu-Heng Chang, You-Yang Wang, Yang Jiao

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Abstract

BACKGROUND

Acute acalculous cholecystitis (AAC) is inflammation of the gallbladder without evidence of calculi. Although rarely reported, its etiologies include hepatitis virus infection (*e.g.*, hepatitis A virus, HAV) and adult-onset Still's disease (AOSD). There are no reports of HAV-associated AAC in an AOSD patient.

CASE SUMMARY

Here we report a rare case of HAV infection-associated AAC in a 39-year-old woman who had a history of AOSD. The patient presented with an acute abdomen and hypotension. Elevated hepatobiliary enzymes and a thickened and distended gallbladder without gallstones on ultrasonography suggested AAC, but there were no signs of anemia nor thrombocytopenia. Serological screening revealed anti-HAV IgM antibodies. Steroid treatment did not alleviate her symptoms, and she was referred for laparoscopic cholecystectomy. The resected gallbladder was hydropic without perforation, and her clinical signs gradually improved after surgery.

CONCLUSION

AAC can be caused by HAV in AOSD patients. It is crucial to search for the underlying etiology for AAC, especially uncommon viral causes.

Key Words: Acalculous cholecystitis; Hepatitis A virus; Adult-onset Still's disease; Acute abdomen; Cholecystectomy; Case report

Core Tip: Acute acalculous cholecystitis (AAC) can be caused by hepatitis A virus (HAV) infection or adult-onset Still's disease (AOSD). Cholestasis is more likely to occur in HAV-associated AAC, whereas hematological complications are more common in AOSD-associated AAC. When AAC cannot be explained by AOSD, it is necessary to find other causes of AAC. An acute abdomen caused by HAV-related AAC requires careful consideration of the surgical necessity, since most cases are self-limiting and gallbladder perforation is rare.

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INTRODUCTION

Acute acalculous cholecystitis (AAC) accounts for 2%-15% of all acute cholecystitis cases[1]. In contrast to acute calculous cholecystitis (ACC), no gallstones can be identified in the gallbladder in AAC, and its pathogenesis is thought to be related to ischemia-reperfusion injury after surgery or trauma, cholestasis caused by long-term fasting or intestinal obstruction, bacterial infection, or abnormal biliary tract anatomy[2-4]. Although rarely reported, hepatitis A virus (HAV) infection or adult-onset Still's disease (AOSD) can also cause AAC. HAV-associated AAC has mostly been reported in children and teenagers in developing countries, and it is often accompanied by fever, vomiting, transient liver dysfunction, and cholestasis[5,6]. On the other hand, AOSD is a chronic, systematic inflammatory disease characterized by recurrent fever, arthralgia, rash, and anemia or thrombocytopenia[7]. Patients with AOSD also may have high ferritin levels and sometimes concurrent AAC[8].

However, there are no reports of co-morbid AAC, HAV infection, and AOSD, which would represent a diagnostic and management challenge. Here we describe the case of a 39-year-old woman with AAC complicated by AOSD who was found to be anti-HAV IgM positive. We also searched the PubMed database with the keywords "[(hepatitis A virus) OR (adult-onset Still's disease)] AND acalculous cholecystitis" and found 14 HAV-associated AAC cases and three AOSD-associated AAC cases. Our case and review allow us to identify diagnostic clues that might help favor a particular diagnosis and discuss the necessity for surgical intervention to treat the AAC under these circumstances.

CASE PRESENTATION

Chief complaints

A 39-year-old woman presented to our hospital with a one-week history of fever (39-40 °C) and headache, chest tightness, and a sharp right upper quadrant pain.

History of present illness

The woman had a five-month history of AOSD, for which she had been taking oral methylprednisolone (26 mg/d) as maintenance therapy. She had suddenly developed a cough and sore throat two weeks previously, for which she was prescribed amoxicillin and clavulanate potassium (3.75 g/d), which was ineffective. In the week preceding admission, she had a fever of 39 °C accompanied by malaise, cutaneous icterus, and loss of appetite. Her methylprednisolone dose was increased to 48 mg/d and moxifloxacin hydrochloride (0.4 g iv, once) was administered, but this failed to control the symptoms.

History of past illness

The patient had ovarian endometriosis ten years previously and underwent laparoscopic ovarian cystectomy. She also had a history of a skin rash after taking a cephalosporin antibiotic.

Personal and family history

There was no personal nor family history of cholecystitis, nor was there a family history of AOSD or other auto-immune diseases.

Physical examination

On admission, she had cutaneous icterus and her temperature was 40 °C. Her blood pressure dropped to 83/45 mmHg and her heart rate increased to 100-110 bpm. Her liver was palpable under the costal margin, and she had abdominal distension and tenderness in the right upper quadrant and a positive Murphy's sign.

Laboratory examinations

Laboratory tests (Table 1) showed elevated lactate (1.9 mmol/L), white blood cell (WBC) count (17.34 × 10^9/L), and inflammatory markers [high-sensitivity C-reactive protein (hsCRP) 15.35 mg/L]. Moreover, total/direct bilirubin (TBil/DBil) (12.2/10.5 mg/dL) and hepatobiliary enzymes [aspartate aminotransferase (AST) 724 U/L, alanine aminotransferase (ALT) 223 U/L, gamma-glutamyl transferase (GGT) 735 U/L, alkaline phosphatase (ALP) 336 U/L] were elevated, and the prothrombin time (PT) was prolonged at 15.1 s. Her hemoglobin 14.7 g/dL and platelets 292 × 10^9/L were within normal limits. Further serological screening demonstrated anti-HAV IgM antibodies.

Imaging examinations

Ultrasonography revealed a dilated gallbladder (9.1 cm × 4.1 cm) with an evenly thickened wall (approximately 1.8 cm) and hepatosplenomegaly, but the intrahepatic bile duct was not dilated. Computed tomography (CT) suggested pericholecystic and hepatic fluid collection, a thickened gallbladder wall, a right pleural effusion, and ascites (Figure 1). No calculi were present.

FINAL DIAGNOSIS

The evidence suggested that the patient had HAV-associated AAC. The AAC could not be explained by the active state of AOSD, since steroid treatment did not alleviate the symptoms.

TREATMENT

Hypovolemia and septic shock were considered, and she was given supportive intravenous fluid treatment and norepinephrine as a vasoactive agent (0.2 μg/kg/min). However, the acute abdominal pain, chest tightness, and acute abdomen signs such as positive Murphy's sign and epigastric guarding continued. Gallbladder perforation was suspected, and she was referred for emergent laparoscopic cholecystectomy. During the surgery, the gallbladder was found to be hydropic without perforation with no evidence of calculi. Prednisone was maintained at the same dose (48 mg/d) after cholecystectomy.

OUTCOME AND FOLLOW-UP

Her clinical signs gradually improved after surgery. Microscopic examination of the gallbladder revealed normal epithelial architecture with mild lymphocyte infiltration. There was no perforation nor necrosis. During follow-up, her liver function returned to normal and the cutaneous icterus resolved.

DISCUSSION

Literature review

Here we present a case of AAC complicated by HAV infection and AOSD. We searched the PubMed database for published articles on the topic using the search terms "acalculous cholecystitis", "hepatitis A virus", and "adult-onset Still's disease". Fourteen patients have been reported in the literature with AAC due to acute HAV infection and three due to AOSD, and we compared these with our case.

Previous studies reporting HAV-associated AAC are summarized in Table 2. These patients commonly presented with fever (11/14), fatigue (7/14), nausea (5/14), vomiting (9/14), and abdominal pain (12/14). On physical examination, icterus (12/14), right upper abdominal tenderness (12/14), and an enlarged liver or spleen (6/12) were common. Ultrasonography and CT revealed thickened gallbladders accompanied by pericholecystic fluid and hepatosplenomegaly. Laboratory tests showed that all patients had elevated TBil/DBil, ALT, and AST. Anemia (2/8) and thrombocytopenia (3/10) occurred in several cases. However, despite advanced imaging and laboratory techniques, the diagnosis of complicated HAV-associated AAC as a cause of an acute abdomen seems to be challenging. Ciftci *et al* [10] presented a case of HAV-associated AAC in a child whose initial diagnosis was an acute abdomen due to blunt abdominal trauma. After physical examination, laboratory testing, and CT scanning, the patient was suspected to have gangrenous cholecystitis, but the exploratory laparotomy revealed no gallbladder necrosis nor perforation.

