DOI: 10.53469/jcmp.2025.07(02).27

Progress in the Study of Combined Immunosuppression in Patients with Cryptogenic Hepatitis B

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Abstract: ***Occult hepatitis B virus infection (OBI), as a special form of HBV infection, refers to HBsAg-negative body, but can be detected in liver tissues and/or serum with a low load of HBV DNA, often less than 200 IU/mL, and is still pathogenic and infectious. OBI does not lead to obvious damage to the liver in general, but when it is necessary to receive immunosuppressive treatment for coexisting diseases, reactivation of hepatitis B virus may occur, with the risk of developing into viral hepatitis, cirrhosis and liver cancer. In general, OBI does not cause significant liver damage, but when immunosuppressive therapy is required due to other diseases, reactivation of hepatitis B virus may occur, and there is a risk of developing viral hepatitis, cirrhosis and hepatocellular carcinoma. In this paper, we review the definition of OBI, its clinical characteristics, and the related research progress when receiving immunosuppressive therapy under different circumstances.***

Keywords: Cryptogenic hepatitis B virus infection, Immunosuppression, Hepatitis B virus reactivation.

1. Introduction

Hepatitis B virus infection is one of the major liver diseases in the world. The World Health Organization (WHO) reported that there are about 300 million chronic hepatitis B virus-infected people in the world, among whom OBI has not yet attracted widespread attention and urgently needs in-depth basic research and clinical diagnosis and treatment [1]. Previous studies have shown that OBI is defined as hepatitis B surface antigen negativity with detectable HBV DNA in liver tissue and/or serum [2]. OBI generally does not lead to significant liver damage when the body's immune function is normal, but when the body is in a state of immunosuppression, reactivation of the HBV virus may occur, leading to liver damage and the risk of progression to fulminant viral hepatitis, cirrhosis, and hepatocellular carcinoma [2]. As the technology of immunosuppressive therapy has matured, the understanding of hepatitis B virus reactivation in the context of OBI patients receiving immunosuppressive therapy has increased. With the growing maturity of immunosuppressive therapy, the understanding of hepatitis B virus reactivation in the context of immunosuppressive therapy in patients with OBI has gradually deepened. In this paper, we review the definition of OBI, clinical characteristics, the clinical situation of OBI patients receiving immunosuppression, and the prevention of reactivation in OBI.

2. Definition and Clinical Features of OBI

The International Conference on OBI (Italy, 2008) and the European Society of Hepatology (2012) defined occult hepatitis B virus infection (OBI) as a condition in which serum hepatitis B virus (HBs) antigen (HBsAg)-negative by conventional tests is usually accompanied by HBV DNA-negative, but the presence of HBV DNA can be detected in liver tissue and/or serum by liver tissue biopsy or by more accurate tests. HBV DNA is present, usually at low levels (<200 IU/mL) [2]. The diagnosis of OBI is currently difficult, and for the current definition of OBI, the gold standard is the detection of HBV DNA by liver tissue biopsy, an invasive test that is rarely used in clinical practice and for which there is no standardized detection method. Another method is to detect HBV DNA in the blood, the main problem of this method is that the HBV DNA load in the blood is low, and a more sensitive detection method is needed, and the best standard is to analyze the HBV DNA extracts in the plasma by PCR. The serological characteristics of OBI can be classified into two kinds, one is seropositive, which refers to the positivity of anti-HBc with or without the positivity of anti-HBs, and one is seronegative, which means that anti-HBc is positive with or without the positivity of anti-HBs, the seronegative, which means that anti-HBc is positive with or without the positivity of HBs. One is seropositive, which means anti-HBc positive with or without anti-HBs positive; the other is seronegative, which means all the serum markers of hepatitis B virus are negative. Seropositivity accounts for about 80% of OBI, while seronegative OBI is more difficult to diagnose because both antibodies are negative and serum HBV DNA is the only serum marker [2]. OBI has attracted increasing clinical attention because 1. OBI can still transmit hepatitis B virus, which can lead to HBV infection in clinical blood transfusion, hemodialysis filtration, liver transplantation, bone marrow transplantation, childbirth, etc. 2. OBI patients have their own chronic and insidious liver injuries and their strong correlation with chronic liver disease and HCC [3]. The majority of patients with OBI have normal or only mild fibrosis of the liver and normal liver biochemistry. The majority of patients with OBI have normal or only mildly fibrotic liver tissue and normal liver biochemistry, but they are still at risk of developing cirrhosis and hepatocellular carcinoma. Patients with a history of acute hepatitis B can carry small amounts of HBV DNA for long periods of time without any clinical features of liver damage, but the mild necroinflammation or fibrosis in the liver caused by this small amount of viral replication can persist for long periods of time. Many studies have shown that OBI is an important factor in the progression of liver disease to cirrhosis in HBV patients [3]. This suggests that OBI is not directly damaging in most cases, but can accelerate the progression of

