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Hepatitis B Virus Infection Related Scleritis and Ovarian Cancer: A Case Report

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Abstract

Hepatitis B virus (HBV) infection is a global public health issue that can lead to liver related complications such as abnormal liver function, cirrhosis, and liver cancer. Some patients may also present with extrahepatic manifestations, including polyarteritis nodosa, arthritis, and glomerulonephritis. Eye involvement may also occur, with most cases presenting as dry eye syndrome. However, there are few reports on HBV infection related scleritis. Here, we report a case of recurrent scleritis with joint pain and multiple abnormal immune and tumor indicators. After thorough identification at the time, it was ultimately considered that the primary disease was HBV infection, and symptoms and various indicators were restored only after antiviral treatment. However, follow-up observations revealed that the patient developed ovarian malignant tumors 3 years later. Through this case, we will strengthen our understanding of the multiple clinical manifestations of hepatitis B virus infection and help identify diseases as soon as possible and try to avoid the waste of medical resources, but we need to be alerted to the occurrence mechanism of extrahepatic manifestations of hepatitis B infection and its correlation with the risk of tumor occurrence.

Keywords: Hepatitis B, Scleritis, Monoclonal gammopathy of undetermined significance, Ovarian cancer

Introduction

Hepatitis B virus (HBV) infection remains a serious global public health problem [1]. Hepatitis B virus infection can cause acute or fulminant hepatitis and develop into cirrhosis and liver cancer [2]. In addition, with liver function impairment, HBV infection can also lead to various extrahepatic manifestations, including polyarteritis nodosa (PAN), glomerulonephritis, arthritis, cryoglobulinemia vasculitis, and non-Hodgkin lymphoma [3]. However, the extrahepatic manifestations of acute or chronic HBV infection have been underestimated to some extent for a long time.

Scleritis is a chronic, destructive inflammatory scleral disease characterized by eye pain, and in severe cases, it can lead to vision loss or even blindness [4]. Although it is known to be associated with systemic diseases such as rheumatic and infectious diseases [5], but there are relatively few reports of hepatitis B causing scleritis.

Ovarian cancer is the leading cause of gynecological cancer death, and a major challenge in treating ovarian cancer is that most patients are already in the late stage of initial diagnosis [6], so early identification of high-risk populations is of great significance. A study shows that compared with the general population, the incidence rate of ovarian cancer in HBV infected people is significantly higher [7]. However, there have not been many reports on the identification of high-risk populations for extrahepatic tumors among HBV infected individuals.

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Here, we report a case of chronic HBV infection accompanied by recurrent scleritis and joint pain, which ultimately improved after antiviral treatment. After a 3-year follow-up, ovarian cancer appeared and is currently undergoing active treatment. Through this case, we hope to help identify potential high-risk populations for tumors in HBV patients at an early stage.

Case Presentation

A 53-year-old female had a history of recurrent bilateral eye swelling, redness, photophobia, and tearing since 2018. In March 2021, she sought medical attention for severe pain in her right eye that had persisted for two weeks. She also experienced headaches, photophobia, tearing, and swelling and pain in her right knee. There was no fever, rash, or numbness in her limbs. She has a history of HBV infection and hypertension. Physical examination revealed conjunctival congestion and redness in both eyes (Figure 1). Laboratory tests showed normal complete blood count and complement levels. C-reactive protein was 11.23 mg/L, erythrocyte sedimentation rate (ESR) 73 mm/h, total protein 85.23 g/L, albumin 35.55 g/L, alanine aminotransferase 200.15 IU/L, aspartate aminotransferase 187.78 IU/L, alkaline phosphatase 144.09 IU/L, gamma-glutamyl transferase 276.01 U/L, creatinine 60.42 μmol/L, uric acid 281.22 μmol/L, alpha-fetoprotein (AFP) 88.4 ng/ml, immunoglobulin(Ig) G 45.93 g/L, IgA 6.33 g/L, IgM 5.66 g/L, IgG4 2.91 g/L, rheumatoid factor (RF) 6032.98 IU/ml (<20 IU/ml) and anti-cyclic citrullinated peptide (CCP) antibody 9.1 U/ml. Positive of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and hepatitis B core antibody (HBcAb). The HBV DNA level was 4.9×10^6 IU/mL. Negative of anti-nuclear antibodies, anti-extractable nuclear antigens (ENA) antibodies, anti-neutrophil cytoplasmic antibodies, human leukocyte antigen-B27, and autoimmune liver disease antibody spectrum. And negative of Epstein-Barr virus and cytomegalovirus. Serum immunofixation electrophoresis suggested monoclonal gammopathy with the type of IgG-λ. Further investigations including bone marrow aspiration and Positron Emission Tomography-Computed Tomography scan did not reveal malignant tumors.

The patient was eventually diagnosed with chronic HBV infection, secondary scleritis, and monoclonal gammopathy of undetermined significance (MGUS). She received liver protection and antiviral treatment, and her scleritis gradually improved and did not recur. One year later, the patient came for a follow-up visit and reported no recurrence of scleritis. Laboratory tests indicated ESR 11 mm/h, AFP 4.71 ng/ml, IgG 12.94 g/L, IgA 3.24 g/L, IgM 1.73 g/L, RF 36.06 IU/ml, HBV-DNA levels below the detection limit, and serum immunofixation electrophoresis was negative.