With respect to treatment and prognosis, most patients received conservative treatment (12/14) and only two patients underwent surgery. All patients had good outcomes. Most HAV-associated AAC cases were self-limiting, and the thickened, hydropic gallbladder decompressed within two weeks following conservative treatment. These findings were consistent with those of Kaya *et al*[18].

Table 1 Laboratory findings (at time of current admission)

Laboratory test	Laboratory value	Reference range
White blood cell count (WBC)	17.34	3.5-9.5 (× 10^9/L)
Hemoglobin (Hb)	14.70	11-15 (g/dL)
Platelets (PLT)	292.00	125-350 (× 10^9/L)
High-sensitivity C-reactive protein (hsCRP)	15.35	< 8.2 (mg/L)
Erythrocyte sedimentation rate (ESR)	7.00	0-20 (mm/h)
Aspartate aminotransferase (AST)	724.00	10-40 (U/L)
Alanine aminotransferase (ALT)	223.00	9-50 (U/L)
Gamma-glutamyl transferase (GGT)	735.00	8-55 (U/L)
Alkaline phosphatase (ALP)	336.00	40-100 (U/L)
Total bilirubin (TBil)	12.20	0.2-1.2 (mg/dL)
Direct bilirubin (DBil)	10.50	0-0.3 (mg/dL)
Creatinine (Cr)	58.00	45-84 (μmol/L)
Lactate	1.90	0.5-1.0 (mmol/L)
Prothrombin time (PT)	15.10	11-13 (s)
Activated partial thromboplastin time (APTT)	40.20	20-25 (s)

Cases of AAC in patients with AOSD (three cases) are summarized in Table 3. AOSD-associated AAC patients, all female, had recurrent fever, rash, and arthritis. On physical examination, two presented with a palpable liver and spleen, which was further confirmed by CT. All cases showed gallbladder enlargement or wall thickening but no calculi by ultrasonography or CT. Laboratory findings showed liver dysfunction (elevated TBil and hepatobiliary enzymes), anemia, and thrombocytopenia. Moreover, hyperferritinemia was presented in these patients, which might reflect the inflammatory state in autoimmune disease.

Arai *et al*[8] found several shared characteristics in AOSD patients. Two cases were complicated by macrophage activation syndrome (MAS) based on the findings of splenomegaly, cytopenia, and pathological changes in myeloid cells revealed by bone marrow biopsy. In addition, two cases were complicated by disseminated intravascular coagulation (DIC). The hypercytokinemia caused by MAS and widespread hypercoagulable state might aggravate multi-organ failure and severe illness. Furthermore, they showed that by inhibiting cytokine production and immune activation with glucocorticoids and cyclosporin A, both AAC and AOSD-related MAS or DIC could be resolved, suggesting that MAS and DIC might be secondary to their primary AOSD and that prompt and correct management of the primary disease can also slow or halt the progression of MAS and DIC.

It is worth considering whether surgery is needed in patients with AOSD-associated AAC. From the three previously reported cases, two patients received conservative treatment and one had cholecystectomy. The patient who underwent surgery[21] experienced hypovolemic shock, including no peripheral pulse and a systolic blood pressure of 50 mmHg. However, the surgery did not fully ameliorate the disease, since the patient experienced a rise in temperature after surgery and was later successfully treated with prednisone and naproxen. This leads us to consider whether surgical intervention is necessary in these cases. However, Arai *et al*[8] claimed that surgery should remain a treatment option for AOSD-associated AAC due to the possibility of gallbladder perforation as a complication. All three patients survived and had good outcomes. Overall, given the rarity of the condition, further reporting of individual cases would be helpful for guiding evidence-based treatment of AOSD-associated AAC.

Discussion

AOSD-associated AAC and HAV-associated AAC share several common characteristics. They both present with acute abdomen symptoms, elevated bilirubin and hepatobiliary enzymes, and imaging findings of hepatosplenomegaly and a thickened gallbladder without gallbladder calculi. However, cholestasis is often more severe in HAV-associated AAC, resulting in higher bilirubin levels and cutaneous icterus[22]. Meanwhile, hematological abnormalities are more obvious in AOSD-associated AAC: Anemia and thrombocytopenia were more frequent in AOSD-associated AAC, as was MAS or DIC[20]. In this patient, a differential diagnosis of MAS was considered. However, anemia, thrombocytopenia, and DIC were not present. Steroid treatment did not alleviate the patient's symptom, disfavoring AOSD as the cause of AAC in this case. Thus, based on serology and other laboratory

Table 2 Acute acalculous cholecystitis associated with hepatitis A virus infection

Ref.	Age/sex	Symptoms	Physical examination	Vital signs	Ultrasound/CT findings	Bilirubin (total/direct, mg/dL) (0.2-1.2/0-0.3)	AST/ALT (U/l) (10-40/9-50)	WBC (10^9/L) (3.5-9.5)	Hb (g/dL) (11-15)	Platelets (10^9/L) (125-350)
Mourani *et al* [9], 1994	68/M	Fever, chills, nausea, vomiting	Icterus, diaphoretic, hypotensive	/	Thickened gallbladder wall, acalculous	4.8/	5629/8670	/	/	/
Ciftci *et al* [10], 2001	7/M	Fever, fatigue, abdominal pain, mild respiratory distress	Icterus, abdominal distention, right upper quadrant tenderness	T 37.8 °C, HR 100 bpm, BP 100/70 mmHg	Subhepatic fluid, thickened gallbladder wall, acalculous	7.6/4.8	221/1288	8.8	13.9	/
Ozaras *et al* [11], 2003	28/M	Fatigue, abdominal pain, dark urine, anorexia, pale stool	Icterus, palpable liver with tenderness, murphy's sign (+)	/	Perihepatic fluid, thickened gallbladder wall, pericholecystic	8.4/3.9	370/1386	3.7	/	199
	20/F	Nausea, vomiting, fatigue, pruritus, and anorexia	Icterus, right abdominal tenderness, enlarged liver and spleen	/	Hepatosplenomegaly, hydropic gallbladder, acalculous	6.58/2.90	400/815	5.9	/	287
Basar *et al* [12], 2005	19/F	Fever, right upper abdominal pain	Icterus, right upper quadrant tenderness Murphy's sign (+)	/	Hepatomegaly, thickened gallbladder wall, acalculous, pericholecystic, intraabdominal fluid	11.6/5.7	984/1213	4.1	/	215
Bouyahia *et al*[13], 2008	14/M	Fever, vomiting, abdominal pain, myalgia	Right hypochondrium tenderness, enlarged liver and spleen	/	Thickened gallbladder wall, acalculous, pericholecystic fluid collection	4.97/3.33	1327/1112	5.2	13	130
Arroud *et al* [14], 2009	11/M	Fever, fatigue, vomiting, abdominal pain. myalgia, dark urine, pale stool	Icterus, enlarged liver and spleen	T 38.8 °C	Thickened gallbladder wall, acalculous, pericholecystic fluid collection	4.8/2.7	2953/1918	6.3	11.4	/
Suresh *et al* [15], 2009	2.5/F	Fever, fatigue nausea, vomiting, abdominal pain, loss of appetite, dark urine, pale stool	Icterus, tenderness in right side abdomen, Murphy's sign (+), enlarged liver and spleen	T 38.5 °C, HR 86 bpm, RR 22, BP 100/70 mmHg	Hepatosplenomegaly, thickened gallbladder wall, acalculous, perich-olecystic fluid	2.8/0.9	20.6/23.4	6.1	13.6	186
Souza *et al* [6], 2009	16/M	Fever, fatigue, nausea, vomiting, abdominal pain, cephalalgia	Diffuse abdominal pain to superficial and deep palpation	/	Hepatomegaly, thickened gallbladder wall, acalculous	5.01/3.69	1265/1046	/	14.2	112
Al-Amir *et al* [16], 2015	13/F	Fever, fatigue, vomiting, abdominal pain, dark urine, pale stool	Icterus, epigastric and right upper quadrant tenderness, Murphy's sign (+)	T 38.8 °C, other vital signs were normal	Thickened gallbladder wall, acalculous, pericholecystic fluid collection	16.1/12.3	3242/4298	4.5	15.4	/
Herek *et al* [5], 2011	9/M	Fever, nausea, vomiting, abdominal pain	Icterus, tenderness in the right upper quadrant, enlarged liver	T 37.9 °C, HR 84 bpm, BP 100/55 mmHg	Thickened gallbladder wall, acalculous, pericholecystic-free fluid	4.3/3.0	2261/2586	8.1	/	254
Prashanth *et al*[17], 2012	12/F	Abdominal pain and vomiting	Icterus, tenderness in the right hypochondrium	T 36.9 °C, HR 102 bpm, RR 18, BP 110/80 mmHg	Thickened gallbladder wall, acalculous	3.5/1.05	2150/2580	9	10	180

