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Occult Hepatitis B: Particular form of Viral Infection B that should not be ignored

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Abstract **Review Article**

Occult hepatitis B virus (OBI) infection is one of the most difficult entities in the field of viral hepatitis. Occult hepatitis B corresponds to the presence of hepatitis B virus DNA in the serum and/or in the liver of a patient despite the negative HBsAg. It is a clinical form usually asymptomatic. Its reactivation is rare and generally occurs in immunocompromised subjects. Occult hepatitis B is a particular form of HBV infection that is attracting increasing attention from clinicians. The objective of this development is to underline the importance of systematically looking for occult hepatitis B in the face of immunosuppression.

Keyword: Isolated anti-HBc antibodies, HBV viral load, reactivation, occult hepatitis B.

INTRODUCTION

The hepatitis B virus is a major public health problem worldwide. The natural history of HBV depends on a complex interaction between the virus and the host immune system, less than 5% of immunocompetent adults infected with HBV will develop chronic hepatitis B [1].

Any situation that decreases host immunity is at risk of leading to HBV reactivation. The clinical repercussions are sometimes null, but can also lead to severe acute viral hepatitis involving the vital prognosis [2].

Occult hepatitis is a complex entity comprising a wide spectrum of conditions that are very divergent from each other from a virological and immunological point of view and are also likely to have a clinical impact. The very heterogeneous series published in the literature give extremely variable prevalence figures. It is usually asymptomatic and characterized by very low levels of HBV DNA. However, rare cases of reactivation of occult hepatitis B have been described in the literature on grounds of immunosuppression.

What is Occult Hepatitis?

Occult hepatitis B is an entity described in the early 1980s which corresponds to the presence of hepatitis B virus (HBV) DNA in the serum and/or in the liver of patients in whom the antigen (Ag) HBs is undetectable by the usual serological tests [3].

Occult infection with the hepatitis B virus is characterized by: the existence of a low level of HBV DNA in the serum (<200 IU/mL), outside the window period of the acute phase in patients with or without serological markers of a previous infection: positive anti-HBc and/or anti-HBs and absence of serum HBs Ag [4].

Antibody titer may become undetectable over time, leaving HBV DNA as the only marker of infection. Thus, depending on the anti-HBV antibodies (anti-HBc and/or anti-HBs), the occult infection can be seropositive or seronegative.

Physiopathology

In this particular phase of HBV infection, the covalently closed circular DNA (cccDNA) is in a weak state of replication.

Although the pathophysiology of occult hepatitis B is not well understood, several mechanisms could play important roles in inducing occult hepatitis B status: the immune response, co-infections with other infectious agents and epigenetic factors.

It may be the production of an S protein by HBV that is antigenically modified and not detectable by the available tests. The virus can also make mutations capable of inhibiting the expression of the S gene and/or viral replication. But most often it is a strong suppression of viral replication and gene expression [5].

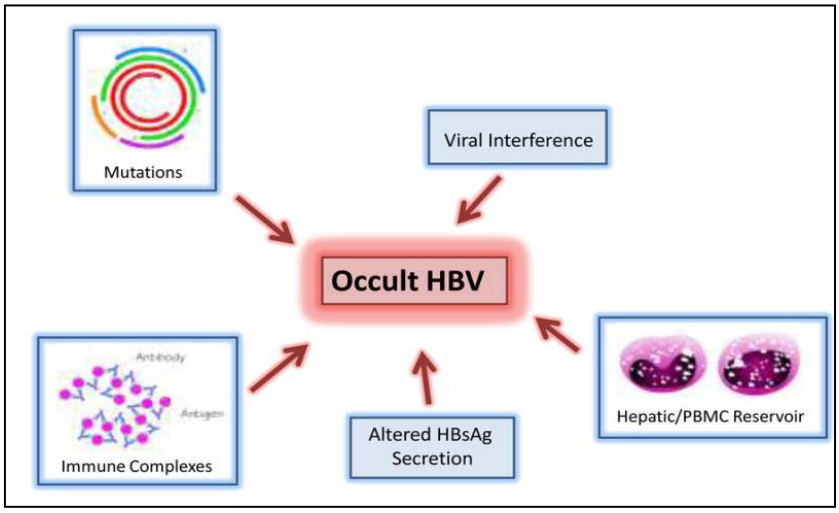

Figure 1: The mechanisms involved in the pathophysiology of occult hepatitis [5]

How to Diagnose?