the disease to advanced stages when combined with other liver diseases. Several retrospective or prospective studies on OBI and HCC (hepatocellular carcinoma) have shown a strong correlation between OBI and HCC, with a significantly higher prevalence of HCC in patients with OBI than in those without OBI. Numerous studies have shown that OBI maintains the cancer-promoting properties of chronic hepatitis B overt infection. This may be related to the following factors: (a) integration of HBV DNA into host genes; (b) production of proteins with potentially transformative properties; and (c) induction of chronic necroinflammation of the liver and progression to cirrhosis [4] The difficulty of diagnosing OBI and the absence of clinical features in most cases have led to a lack of uniformity in its clinical management, but with regard to the combination of immunosuppression in patients with OBI, the most recent guidelines of the European Association for the Study of the Liver (EASL) on the management of HBV infections recommend that all HBsAg-negative/anti-HBc-positive patients at high risk of immunosuppression should be treated with prophylactic antiviral therapy. prophylactic antiviral therapy [5].

3. Immunological Characterization of OBI

During OBI, the virus develops a dynamic immune balance with the host immune system. Host immune system surveillance plays an important role in the development of OBI. The covalent closed-circle DNA (ccc DNA) of hepatitis B virus exists stably in the nucleus of hepatocytes in the form of a chromatin free body for a long period of time. Despite the persistence of ccc DNA, it is now generally accepted that the host suppresses the overall replicative activity and protein expression of hepatitis B virus through epigenetic and immune responses, rendering HBsAg undetectable in the serum of patients with OBI [6]. Cellular immunity plays a central role in the immune response.CD8+ CTLs recognize and clear HBV-infected hepatocytes and maintain immune stability during acute hepatitis B infection, but long-term chronic hepatitis B infection depletes the number and function of T cells [7]. Studies have shown that the number of lymphocytes, T-lymphocytes, CD8T-lymphocytes and CD4-lymphocytes in patients with OBI are higher than those in HBsAg-positive patients, but still lower than those in normal people. Therefore, the HBsAg conversion in patients with OBI and the weakening of viral replication may be related to the enhancement of the cellular immune response, but a small amount of ccc DNA still remains in the liver, which doesn't mean that the virus has been completely cleared [8]. In addition, the balance between different T cell subsets shapes the immune response during HBV reactivation. In addition, the balance between different T-cell subsets shapes the immune response during HBV reactivation, and CD4 T cells also participate synergistically in cellular immunity, playing an important role in maintaining the immune response and preventing chronic inflammatory injury in the liver [6]. In addition, the balance between different T cell subsets shapes the immune response during HBV reactivation in OBI patients. In addition, the balance between different T-cell subsets shapes the immune response during HBV reactivation in patients with OBI.B lymphocytes also play an important role in adaptive immunity to hepatitis B virus through antibody production, immune response modulation. When recognizing hepatitis B virus antigens, the [9]. B-cells can eliminate the virus by differentiating plasma cells to produce antibodies specific to HBV. B-cells also have an immunosuppressive function, preventing excessive immune responses that can lead to liver damage. Similarly, chronic hepatitis B infection can lead to B-cell dysfunction. The innate cellular immune response (NK cells, DCs, macrophages, etc.) also plays an important role in maintaining the low replication state of the virus in OBI [10].

In clinical practice, studies have shown that patients with a history of hepatitis B still have strong T-cell immune responses against HBsAg after many years, which may be related to the insidious production of undetectable antigens by OBI over a long period of time. OBI with different serologic characteristics also had different HBV-specific T-cell responses, and the in vitro expansion of HBV-specific T-cells in seronegative (anti-HBc-negative) patients was significantly weaker than that in seropositive (anti-HBc-positive) OBI patients. In addition to the T-cell response, cytokines synthesized by the liver itself, such as tumor necrosis factor α and interferon γ, could also inhibit the replication and expression of HBV [10].

4. OBI and Immunosuppression in Different Contexts

The role of the immune response in OBI is suggested by the recurrence of HBV in many OBI patients on immunosuppressive therapy or with auto-induced impairment of the immune system. Long-term cryptogenic presence of ccc DNA in the nuclei of hepatocytes is thought to be the source of hepatitis B virus recurrence during immunosuppression, which is clinically characterized by hepatic serologic changes and fulminant hepatitis. Common clinical conditions of immunosuppression are hematologic diseases, malignancies, rheumatic diseases, and HIV-positive individuals.

4.1 OBI and Malignant Tumors

An increasing number of patients with OBI combined with malignant tumors undergoing radiotherapy or chemotherapy have HBV recurrence, and the recurrence is more obvious in patients with hepatocellular carcinoma [3, 11]. A report showed that the recurrence rate of HBV in chronic hepatocellular carcinoma patients treated with radiotherapy ranged from 4% to 67%, which may be related to the presence of intrahepatic ccc DNA [12-14]. There is a significant association between recurrence of HBV in patients with OBI combined with HCC and reduced overall and recurrence-free survival. Treatment of HBV recurrence before planned treatment of HCC has been recommended [5]. The rate of relapse is not only related to the level of immune response, but also to immune escape due to mutations in HBsAg after immunosuppression. The rate of relapse is related not only to the level of immune response, but also to immune escape due to mutations in HBsAg following immunosuppression, and several cases have been reported of amino acid mutations in HBsAg escaping from the immune response [15].