Kaya *et al* [18], 2013	31/F	Fever, nausea, abdominal pain, loss of appetite, back and joint pain, darkening of urine	Icterus, tenderness in the right side of the abdomen, Murphy's sign (+), enlarged liver	37.5 °C, HR 92 bpm, BP 110/60 mmHg	Hepatosplenomegaly, thickened gallbladder wall, acalculous, ascites	2.11/1.92	559/618	3.3	9.5	139
Aldaghi *et al* [19], 2015	5/M	Fever, abdominal pain	Icterus, mass in the right upper quadrant with tenderness	38 °C, HR 100 bpm, RR 30, BP 100/60 mmHg	Distended gallbladder, normal thickness, acalculous	5.3/3.9	516/722	8	/	426

HAV: Hepatitis A virus; AST: Aspartate transaminase; ALT: Alanine aminotransferase; BP: Blood pressure; RR: Respiratory rate; T: Temperature; WBC: White blood cell count; Hb: Hemoglobin; HR: Heart rate.

Table 3 Acute acalculous cholecystitis associated with adult-onset Still's disease

Ref.	Age/Sex	Symptoms	Physical examination	Vital signs	Ultrasound/CT findings	Bilirubin (total/direct, mg/dL) (0.2-1.2/0-0.3)	AST/ALT (U/l) (10-40/9-50)	WBC (10^9/L) (3.5-9.5)	Hb (g/dL) (11-15)	Platelets (10^9/L) (125-350)
Park *et al* [20], 2004	49/F	Recurrent fever, rash, and polyarthritis. Confused mental status on admission	Icterus, Murphy's sign (+), enlarged liver and spleen, facial rash, dehydrated tongue, equivocal neck stiffness, purpuras over the limbs, scabs of zoster	T 39 °C, BP 90/60 mmHg, HR 100 bpm, RR 30	Hepatosplenomegaly, thickened gallbladder wall, pericholecystic fluid collection, ileocolitis, right pleural effusion and ascites	3.7/2.8	453/154	7.1	9.5	17
Vallianou *et al*[21], 2014	28/F	Fever, vomiting, confused mental status, abdominal pain	Severe and diffuse abdominal tenderness	T 40 °C, no peripheral pulse, systolic BP 50 mmHg	Gallbladder enlargement with edema	/	/	/	/	/
Arai *et al* [8], 2021	21/F	Recurrent fever, rash, polyarthritis, nausea, vomiting, right hypochondriac pain	Rash, enlarged liver and spleen, tenderness in both shoulder and knee joints	T 40 °C	Hepatosplenomegaly, gallbladder enlargement and wall thickening, acalculous, cervical lymphadenopathy	2.15/1.56	763/469	2.3	11	79

AOSD: Adult-onset Still's disease; AST: Aspartate transaminase; ALT: Alanine aminotransferase; BP: Blood pressure; RR: Respiratory rate; T: Temperature; WBC: White blood cell count; Hb: Hemoglobin; HR: Heart rate.

findings, our final diagnosis for the patient was HAV-associated AAC.

Viral infections other than HAV may also lead to AAC. Hepatitis B virus[23,24] and hepatitis C virus [25,26] have both been reported as causes of AAC. Other viruses such as Epstein-Barr virus (EBV)[27,28], dengue virus[29,30], and human immunodeficiency virus[31,32] have also been implicated in AAC and have presented with an acute abdomen. More recently, coronavirus (COVID-19) has been reported in AAC cases[33], even leading to gangrenous cholecystitis[34]. Therefore, viral serology is an important diagnostic modality to search for a possible underlying etiology when a patient presents with AAC of unknown cause.

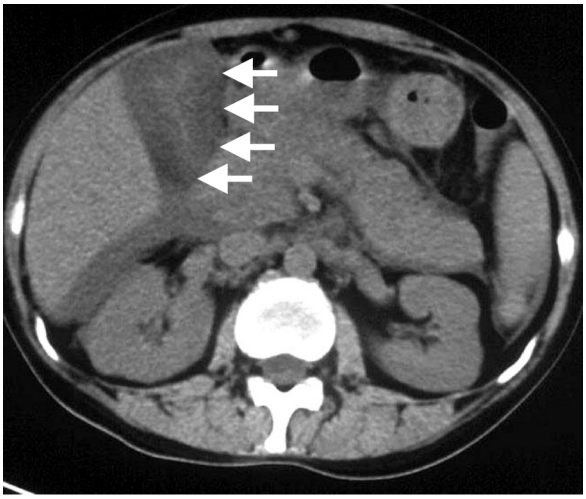

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Figure 1 Computed tomography scan of the gallbladder and its surroundings. Axial computed tomography image confirmed distended gallbladder (9.1 cm × 4.1 cm) with an evenly thickened, hydropic gallbladder wall (approximately 1.8 cm). Pericholecystic and hepatic fluid was also seen. No calculi were present.

Due to the complexity of the case, our patient received intravenous fluid support, a vasoactive agent, steroid treatment, antibiotic management, and surgical intervention. Surprisingly, no perforation nor necrosis was found in the gallbladder after cholecystectomy. Due to the limitations of current imaging modalities and laboratory testing, it can be difficult to accurately determine the actual condition of the gallbladder prior to operation. However, as summarized previously, most HAV-associated AAC cases are self-limiting, and conservative management of AAC may be adequate[18]. Thus, cholecystectomy may be an option when faced with AAC but requires careful consideration and evaluation of the surgical necessity, not least given the positive outcomes of most patients with HAV-associated AAC with conservative therapy alone.

This study has several limitations. First, we only showed the association between hepatitis virus infection and AAC, and the cause-effect relationship between them is still debatable. Further validation of the cause of HAV-associated AAC requires evidence from animal experiments or cohort studies. Second, we did not examine whether the patient had hyperferritinemia, which is often present in active AOSD. However, our patient did not have anemia, thrombocytopenia, and did not develop DIC, and steroid treatment did not control the clinical course. These findings strongly disfavor active AOSD causing the AAC. This study is also limited by the availability of only three cases of AOSD-associated AAC, so we cannot be certain that these cases are representative. More cases of AOSD-associated AAC need to be described to verify our conclusions.

CONCLUSION

In conclusion, although AAC caused by HAV or AOSD is rare, it is possible that these conditions can overlap and complicate the diagnosis and management of AAC. When AAC cannot be explained by AOSD, it is important to search for other primary causes of AAC, and viral serology should form part of the diagnostic work-up. HAV-associated AAC is mostly self-limiting, and conservative therapy is usually adequate management for these patients unless gallbladder perforation is likely. Overall, however, the prognosis of AAC caused by HAV is very good, with conservative management the cornerstone of treatment.

FOOTNOTES

Author contributions: Jiao Y conceived this study; Chang CH and Wang YY drafted the manuscript; Jiao Y critically revised the manuscript; all authors have revised the final version of the manuscript and approved it for publication.

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CASE REPORT

Transverse myelitis caused by herpes zoster following COVID-19 vaccination: A case report

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Abstract

BACKGROUND

Transverse myelitis (TM) is characterized by sudden lower extremity progressive weakness and sensory impairment, and most patients have a history of advanced viral infection symptoms. A variety of disorders can cause TM in association with viral or nonviral infection, vascular, neoplasia, collagen vascular, and iatrogenic, such as vaccination. Vaccination has become common through the global implementation against coronavirus disease 2019 (COVID-19) and reported complications like herpes zoster (HZ) activation has increased.

CASE SUMMARY

This is a 68-year-old woman who developed multiple pustules and scabs at the T6-T9 dermatome site 1 wk after vaccination with the COVID-19 vaccine (Oxford/AstraZeneca ([ChAdOx1S{recombinant}]). The patient had a paraplegia aggravation 3 wk after HZ symptoms started. Spinal magnetic resonance imaging (MRI) showed transverse myelitis at the T6–T9 Level. Treatment was acyclovir with steroids combined with physical therapy. Her neurological function was slowly restored by Day 17.

