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Case Report

Role of Laboratory in the Management of HBV Reactivation in Rheumatic Diseases

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Abstract

In patients with rheumatic diseases undergoing immunosuppressive treatment, hepatitis B virus reactivation (HBVr) has been long recognized as a major treatment-related adverse event with substantial morbidity and mortality. HBVr is easily preventable with appropriate screening and monitoring strategies. A forty three-year old female is diagnosed on 03.03.2022 with diffuse scleroderma. She started treatment with Methotrexate (25 mg/week) and Prednisone (40 mg/day) for 6 months. No screening for HBV was performed before starting treatment. After 7 months was performed the first screening which included ALT and AST. The enzymes resulted higher than normal range. Then the other examinations were requested to diagnose or exlude autoimmune hepatitis, HCV, HBV. All results confirmed HBVr, second stage. Immunosuppressive treatment was discontinued and Antiviral treatment started on 28.10.2022. Three months later the HBsAg was 5 times less than the previous measurement. Four months later the transaminases were normalized. We can say that HBVr is a potentially complication that depend on baseline HBV status of the patient and on the therapeutic agent used. So before immunosuppressive treatment, serological tests should be performed to assess the status of HBV infection and monitoring during therapy must be performed with serial measurements of ALT, HBsAg, DNA-HBV (every 3 - 6 months).

Keywords: Hepatitis B Virus reactivation; American Gastroenterological Association; Antimitochondrial; Smooth muscle antibody

Introduction

Hepatitis B virus (HBV) infection is a major global health problem. This infection continues to be a problem of morbidity and mortality despite the availability of an efficacious vaccine and antiviral treatment [1]. It can cause liver diseases ranging from acute hepatitis to chronic hepatitis, cirrhosis and hepatocellular carcinoma [2,3].

The virus itself does not have a direct cytopathic effect. On the contrary, hepatocellular injury is mediated by innate and adaptive immunity. A strong immune response is associated with viral clearance in acute HBV infection, but is also responsible for hepatocyte damage and fibrosis in the immune active phases of chronic HBV infection [4].

The majority of infected people are unaware that they have chronic HBV infection, or have been exposed to HBV, but is fact that HBV remains present in individuals who have passed the infection. HBV reactivation (HBVr) is a well-recognized complication of immunosuppressive treatment in cancer, rheumatic diseases, and organ transplantation [5]. HBVr is a clinical syndrome characterized by:

A sudden increase in HBV DNA replication and a moderate increase in ALT 2 - 3 times up to normal range. Reactivation occurs in individuals who have passed HBV (HBsAg-negative) and antibodies (anti-HBc-positive) and in individuals suffering from chronic hepatitis (HBsAg-positive and anti-HBc-positive) [6]. It is generally considered a failure of the immune system's control over HBV replication.

This can occur either spontaneously or whenever the immune system is compromised. Factors that influence the risk of HBVr are related to the patient, the virus, and the type and duration of immunosuppression used [7] **(Table 1)**. Recent years, there has been an effort to stratify HBVr risk according to the patient's serological status and the type and duration of the immunosuppressive treatment used. The American Gastroenterological Association (AGA) classified HBVr risk as low, moderate, and high based on the above factors [8] **(Table 2)**.

The best way to assess risk of HBVr is serological testing for HBV as follow:
HBsAg, HBeAg, HBV-DNA, anti-HBc total =Positive, anti-HBc IgM. When anti-HBc IgM is negative indicates the HBVr.

Table 1: Factors that influence the risk of HBVr.

Host factors	Male sex
	Older age
	Cirrhosis
	Type of disease needing immunosuppression (lymphoma)
	Co-infection status (HCV, HIV, HDV)
Virological factors	High baseline HBV-DNA
	Chronic HBV infection
	HBeAg positivity
Immuno suppression	Type
	Duration

Table 2: Type of mmunosuppression and HBVr risk [8-14].