4.2 OBI and Hematologic Disorders

The damage to the immune system caused by hematologic disorders themselves and the immunosuppression caused by subsequent chemotherapy administered to those infected with OBI are of great significance [11]. It is now believed that drugs commonly used in hematologic disorders such as rituximab, anthracyclines, and corticosteroids are important for HBV reactivation in OBI-infected patients [16]. In a retrospective study that analyzed 101 cases of previous history of hepatitis B combined with hematologic disease, approximately 5% of patients who received chemotherapy or immunosuppressive therapy for hematologic disease developed HBV recurrence [17]. Moreover, several studies have examined the HBV relapse rate in HBsAg-negative/anti-HBc-positive (which is considered to be an important serologic feature of OBI) patients treated with rituximab-based immunosuppressive therapy in the range of 2.3%-10% [18, 19]. Therefore. Therefore, antiviral prophylaxis is necessary for such patients before receiving immunotherapy for hematologic diseases [20].

4.3 OBI and Rheumatic Diseases

Rheumatic diseases are now widely treated with biologics and hormones, but there is no consensus on the preventive treatment of HBV recurrence during systemic treatment of rheumatic diseases. It is now believed that there is a certain correlation between HBV recurrence in rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis and other diseases treated with high-dose hormones and anti-tumor necrosis factor-alpha (TNF-alpha), and so on [21]. Tumor necrosis factor stimulates HBV-specific cytotoxic T-cell responses and plays an important role in the clearance of HBV [22, 23]. A prospective study analyzed 50 HBc-positive patients treated with antirheumatic drugs, including the addition of TNF-α. In a prospective study analyzing 50 anti-HBc-positive patients treated with antirheumatic drugs, including the addition of TNF-alpha, two of five HBsAg-positive patients experienced HBV recurrence, and one of 45 patients who were only anti-HBc-positive experienced recurrence [18]. Another retrospective study investigated virologic and serologic data on HBV reactivation in 88 patients with different HBV infection status who received TNF-α therapy. Another retrospective study investigating the virologic and serologic data on HBV reactivation in 88 patients with different HBV infection status who were treated with TNF-α suggests that not all patients with OBI are at risk of HBV relapse during TNF-α treatment. [18].

4.4 OBI and HIV Infection

Regarding the true incidence and outcome of OBI in the HIV population, there is no literature available to clarify the specifics, which may be related to the different epidemiology, testing methods, and composition of the study population in different regions [24]. The viral regulatory point and the number of CD4+ T-cells in HIV infection are considered to be important predictors of HIV progression and prognosis, and it has recently been shown that chronic HBV infection attenuates CD4+ T-cell function and increases HIV morbidity and mortality [25]. The development of OBI appears to be more common in patients with HIV combined with HCV infection. It has also been shown that the occurrence of OBI appears to be more common in patients with HIV co-infection with HCV. [26, 27].

5. OBI Reactivation and Prevention

Recurrent reactivation of HBV can occur in OBI under immunosuppression, causing hepatitis B virological and hepatic serologic changes and fulminant hepatitis. Therefore, early prophylaxis of OBI patients in an immunosuppressed state is considered necessary. This is most commonly seen in rituximab-containing chemotherapy regimens or hematopoietic hepatocyte transplantation. Prophylaxis is effective in reducing the rate of HBV recurrence in OBI-infected patients. The primary goals of available prophylactic therapy are to suppress viral replication and restore the immune response. Nucleoside and nucleotide analogs such as lafmidine and entecavir inhibit viral activity and reduce HBV DNA levels, helping to prevent relapse [28] It is noteworthy that international guidelines recommend that entecavir be used first for the prevention of HBV relapse in advanced liver disease. It is worth noting that international guidelines recommend that entecavir be the first choice for the prevention of HBV relapse in advanced liver disease. Immunomodulatory drugs such as Toll-like receptor agonists and interferon can trigger an antiviral response and enhance the immune system's ability to fight viral infection. The use of hepatitis B vaccination has also been shown to be effective in preventing reactivation of OBI infection. It is worth pointing out that once reactivation of OBI occurs, antiviral drugs should be used aggressively as soon as possible.

6. Looking ahead

Although the mechanism of OBI has not been fully clarified, its pathogenicity and infectiousness have received considerable attention. OBI can be transmitted through blood transfusion, hemodialysis, filtration, organ transplantation, etc. In the case of impaired immune response, HBV reactivation can also occur, leading to the progression of liver disease and the development of hepatocellular carcinoma. Therefore, clinical workers should have a deeper understanding of OBI, a special form of HBV infection, especially for patients who are about to receive immunosuppressive therapy, to carry out more detailed clinical monitoring and preventive treatment when necessary. More clinical studies are needed to clarify the indications and timing of prophylaxis.

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