CONCLUSION

HZ developed after COVID-19 vaccination, which may lead to more severe complications. Therefore, HZ treatment itself should not be delayed. If neurological complications worsen after appropriate management, an immediate diagnostic procedure, such as magnetic resonance imaging and laboratory tests, will start and should treat the neurological complications.

Key Words: Herpes zoster; Transverse myelitis; Paraplegia; COVID-19; Vaccination; Case report

Core Tip: Reports are increasing that transverse myelitis (TM) is a rare herpes zoster (HZ) complication and is linked to coronavirus disease 2019 (COVID-19) vaccines. HZ following the COVID-19 vaccination may lead to more severe complications due to the vaccine immunocompromising the patient. Typically, complications like TM from HZ may be rare, and difficult to diagnose. If there is diagnosis confusion, TM will progress rapidly, delaying the appropriate treatment. A critical point is to implement appropriate HZ therapy without delay simultaneously with neurological examination to evaluate TM progress and treatment and HZ care with pain control to protect against complications like postherpetic neuralgia.

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INTRODUCTION

Herpes zoster (HZ) disease is caused by the varicella-zoster virus (VZV), another herpes virus member. The virus becomes dormant in the cranial nerve and dorsal root ganglia in the spine alongside the spine. It is later frequently reactivated, bringing about zoster and postherpetic neuralgia[1]. In immunocompromised patients, even in immunocompetent elderly, VZV can cause central nervous system diseases including encephalopathy, myelitis, and neuralgia[2]. Commonly, it begins to recover within a week of the outbreak. Still, it may last for weeks or even months, and it is a disease that can leave complications, such as urinary dysfunction and lower extremity motor or sensory weakness.

There are increasing reports regarding HZ activation after the coronavirus disease 2019 (COVID-19) vaccination administration, which is ongoing during the pandemic[3]. HZ is presumed to be caused by certain immunomodulation that allows VZV to arise from latency due to the vaccination, but its exact mechanism is unknown. It has been reported that transverse myelitis (TM) rarely occurs as an HZ complication. Nonetheless, reports that TM has occurred after COVID-19 vaccination is also increasing as vaccination has become widespread[4].

This is a transverse myelitis case, an unusual complication caused by VZV reactivation or COVID-19 vaccination. This case was diagnosed *via* spinal magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) examination. The patient experienced almost complete recovery with only minor muscle strength and sensory impairment after treatment.

CASE PRESENTATION

Chief complaints

A 68-year-old woman presented with 3 d of both lower limb weakness, associated with both lower limb numbness and multiple skin lesions in the left thoracic area.

History of present illness

4 wk before the visit, the patient received the AstraZeneca COVID-19 vaccination. A week later, multiple skin lesions developed on her back and buttock. Thoracic pain developed with hyperesthesia, for which she consulted the pain clinic. T-spine epidural nerve block two times was performed to control the pain. Worsening pain spread to the back 3 days after the procedure. Afterward, weakness and numbness were felt in both lower legs, and the patient developed a gait disorder.

History of past illness

After a slip and fall accident at the age of 7, the patient felt lower body weakness but could still ambulate. Gait instability became very severe 5 years ago ambulation could only be performed with a walker. No other specific findings were found in the patient's history.

Personal and family history

The patient had no family history or genetic disease.

Physical examination

On physical examination, the patient's mental status was alert with stable vital signs; body temperature was 36.8 °C. Multiple rashes and crusts were observed from the back to the chest, corresponding to the T6-T9 unilateral dermatome (Figure 1).

Motor and sensory examination showed decreased sensation (including vibratory and thermal) below the T7 Level by 50%-60% compared to the right side. The upper limb power average is grade 5 with grade 1 power in both lower limbs. Deep tendon reflexes were 2+ in the ankle, and 4+ in the knee, activated. Babinski's sign was positive bilaterally with clonus at the right ankle. Along with the lower extremity weakness, there were limb numbness and urinary retention symptoms.

Based on the above symptoms, nerve damage by physical compression was considered, such as epidural hematoma; central nervous system diseases, such as TM by zoster and demyelinating diseases, such as multiple sclerosis, as differential diagnosis.

Laboratory examinations

Investigations done were as follows: White blood count 9.7 × 10^3/mL, hemoglobin 12.2 g/dL, platelet count 231 × 10^3/mL, and ESR of 3.5 mm/h and CRP of 2.3 mg/dL. VZV DNA was detected *via* polymerase chain reaction (PCR) amplification in blood. The blood sample results for herpes simplex virus, cytomegalovirus, and Epstein–Barr virus were negative.

Lumbar CSF study showed the following: Intracranial pressure (ICP) 170 mmH_2O, red blood cell count 100 cells/uL, white blood cell count 402 cells/uL (99% monocytes, 1% lymphocyte), protein 133 mg/dL, and glucose 66.7 mg/dL. VZV DNA was not detected *via* PCR amplification in CSF. AFB stain, Gram stain, cytology for malignant cells, and cultures were all negative.

Demyelinating workup was negative for AQP4-Ab, oligoclonal band, and IgG index.

Imaging examinations

Brain computed tomography (CT) & magnetic resonance imaging (MRI) finding is nonspecific. Spine MRI showed old T5 compression fractures with some kyphotic deformity at the upper T-spine and subtle intramedullary T2 signal hyperintensity at the T6–T9 Levels, which suggested TM (Figure 2).

Neurologic examinations

Somatosensory-evoked potential (SSEP) was performed. Median SSEP showed normal conduction, whereas tibial SSEP was delayed in the iliac crest and cerebral cortex level, right dominantly (Figure 3).

FINAL DIAGNOSIS

The diagnosis was TM with HZ.

TREATMENT

With the HZ diagnosis, the patient was started on intravenous acyclovir for 14 days with methylprednisolone 1 g pulse therapy for 3 days. Because the symptom slowly improved, HZ treatment was decided to be continued with physical therapy and oral prednisolone for TM treatment. Because of continued pain from HZ, intravenous (IV) Ketorolac was administered as well as oral gabapentin.

OUTCOME AND FOLLOW-UP

On admission on Day 13, both lower limb distal motor power improved from grades I to grades III. On Day 17, standing and gait disturbance improved to partial impairment.

Subsequently, neurosurgery evaluation determined that it was not a surgical indication. Lower extremity muscle strength and sensation improved to some extent, 3 mo later, similar to before the HZ.

DISCUSSION

HZ is a disease that occurs when the VZV exists in a dormant state in the body and is reactivated. Usually, rashes and characteristic blister-type lesions appear on the skin within a few days, with accompanying pain in the area. Zoster is rare in young people and usually occurs in adults > 60 years old with poor immunity[5]. Zoster is not limited to the skin areas and sensory nerve distribution in immunocompromised patients. Still, it may appear with various neurological complications like encephalopathy, cerebral infarction, neuralgia, and myelitis[6].

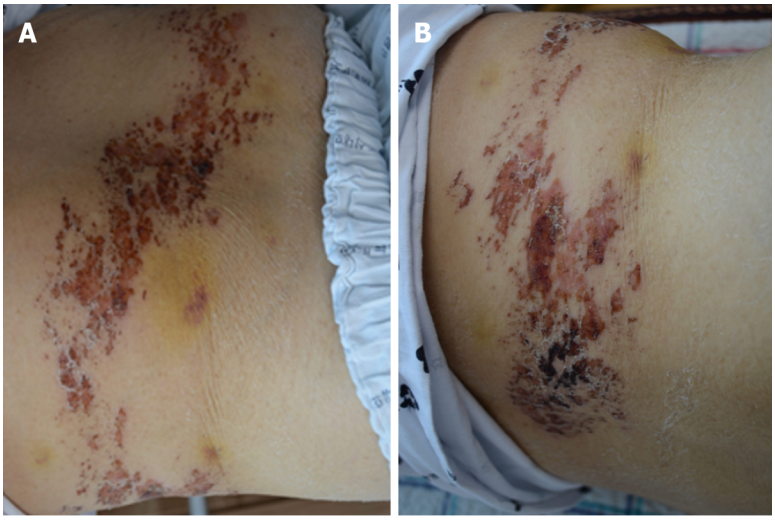

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Figure 1 Unilateral multiple crusts on an erythematous base on the right side of the lower back, corresponding to the right T6-9 dermatomes. A: Back; B: Rt. Side buttock.