Immunosuppressive treatment	**Chronic hepatitis**	**Past infection**
	*** H B s A g - pos**	**HBsAg-Neg / anti-HBc - pos**
Glucocorticoids (< 20 mg, > 4 weeks)	Moderate risk	Low risk
Metotroxate	Low risk	Low risk
TNFi	Moderate risk	Low risk
IL-6 inhib	Moderate risk	Low risk
IL-17 inhib	Moderate risk	Low risk
IL-12/23 inhib	Moderate risk	Low risk
Rituximab	High risk	Moderate risk
JAK inhib	Moderate risk	Low risk

*HBsAg-Australian Antigen

The anti-HBc IgM positive indicates the acute infection of HBV.A past HBV infection is assessed by the titer of anti-HBs antibodies.The presence of high-titer anti-HBs significantly reduces the risk of HBVr in immunosuppressive treatments [15].

Case Report

A forty-three-year-old female is diagnosed on 03.03.2022 with diffuse scleroderma. She started treatment with Methotrexate (25 mg/week) and Prednisone (40 mg/day) for 6 months. No screening for HBV was performed before starting treatment. After 7 months was performed the first screening which included ALT and AST. The enzymes resulted higher than normal range **(Table 4)**. Then the other examinations were requested to diagnose or exlude autoimmune hepatitis, HCV, HBV **(Table 4)**. All results confirmed HBVr, second stage **(Table 3)**. Immunosuppressive treatment was discontinued and Antiviral treatment started on 28.10.2022. Three months later the HBsAg was 5 times less than the previous measurement. Four months later the transaminases were normalized **(Table 4)**.

Table 3: Laboratory alterations in HBVr after immunosuppressive treatment [16-18].

Laboratory parameters	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**
HBsAg	Pos	Pos	Pos	Pos	Neg
*ALT and AST	Normal	↑↑	↑↑↑↑	↑↑↑↑	Normal
HBV-DNA	↑↑	↑↑↑↑	↑↑↑↑	↑↑↑↑	↓↓↓↓
Total Bilirubin	Normal	Normal	↑↑	↑↑↑↑	Normal
Liver	None	None	Jaundice	↑↑ INR	Resolved
Decompensation				Ascites	

*ALT-alanine aminotransferase; AST-aspartate aminotransferase

Table 4. Laboratory tests results.

04.10.2022	**13.10.2022**	**24.01.2023**	**25.02.2023**
ALT=168.6 U/L (<42)	HBsAg =5372 IU/mL (<0.05) Positive	HBsAg =1133 IU/mL	ALT=22.1 U/L Normal
AST=104.1 U/L (<37)	*Anti-HCV =0.082 COI (<1) Negative		AST=23.5 U/L Normal
	*AMA= Negative *SMA= Negative		
	HBV-DNA =48139 IU/mL ↑↑↑↑		

*AMA-Antimitochondrial antibody, SMA-anti-smooth muscle antibody, HCV-hepatitis C virus.

Management of HBVr for therapy decision

The management of HBVr should be based on individual HBVr risk according to the patient's HBV status (chronic or resolved infection), but also on the HBVr potential of the immunosuppressive treatment used.

1. HBsAg positive and Anti-HBc positive patients. HBsAg positive patients are at high risk for HBVr from immunosuppressants. In this case, antiviral therapy is recommended before starting immunosuppressants [19-21].

2. HbsAg negative and Anti-HBc positive patients. The dose of immunosuppressants depends on the level of anti-HBs antibodies. High dose corticosteroids require regular monitoring of liver function and viral load as they pose a high risk for HBVr. If an increase in the viral load is observed, antiviral therapy is recommended before treatment with immunosuppressants [19-21].

3.HBsAg negative / Anti-HBc negative / Anti-HBs negative patients (Individuals who have not been exposed to HBV)

Hepatitis B vaccine is recommended (individuals who are at risk of being infected with HBV) [19-21].

Conclusion

In patients with rheumatic disease under immunosuppressive treatment and HBV infection, HBVr is a complication that rheumatologists need to be aware of HBVr rates depend on baseline HBV status of the patient and on the therapeutic agent used. So before immunosuppressive treatment, serological tests should be performed to assess the status of HBV infection and monitoring during therapy must be performed with serial measurements of ALT, HBsAg, DNA-HBV (every 3 - 6 months).

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