The gold standard for diagnosis is detection of HBV DNA in DNA extraction from the liver, because cccDNA persists in hepatocytes and HBV DNA is sometimes detected in the liver in the absence of cccDNA. HBV DNA in serum. However, obtaining liver tissue is an invasive procedure, therefore, obtaining liver HBV DNA is challenging in clinical practice. Additionally, real-time PCR-based assays for the detection of HBV DNA in serum (or plasma) have been used with sufficient sensitivity to detect occult hepatitis B in many cases, therefore, serum HBV DNA assays are widely used to diagnose occult hepatitis B [7].

Performing HBV DNA testing periodically will improve the diagnosis of OBI especially in high-risk patients, as intermittent viremia may occur in occult HBV infection.

Why Look for Occult Hepatitis?

Table 1: Table showing the implications and consequences of occult hepatitis B [7]

Risks Transmission of hepatitis B	Consequences
(blood transfusion, organ transplant) Hepatitis B reactivation (Immunosuppression) Contribution to liver injury induced by a coexisting major cause of liver disease. Maintenance of the pro-oncogenic property of the hepatitis B virus	Active hepatitis B Typical hepatitis in carriers of occult hepatitis. Acceleration of progression to cirrhosis Development of hepatocellular carcinoma**.**

1/Risk of Contagiousness

There is considerable evidence that carriers of OBI can transmit HBV infection through blood transfusion, resulting in the development of typical hepatitis B [8].

2/Risk of Reactivation

Many clinical situations are associated with HBV reactivation, including HIV co-infection, natural history of chronic HBV infection, infection with other hepatotropic viruses, and ultimately immunosuppression [9].

Risk Factor for HBV Reactivation

- The intensity of immunosuppression, in particular with rituximab alone or associated with steroids and transplantation of hematopoietic stem cells, as well as aggressive forms of chemotherapy or immunosuppression as in the case of lymphomas than in that of solid tumors and/or autologous hematopoietic stem cell transplantation for hematological malignancies ++
- Viral factors: absence of anti-HBs before chemotherapy, decrease in anti-HBs during chemotherapy, detectable HBV DNA in serum, HBV genotype B and mutations of the precore and core promoters.
- Note that male gender is also an independent factor increasing the risk of HBV reactivation [7].

3/Risk of Cirrhosis

Prolonged persistence of the virus in the liver can cause very mild but continuous necroinflammation which over time contributes to the progression of chronic liver damage to cirrhosis.

In studying the situation of HBV and HCV co-infection, several cross-sectional studies have suggested that HBV and HCV are important risk factors [8].

4/Risk of Hepatocellular Carcinoma

Occult hepatitis B is assumed to be an important risk factor for the development of HCC since it retains the pro- oncogenic properties typical of the declared infection. It has been suggested that occult viral strains, by retaining transcriptional activity and pro-oncogenic assets from clear HBV infection, may pose a potential risk for development of liver cancer.

A recent study from Japan confirmed the existence of serum HBV DNA in occult hepatitis as a predictor of a high rate of hepatocellular carcinogenesis in a cohort of patients with non-B cirrhosis, non-C [9].

Management

Who and how to Screen?

In our context, screening should be performed in all patients who are candidates for chemotherapy or immunosuppression or even long-term high-dose corticosteroid therapy.

Screening should include at least HBs antigen and anti-HBs and anti-HBc antibodies.