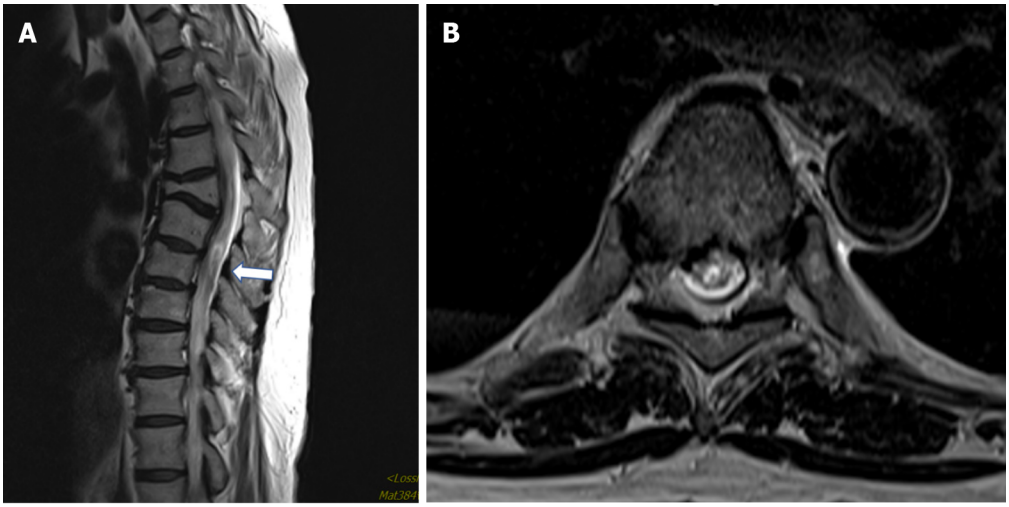

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Figure 2 Magnetic resonance imaging of the patient. A: Whole spine magnetic resonance imaging (T2 weighted sagittal image) shows old compression fractures of T5 and diffuse hyperintensity from T6 to T9 Level (white arrow); B: The axial image shows signal elevation centrally at the T7 Level.

There are numerous TM causes, including bacterial, fungi, parasitic, and viral infections. Autoimmune system disorders like lupus attack the body's tissues, and multiple sclerosis can be connected to TM as the first sign. Other myelin disorders, such as multiple sclerosis and neurosarcoidosis could also cause it[7]. Other conditions, such as a spinal cord stroke, are often confused with TM, requiring different treatment approaches[8]. TM diagnosis can be found in immunological and virological examinations, CSF examination results, MRI findings, and clinical manifestations[9]. MRI efficacy is unclear, but the typical MRI appearance in TM was iso or hypointense on T1 weighted imaging (T1WI) and poorly delineated hyperintense signal on T2WI in the central spinal cord lesion extending up to three to four spinal segments, involving more than two-thirds of the cord's cross-sectional area[10]. CSF laboratory findings describe pleocytosis with moderate lymphocytosis and a slightly elevated protein level (100–120 mg/dL). Glucose levels are normal. Likewise, the CSF analysis, in this case, revealed an increased white blood cell count of 402/μL, a protein level of 133 mg/dL, and average glucose of 66.7 mg/dL, which is suggestive of inflammation.

In parainfectious TM, the injury may be associated with the systemic response to VZV reactivation, especially in immunocompromised patients, with inflammation on either side of the spinal cord. This neurological disorder often damages nerve myelin and interferes with nerve pathways transmitted throughout the body[11]. The most common first symptoms were sensory change, weakness, and pain. It can cause bowel and bladder dysfunction[12]. Because of its rarity, definitive treatment has not yet been established, but it is reported that symptoms improve when treated with antiviral drugs and

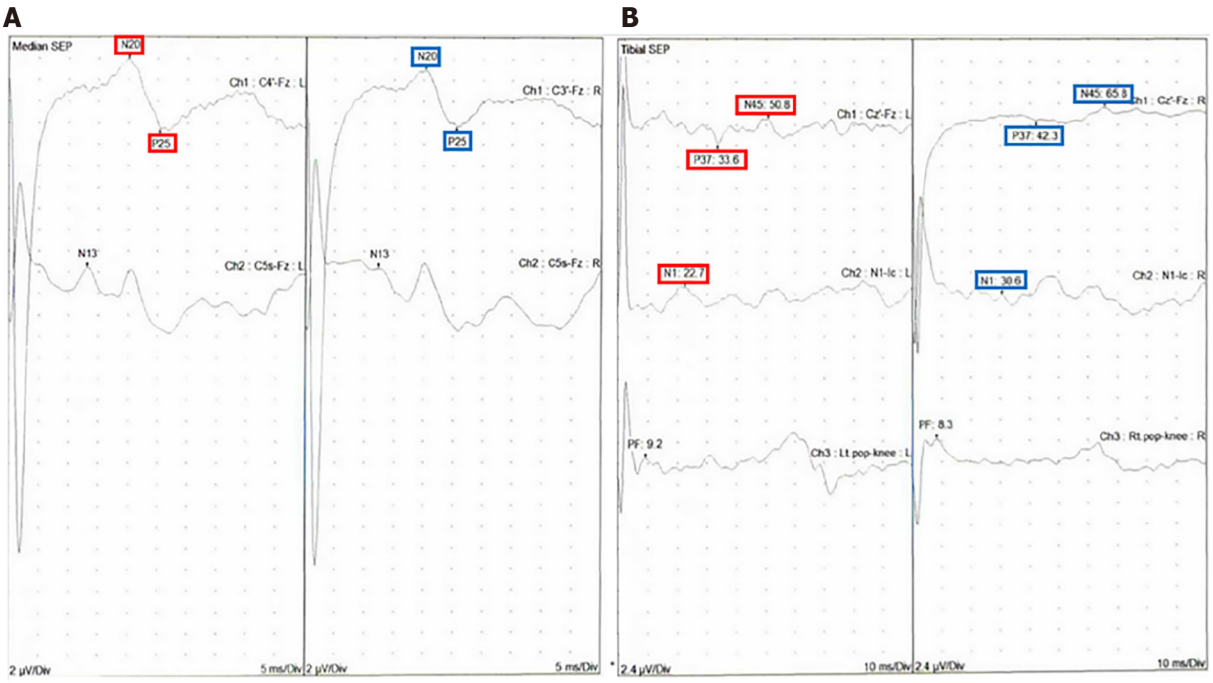

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Figure 3 The somatosensory evoked potentials were recorded by alternately stimulating each posterior tibial nerve at the ankle region behind the medial malleolus or the median nerve at the wrist. Two averages of 120 trials were obtained to stimulate each nerve. The somatosensory evoked potentials revealed well-developed cortical peaks for either arm. A: The principal peaks of N20 and P25 were 17 and 21 ms for both MNs; B: The peaks of both P37, N45, and N1 were delayed with the right specific in posterior tibial nerve. No side-to-side latency difference was noted.

steroids, which are zoster treatments[13]. VZV DNA and VZV antibody are detected in CSF to confirm the TM diagnosis by varicella zoster. However, in most cases, PCR tests in the CSF are confirmed negative, and there are only a small number of cases in which DNA was detected in PCR tests. Therefore, this disease cannot be completely excluded even if CSF PCR is negative[14,15].

This patient's MRI findings and CSF examination suggested TM. After the skin symptoms of zoster appeared, neurological symptoms appeared consecutively. Accompanying neurological symptoms improved after antiviral and steroid therapy. The timing of recovery of the neurological symptoms and the time of negative zoster in the blood test PCR results are consistent to some extent.

This patient underwent a thoracic epidural block treatment before paraplegia occurred. There may be a suspicion of nerve damage due to direct trauma to the spinal cord from the epidural block needle or hematoma by bleeding in the epidural area, causing pressure on the spinal cord. In the event of paralysis due to mass effects caused by hematoma or drug, immediate decompression is required and permanent nerve damage may remain[10,16]. However, based on the imaging findings, it may be considered that the possibility is not high because cord damage and hematoma were not observed in the MRI image, and the symptom progression after the treatment continued to improve but could not be completely excluded.