During the follow-up process, the patient received long-term antiviral treatment. In May 2024, due to abdominal distension, a complete examination revealed a left ovarian mass, and pathology showed clear cell carcinoma. No lymph node metastasis was observed, and active surgical and chemotherapy treatment was given.

Discussion

HBV infection is still a serious public health problem accompanied by progressive liver damage and can lead to various extrahepatic manifestations such as rheumatic, renal, and hematological disorders, which can affect patient mortality rates [8]. Eye involvement during HBV infection is not common. In the initial diagnosis, we fully excluded rheumatic diseases, other infectious diseases and malignant tumors, and finally diagnosed as HBV related secondary scleritis.

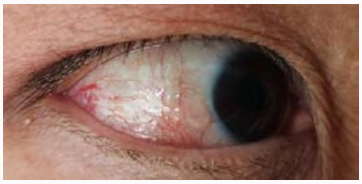

Figure 1: The conjunctiva of the patient's right eye was visibly congested and red.

There are few reports of HBV induced scleritis, and the pathogenesis of HBV related scleritis is not yet clear. The immune system may play a crucial role. As early as the early 1980s, some people proposed the hypothesis of the autoimmune origin of scleritis [9]. Previous studies have found that the pathogenesis of scleritis is related to local vasculitis caused by immune complex deposition [10]. Compared with the posterior sclera, immune complexes (ICs) preferentially deposit in the anterior sclera [11]. During the chronic phase of HBV infection, ICs containing HBs and/or HBe antigens can deposit outside the liver, leading to activation of the complement cascade and recruitment of inflammatory cells, and higher viral load or persistent infection can further stimulate the production of ICs, leading to their deposition in small and medium-sized arteries and causing vasculitis [12]. PAN is a type of vasculitis that is partially associated with HBV, and the main ocular inflammatory manifestations of this disease are scleritis, peripheral ulcerative keratitis, and retinal vasculitis. Fye et al. [13] reported that the level of circulating ICs is positively correlated with the activity of HBV associated PAN. Previous studies have also found that HBV infection is associated with the progression of IgA nephropathy, and IgA vasculitis can also cause scleritis [14]. Therefore, scleritis after HBV infection may be related to the deposition of circulating immune complex IgA. In addition, HBV infection can cause cryoglobulin vasculitis (CV), and Type II and III cold globulin are immune complexes composed of antigens and monoclonal (type II) or polyclonal (type III) IgM with rheumatoid factor activity [15]. Previous studies have shown that type II and III cryoglobulinemia are closely related to HCV infection (80-90%), but there are also some cases that are secondary to other viral infections, such as HBV (0.5-5.5%) [16]. Therefore, we speculate that scleritis may be an ocular manifestation of HBV infection induced vasculitis.

The patient also had concurrent MGUS. The cause of MGUS is unknown, but several studies have suggested that rheumatic diseases and infectious diseases can lead to MGUS, including Systemic lupus erythematosus (SLE, Sjögren's syndrome, rheumatoid arthritis (RA), and hepatitis [9,10]. After excluding malignant disorders, monoclonal protein (M protein) was considered as a manifestation secondary to HBV infection.

At present, there are no specific treatment guidelines for patients with HBV related scleritis. As HBV replication is a triggering factor, antiviral therapy is usually used as first-line treatment [17]. In addition, other drugs that can be considered may include glucocorticoids [18]. After anti hepatitis B virus treatment, the patient's symptoms such as scleritis and arthralgia improved significantly, and the liver function, liver tumor indicators, RF, anti CCP antibody, immunoglobulin and M protein returned to normal.

Then the patient was followed up for 3 years and found to have ovarian cancer. Previous studies have found that HBV can infect ovaries and eggs and replicate in ovaries, and the level of HBV DNA detected in follicular fluid of hepatitis B virus carriers is related to the

serum level [19]. The specific mechanism of the relationship between HBV and ovarian cancer is not yet clear. Research has shown that hepatitis B virus X protein (HBXIP) is highly expressed in ovarian cancer tissues [20]. HBXIP is a non-structural protein encoded by the HBV gene and is associated with virus replication and host immune response [21], suggesting that HBV may be involved in the occurrence and development of ovarian cancer.

In a word, in addition to virus replication, the patient with chronic hepatitis B virus infection in this case has recurrent scleritis attacks and arthralgia. Laboratory examination showed high levels of immunoglobulin, high levels of rheumatoid factor and MGUS. After early positive identification, the symptoms and the above indicators have significantly improved and returned to normal after antiviral treatment, but ovarian cancer appeared after follow-up 3 years.

Conclusions

This case emphasizes the extensive potential extrahepatic manifestations of HBV infection. It is hoped that we can identify and clarify the root cause as soon as possible under a number of abnormal indicators to avoid the waste of medical resources, but it also reminds us to closely monitor and follow up the occurrence of malignant tumors when chronic HBV infection presents extrahepatic manifestations such as repeated scleritis.

Compliance with Ethics Guidelines

All authors declare that they have no conflict of interest. Ethical board approval is not applicable in this case series.

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