- If one of these markers is positive, complete HBV serological screening should be performed (HBV DNA, HBeAg, anti-HBe Ab and, depending on the clinical situation, screening for hepatitis D).
- If the HBV screening is negative, vaccination against this virus is strongly recommended, in accordance with the vaccination plan of the Federal Office of Public Health.

Scenarios in which occult hepatitis B virus infection is clinically important
After acute hepatitis B
Blood donation
Organ transplant
Immunosuppression
Cryptogenic chronic liver disease
Hepatocellular carcinoma

When to Treat?

Multiple studies have demonstrated the benefit of introducing preventive treatment in patients at risk of HBV reactivation in the context of immunosuppression.

1. In practice, the major risk factors mentioned above is a situation at high risk of reactivation indicating prophylactic treatment.
2. Situations at moderate risk of reactivation are less clear situations where the indication for antiviral prophylaxis must be individualized for each patient.

In moderate-risk situations, if prophylactic treatment is not prescribed, close clinical and biological monitoring is indicated [10].

Risk of Reactivation in HBsAg + patients	Immunosuppressive Therapies
High Risk of Reactivation (rate of HBV reactivation is ≥ 10%)	• B cell depletion agents (i.e. rituximab, ustekinumab, etc) • High dose steroids • Anthracyclines (i.e. doxorubicin) • Potent anti-TNF alpha agents (i.e. infliximab, adalimumab, certolizumab, golimumab) • Local therapy for HCC (i.e. TACE)
Moderate Risk of Reactivation (rate of HBV reactivation is 1-10%)	• Systemic chemotherapy • Less potent anti-TNF alpha agents (i.e. etanercept) • Cytokine based therapies • Immunophilin inhibitors (i.e. cyclosporine) • Tyrosine kinase inhibitors • Proteasome inhibitors • Histone deacetylase inhibitors • Moderate dose corticosteroids (10-20 mg orally daily)
Low Risk of Reactivation (rate of reactivation is < 1%)	• Antimetabolites, azathioprine, 6-mercaptopurine, methotrexate • Short term low dose corticosteroids (< 10 mg orally daily) • Intra-articular steroid injections

Figure 2: Table showing the different therapies at risk of reactivation

Which Molecule to Choose?

Entecavir or Tenofovir (TDF/TAF) are recommended by various learned societies (EASL, AGA, IDSA, The National Institute for Health and Care Excellence (NICE) and ASCO) for rHBV prophylaxis since they present a high barrier to drug resistance. These recommendations are based on several randomized clinical trials [9].

For how long?

This prophylactic treatment must be started one week before or at the most at the start of the immunosuppressive treatment.

Prophylaxis should continue for at least 12 months (18 months for rituximab-based regimens) after discontinuation of immunosuppressive therapy and discontinued only if the underlying disease is in remission.

Surveillance

Liver function tests and HBV DNA should be tested every 3 to 6 months during prophylaxis and for at least 12 months after nuke withdrawal as a large proportion of HBV reactivations develop after l stopping the nucleoside analogue [12].

CONCLUSION

The prevalence of occult hepatitis B is probably underestimated in our regions. Hence the need to screen for it in any immunocompromised patient or carrier of Hbs Ag negative liver disease.

Occult hepatitis B is a fascinating aspect of the field of viral hepatitis both from a biological and clinical point of view, and the improvement of knowledge in this subject appears necessary for a better understanding of the epidemiology and pathogenesis of the infection. by HBV, which remains one of the major health problems in the world.

Thus, physicians should focus on the appropriate management of these patients, and further studies to clarify the clinical significance of occult hepatitis are needed.

Strong Points

- Screening for viral B infection is recommended in any candidate for immunosuppressive treatment at moderate or high risk of viral B reactivation.
- The initial screening assessment must include the search for HBs Ag and anti-HBc Ab.
- ETV or TDF are recommended as first-line therapy to prevent HBV reactivation.
- The prophylactic treatment must be started one week before or at the most at the start of the immunosuppressive treatment.
- Depending on the virological status and the risk associated with immunosuppressive treatment, therapeutic algorithms must be proposed.

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