In this case, paraplegia occurred in zoster patients, which was thought to be caused by a mass effect due to hematoma secondary to an epidural block but was diagnosed with TM, which does not indicate emergency surgery, after the MRI finding. Many patients with zoster proceeded with epidural blocks due to pain. Still, it is essential to explain the possibility of neurologic symptoms by transverse myelitis and hematoma by nerve compression. The fluoroscopy-guided method is better than the Loss of resistance (LOR)-a blind technique in reducing complications. Supposed neurological symptoms, such as muscle weakness can occur in zoster patients. In that case, additional tests, such as CSF and MRI imaging, are required to consider paraneoplastic and neurologic complications, such as TM. Active antiviral treatment may help the patient's prognosis[17].

As side effects caused by the COVID-19 vaccine are gradually reported, case reports are also increasing. Unlike ordinary cases, HZ by COVID-19 vaccine may have occurred in healthy men (46 and 42 years old) without any comorbid diseases[3]. Vaccination of both mRNA and adenovirus protein methods will cause complications, such as HZ and TM.

In this case, a diagnostic method is essential for differential diagnoses, such as early detection, multiple sclerosis, and neurosarcoidosis. However, it would have been challenging to suspect myelitis caused by the COVID-19 vaccine because it occurred close to the vaccination date. Therefore, hematoma caused by spinal cord damage was constantly suspected. If TM was suspected, there was also a report that symptoms improved 5 d after plasma exchange treatment[4]. The muscle weakness in this patient's

lower extremities has also progressed. The newly developed neurologic symptoms confused with the diagnosis because of the history of leg weakness caused by an accident in childhood. The pain persisted due to HZ at the lesion site, making the differential diagnosis more difficult, especially in rare myelitis caused by the COVID-19 vaccine.

CONCLUSION

This case shows the association between the COVID-19 vaccination and the occurrence of HZ, as well as the association with TM occurrence, a secondary complication of HZ, and a complication of the COVID-19 vaccine. It rapidly progressed during the confusion with the diagnosis and delayed the appropriate treatment. The critical point is to implement appropriate treatment without delay while checking improvements in the neurological examination and HZ wound care with pain control to protect from postherpetic neuralgia.

FOOTNOTES

Author contributions: Lee HY conceived the article; Kim SW and Kim DJ collected the data; Seo JW and Lee HY assembled the data; Cho SY, Seo JW, Kim SW, Lim KJ, Lee HY, Kim DJ provided the study materials, write the manuscript and approved the manuscript.

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CASE REPORT

Primary malignant melanoma of the esophagus: A case report

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Abstract

BACKGROUND

Primary malignant melanoma of the esophagus (PMME) is a rare malignant disease whose clinical and molecular pathological features, origin and pathogenesis, diagnosis and treatment have not been elucidated.

CASE SUMMARY

In this paper, we report a case of a 73-year-old male with PMME. The patient complained of progressive dysphagia accompanied by substantial weight loss. Gastroscopy revealed a purple black bulging-type mass in the lower esophagus with easy bleeding on contact and scattered satellite lesions in the stomach. Histopathological biopsy revealed melanocytes in the esophageal mucosa. Physical examination and multidisciplinary consultation led to diagnostic exclusion of melanoma originating in other organs, such as the skin. Through this case report and literature review, we aimed to describe the clinical and molecular pathological features of PMME and summarize possible pathways of pathogenesis as well as cutting-edge therapeutic advances.

CONCLUSION

PMME is a rare malignancy of the esophagus with a poor prognosis. Clinicians should raise their awareness and be able to identify early lesions.

Key Words: Primary malignant melanoma of the esophagus; Clinicopathological features; Diagnosis and treatment; Pathogenesis; Prognosis; Case report

Core Tip: We report a case of a 73-year-old male with primary malignant melanoma of the esophagus (PMME) and extensive systemic multiple metastases, with an unavoidable mortality outcome despite aggressive diagnosis and treatment. Through this case report and literature review, we aimed to further improve clinicians' understanding of the clinical and molecular pathological features, origin and pathogenesis of PMME, to avoid misdiagnosis and missed diagnoses, to present cutting-edge treatment advances and to develop individualized and comprehensive treatment plans tailored to patients in an effort to improve their clinical outcomes.

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INTRODUCTION

Malignant melanoma is a malignant tumor with extremely high malignancy and associated with a poor prognosis caused by the malignant transformation of melanocytes distributed in the stroma. It occurs mainly in the skin but also in the adjacent mucous membranes of the skin, such as the nasopharynx, oral cavity, and conjunctiva, and in the gastrointestinal tract, including the rectum and anus. However, malignant melanoma originating in the esophagus is extremely rare[1], and there are only 400 published case reports worldwide[2].

Primary malignant melanoma of the esophagus (PMME) accounts for approximately 0.1%-0.2% of primary esophageal malignancies[3], with an estimated incidence of 0.0036 cases per million/year[2]. It is difficult to diagnosis and is characterized by rapid progression, high recurrence and metastasis rates, and poor prognosis. The rarity of PMME, limited awareness of clinicians, and diverse histomorphology of the disease have been shown to lead to a low presurgical confirmation rate and frequent misdiagnosis as esophageal cancer, hemangioma, lymphoma, hematoma or other disease at initial presentation.

Therefore, there is an urgent need to better understand the characteristics of PMME. We report a case of PMME in a 73-year-old male, along with a literature review of previous cases, to summarize the epidemiological features and clinicopathological characteristics of PMME, explore potential pathogenic mechanisms, and report on cutting-edge advances in biologic therapy.

CASE PRESENTATION

Chief complaints

A 73-year-old Chinese male complained of progressive dysphagia for 7 mo.

History of present illness

Seven months prior, the patient began to have dysphagia with no obvious cause that was initially obvious when eating solid food, which required water intake; his condition worsened, and eventually the patient could eat only liquid food and suffered substantial weight loss of approximately 9 kg; there was no chest pain, nausea, vomiting, vomiting blood, black stool or other discomfort. He then consulted a local hospital, and gastroscopy revealed a purple black mass in the lower part of the esophagus (30-39 cm from the incisor); when touched, red blood flowed from this mass. The local hospital proposed a diagnosis of hematoma or hemangioma, and given the risk of bleeding associated with biopsy, no aggressive biopsy was performed to obtain pathology, and the patient was referred to our hospital for treatment.

History of past illness

The patient had a history of fish spikes that had been stuck in the esophagus 1 year prior, a condition that resolved on its own without endoscopy. Forty years previously, he was diagnosed with tuberculous pleurisy and was cured with standardized antituberculosis treatment for 3 years.

Personal and family history

The patient denied any familial history of malignancy.

Physical examination

The admission vital signs were as follows: Body temperature, 36.1 °C; blood pressure, 14.1/9.8 KPa; heart rate, 81 beats per min; and respiratory rate, 21 breaths per min. In addition, the patient was lean

with a body mass index of 18.5 kg/m^2; there was painless enlargement of axillary and inguinal lymph nodes along with abdominal tenderness unaccompanied by pressure pain or rebound pain; no abnormal masses were palpated. Manual anal examination was not performed.

Laboratory examinations

Hemoglobin levels were normal. Serum tumor markers were normal (including carcinoembryonic antigen, carbohydrate associated antigen 19-9, and alpha-fetoprotein). The fecal occult blood test was negative. The coagulation function D-dimer level was 0.82 μg/mL (reference value less than 0.5 μg/mL). The remaining routine blood and urine analysis showed no abnormalities.

Imaging examinations

Enhanced computed tomography (CT) of the chest, abdomen and pelvis showed a soft tissue mass in the middle and lower esophagus, suggesting esophageal cancer, and multiple enlarged lymph nodes on the gastric lesser curvature and retroperitoneum. Enhanced CT of the chest showed a clear intrapulmonary artery filling defect, and pulmonary thromboembolism was considered. Upon cranial magnetic resonance imaging (MRI), no important abnormal signal was seen in the brain parenchyma.

Further diagnostic work-up

Gastroscopy was repeated and showed a bulging mass in the esophagus (30-40 cm from the incisor) characterized by a blackish color, rough surface, seeming erosion in the middle of the lesion, and easy bleeding on contact; it caused a narrowing of the esophageal lumen, but an endoscope could pass by it. The gastric fundus and mucosa of the gastric body were scattered with multiple flat elevated lesions, approximately 0.4-0.6 cm in size and blackish in color (Figure 1A). Ultrasound endoscopy revealed that the lesion had mixed echogenicity, predominantly hypoechogenicity, and involved the entire wall of the duct, with enlarged lymph nodes visible outside the wall (Figure 1B). Gastroscopy and ultrasound endoscopy further validated the enhanced CT findings (Figure 1C). A diagnosis of malignant melanoma of the esophagus was considered with a high possibility.

Upon histopathological examination, the combined morphological and immunohistochemical findings were consistent with malignant melanoma [immunohistochemistry: S-100 monoclonal (+), human melanoma black antibody (HMB45) (+),melanoma antigen protein (Melan-A) (+), Ki67 (MIB-1) (80% +), Sry-related HMg-Box gene 10 (SOX-10) (+), CK (AE1/AE3) (-)] (Figure 1D).

Whole-body positron emission tomography (PET)-CT revealed hypermetabolic occupancy in the lower and middle esophagus, multiple hypermetabolic lymph nodes throughout the body, multiple hypermetabolic foci in bone, and malignant lesions with multiple metastases in lymph nodes and bone. A ground-glass shadow in the lower lobe of the left lung with mild metabolic increase was seen and cited for close follow-up (Figure 1E).

The patient had a brown swelling of approximately 0.5 cm in diameter behind the right ear, which was diagnosed as seborrheic keratosis on dermoscopy.

FINAL DIAGNOSIS

Given the patient's medical history and the results of adjuvant examinations, the final diagnosis was PMME with gastric metastasis, lymph node metastasis, bone metastasis, possible pulmonary metastasis, and acute pulmonary thromboembolism (low- to moderate-risk)[4].

TREATMENT

Considering the patient's tumor stage and physical status, the oncology specialist was invited to develop a first-line treatment plan: Chemotherapy + immunotherapy, including dacarbazine and programmed death 1 (PD-1) (pablizumab). Considering the patient's risk of bleeding from esophageal tumors, the prescribed anticoagulation regimen was edoxaban 30 mg per day orally for pulmonary thromboembolism. In addition, due to the patient's significant dysphagia and weight loss, we gave him individualized intravenous nutrition infusion, including glucose, essential amino acids, fat emulsion and electrolytes.

OUTCOME AND FOLLOW-UP

Telephone follow-up was performed 3 mo after the diagnosis, and the patient had died.

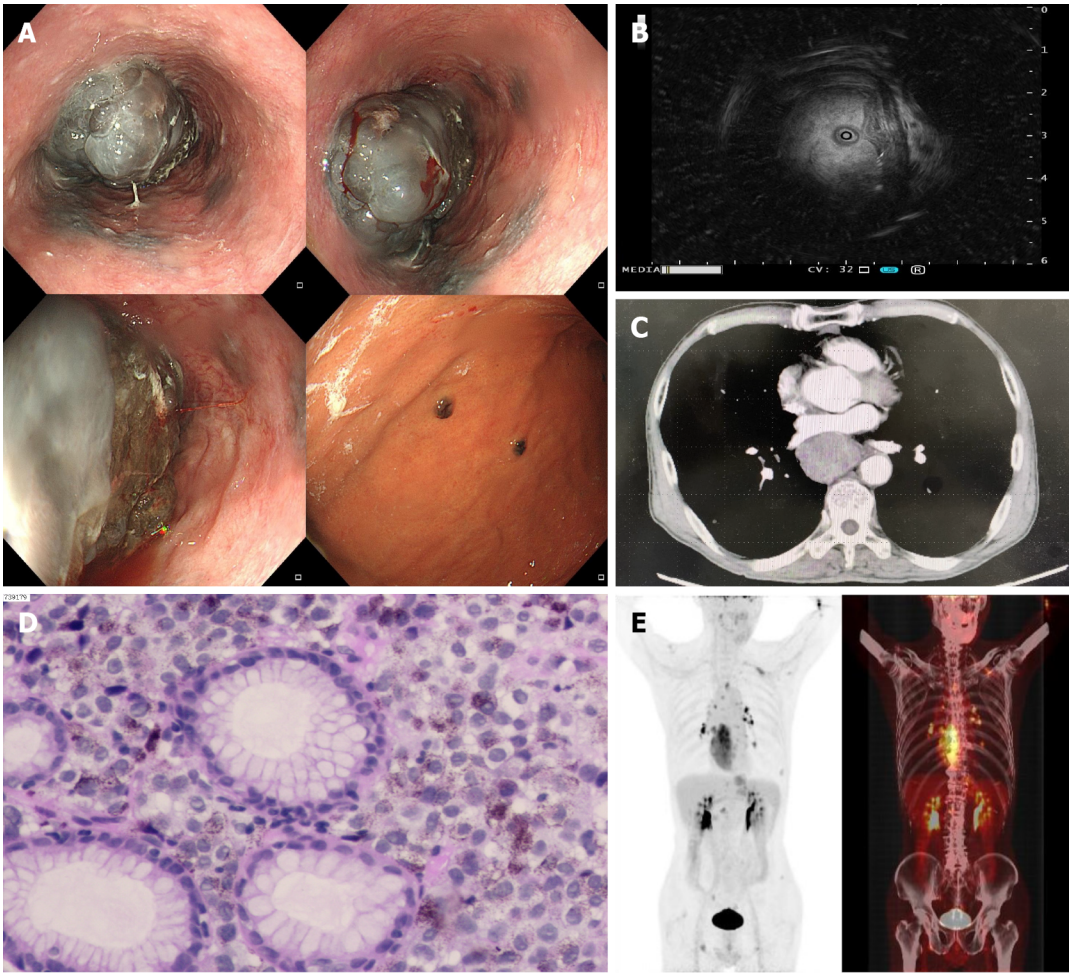

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Figure 1 Imaging and pathological examinations of the patient with primary malignant melanoma of the esophagus. A: Gastroscopy revealed in the esophagus (30-40 cm from the incisor) a bulging mass with blackish color, rough surface, seeming erosion in the middle, and easy bleeding on contact. The gastric fundus and mucosa of the gastric body were scattered with multiple, flat, blackish elevated lesions of approximately 0.4-0.6 cm in size; B: Ultrasound endoscopy demonstrated that the main lesion had mixed echogenicity, predominantly hypoechogenicity, and involved the entire wall of the duct, with enlarged lymph nodes visible outside the wall; C: Chest contrast-enhanced computed tomography showed a soft tissue mass in the middle and lower esophagus; D: Pathology showed uniform and consistent heterogeneous cell infiltration in the intrinsic layer; the cells were small and round with clear boundaries; some of the cytoplasm carried pigment granules; and the nucleus was clearly chromatin fine; E: Whole-body positron emission tomography/computed tomography showed hypermetabolic occupancy in the lower and middle esophagus, multiple hypermetabolic lymph nodes throughout the body, and multiple hypermetabolic foci in bone.

DISCUSSION

In this paper, we report a rare case of PMME that included extensive systemic metastases and concomitant tumor-associated pulmonary thromboembolism and resulted in patient death as the final outcome. PMME is very rare and accounts for approximately 0.1%-0.2% of primary esophageal malignancies[5,6]. It is mostly seen in elderly people approximately 70 years of age and is more common in men than in women, with a male to female ratio of approximately 2:1[7]. It is primarily found in the lower and middle esophagus (> 90% of cases), with the lowest incidence in the upper segment[2,8]. The clinical manifestations are atypical, do not attract sufficient attention and vigilance, and may include progressive dysphagia, retrosternal pain, and weight loss[9,10], with a small number of cases being identified incidentally on physical examination[11]. PMME is highly aggressive and progresses rapidly clinically, with distant metastases observed at the time of diagnosis in 18.4% of patients[6] and lymph node metastases occurring most frequently, followed by liver, lung, and brain metastases[5]. According to previous studies, the median survival time of PMME patients is only 10-20 mo, with an overall 5-year survival rate of 5%[2] to 20%[3]. Early and accurate diagnosis and individualized comprehensive treatment may prolong the survival time of PMME patients.

Early and accurate diagnosis of PMME relies on imaging examinations such as endoscopy, ultrasound endoscopy, CT, MRI, and PET-CT, but histopathological examination remains the gold standard for confirming the diagnosis. Possible findings are summarized in the following list according to examination modality. Endoscopic findings are as follows: Wide basal polyp-like, myxoid mass with black, brown, gray or dark brown surface due to different degrees of pigmentation; some lesions may

have ulcers on the surface and bleed easily when touched; most lesions are solitary, a few are multiple, and surrounding satellite lesions may also be seen. Ultrasound endoscopic findings are as follows: Mainly originating from the mucosal layer; showing a heterogeneous hypoechoic shadow. Histopathological findings are as follows: Gross pathology may show polypoid, myxoid, or nodular elevations with or without melanin deposition. Routine hematoxylin and eosin staining can reveal melanin granules; microscopically, tumor cells infiltrate to varying depths and can infiltrate the plasma membrane with nested clusters, sheets, epithelial-like distribution, and rich interstitial vasculature; tumor cell infiltration can be accompanied by varying degrees of lymphocytic infiltration; melanocytes vary in size and volume and are round, polygonal, or irregular in shape, with large nuclei, partially visible eosinophilic nucleoli, easily seen pathological nuclear divisions, and abundant cytoplasm[12]. Immunohistochemical findings are as follows: Positive expression of proteins such as HMB45, Melan-A, S-100, vimentin, and SOX-10 but not epithelial tumor markers, myogenic markers or lymphoma markers, *etc.*[10].

Among them, HMB45 and Melan-A have shown better specificity[13,14]. Therefore, the Allen-Spitz diagnostic criteria are currently the more accepted diagnostic criteria for PMME[2], which include: (1) Tumors originating from areas of junctional changes within the esophageal squamous epithelium; (2) histology with typical melanoma structure and the presence of melanin granules within the tumor cells; (3) positive immunohistochemical staining for HMB45 and/or S-100; and (4) exclusion of metastasis of primary lesions in melanoma-prone sites such as skin, eye, anus, and rectum.

Patients with PMME have a short survival time and high mortality rate, and the exploration of their treatment options has never stopped. Scholars worldwide have not reached a consensus regarding PMME treatment options, which are mainly derived from treatment experience with cutaneous malignant melanoma. It is currently believed that radical surgical excision remains the treatment of choice for patients with early operable PMME. However, one study found multiple postoperative tumor recurrences despite radical esophagectomy, and further analysis of driver gene heterogeneity and clonality revealed recurrent subclonal drivers originating from the initial tumor, suggesting that early spread already existed beyond the scope of surgical resection[6]. This finding needs to be validated by additional studies and replication in patients with different tumor stages. If migration and implantation of subclones is confirmed to have occurred at an early stage of the tumor, in addition to early diagnosis and early surgical resection, more aggressive adjuvant therapy will be required postoperatively. Postoperative adjuvant therapy can be considered a multidisciplinary combination of radiotherapy, chemotherapy, targeted therapy, immunotherapy, *etc.* However, there is a wide divergence in the findings of previous studies as to whether combination therapy will considerably prolong the survival of patients. A large retrospective study in China showed that radiotherapy was an independent influencing factor on the overall survival of PMME patients, and the longest overall survival time among patients who received radiotherapy was up to 8.4 years, suggesting that individualized radiotherapy may be a key direction for future study regarding PMME treatment. In contrast, some studies have shown that radiotherapy and chemotherapy have limited therapeutic effects on PMME patients and do not prolong their survival time[2,15].

In recent years, the widespread use of molecular biology technologies such as second-generation gene sequencing has made it possible to explore PMME at the level of gene mutations and to develop individualized targeted therapies and immunotherapy[1,3]. For example, Li *et al*[16] found genetic mutations in the MAPK signaling pathway in 55% of PMME samples, suggesting that MEK/MAPK inhibitors may be suitable for the treatment of some PMME patients and help improve their clinical outcomes[16]. In addition, immunotherapy is an emerging area of research in the treatment of PMME[3,17]. PD-1 inhibitors such as pablizumab and nabritumomab and cytotoxic T-cell-associated antigen 4 inhibitors such as ipilimumab have been shown to significantly prolong overall survival in metastatic cutaneous melanoma when combined[2]. Indeed, immune checkpoint inhibitors are currently positioned as first-line therapy for cutaneous melanoma without *BRAF* gene mutations[18], but their effectiveness in the treatment of PMME remains to be evaluated in multiple-phase clinical trials. Wang *et al*[19] conducted a retrospective analysis of clinical data from 76 patients with advanced PMME in China who were classified into chemotherapy, targeted therapy, and PD-1 inhibitor groups. The results found that progression-free survival was significantly longer in the PD-1 inhibitor group than in the chemotherapy group (15.6 mo *vs* 3 mo, $P < 0.001$); it appears that PD-1 inhibitors hold promise for improving survival in patients with advanced PMME[19].

The origin of PMME has been the focus of debate, and its pathogenic mechanism is still unclear. The following hypotheses have been proposed: (1) PMME originates from melanocytes in the basal layer of the esophageal mucosal epithelium, and injury factors and overstimulation of growth factors produced by local cells in the mucosa contribute to the development of PMME; (2) in previous reports, melanocytes were not observed microscopically in some patients, whereas black granules were visible in the adjacent squamous epithelium of nonpigmented melanoma tissue, and melanin markers were positively expressed on the surface of the black granules, thus presumably suggesting an associated pathogenesis that involves black granules near highly proliferating malignant melanoma tissue in normal squamous epithelium[20]. It has also been shown that both pigmented and nonpigmented malignant melanomas are derived from black granules in adjacent squamous epithelium; (3) in addition, it has been proposed that PMME originates from ectodermal neural crest melanocytes and that

neural crest melanocytes migrate or become disoriented during embryonic development and remain in the esophageal epithelium, leading to PMME; (4) molecular biology has provided some clues to the occurrence and progression of PMME[3,16]. In one study, whole-exome testing of primary tumor, recurrent tumor, and normal control tissues from the same PMME patient revealed *ARHGAP35* gene mutations throughout tumorigenesis and recurrence and indicated that *ARHGAP35* gene mutations play an important role in promoting tumor recurrence and metastasis as well as the immunosuppressive microenvironment[6]; and (5) in addition, a series of driver gene mutations, such as *BRAF*, *NRAS*, *PTEN*, and *TP53*, have been observed in PMME samples with a high degree of microsatellite instability, suggesting the involvement of the MEK/MAPK signaling pathway in PMME development [1,2,16,21]. The findings of another study are consistent with this finding, showing a high degree of genetic instability and intratumoral heterogeneity in PMME samples and showing from gene clustering analysis that MAPK, transforming growth factor-β and other signaling pathways are involved in the progression of PMME[6]. However, a study in which the genetic profiles of 20 PMME patients were analyzed did not find mutations in genes common to melanoma, such as *BRAF* and *TP53*[9]. Therefore, the molecular genetic profile of PMME still needs to be analyzed and validated with a larger sample size. In addition to the question of pathogenic mechanism, the metastatic pathway of PMME is also an aspect we need to consider. The metastatic pathways of malignant tumors include direct infiltration, lymphatic metastasis and hematogenous metastasis. However, some patients with PMME have double or multiple primary tumors (approximately 13%)[2], and endoscopic examination mostly shows satellite foci in the stomach and duodenum, which does not exclude the presence of very early tumor cell migration and implantation[6], submucosal dissemination[1], longitudinal spread[22], and tumors with multifocal origin[23].

Compared with previous case reports, our study also has strengths and weaknesses. While previous reports focused on the clinicopathological features of PMME and tumor infiltration and metastasis, our study comprehensively addressed multiple aspects of pathogenesis, early diagnosis, and cutting-edge therapeutic advances in addition to the clinicopathological features and malignant biological behavior of the tumor. Moreover, while previous studies mentioned complications such as pericardial effusion and third-degree atrioventricular block, our study highlights for the first time that pulmonary thromboembolism, a tumor-associated complication, can increase the complexity of the patient's condition and limit more aggressive comprehensive treatment, advocating that clinicians should also enhance the diagnosis and management of tumor-associated complications. The shortcoming of our study is that the patient in our report declined molecular tests such as *BRAF* and *NRAS* due to economic factors, and the presence of meaningful driver mutations could not be clarified, creating a certain obstacle to the development of individualized targeted and immunotherapy regimens. Unfortunately, the patient experienced a fatal outcome.

CONCLUSION

PMME is a rare nonepithelium-derived malignancy of the esophagus with poor prognosis. Due to the atypical clinical presentation and diverse histomorphology, the accuracy of preoperative diagnosis is low. Clinicians and endoscopists should be aware of rare esophageal diseases, increase their vigilance regarding these disease, and identify early lesions in a timely manner. Standardized surgical resection combined with adjuvant therapy is still the mainstream treatment pathway for PMME, and more promising therapeutic targets, radiotherapy and immunotherapy options need to be explored in the future to improve the prognosis of PMME patients.

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