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CASE REPORT | LIVER

Hepatitis B Reactivation and Liver Failure Because of COVID-19 Infection

Muhammad Mushtaq, DO[1], Keegan Colletier, MD[2], and Akshata Moghe, MD[3]

[1]*Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX*
[2]*Department of Internal Medicine, Division of Gastroenterology, University of Texas Medical Branch, Galveston, TX*
[3]*Department of Internal Medicine, Division of Gastroenterology, University of Texas Health Science Center at Houston, Houston, TX*

ABSTRACT

Coronavirus disease 2019 (COVID-19) has been associated with liver injury incidence reported between 15% and 53%. Viral binding to ACE2 receptors in hepatobiliary cells is believed to cause liver inflammation. The relationship between hepatitis B and COVID-19 is poorly understood, but patients treated with immunosuppressive therapy for COVID-19 are at higher risk of hepatitis B reactivation (HBVr). We present a case of a patient with HBVr because of COVID-19, in the absence of any immunosuppressive treatment, leading to fulminant liver failure and subsequent requiring liver transplantation. Given low incidence, limited data, and no current guidelines, further studies are needed to evaluate the benefit and cost-effectiveness of anti-HBV prophylaxis in a patient with chronic hepatitis B (CHB) and COVID-19. Meanwhile, the American Association for the Study of Liver Diseases guidelines for patients with CHB and immunosuppressant use can be considered for anti-HBV prophylaxis for patients with CHB and COVID-19 to prevent HBVr on a case-by-case basis.

KEYWORDS: hepatitis B reactivation; COVID-19; liver failure

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become a major cause of morbidity and mortality worldwide, with more than 6.9 million deaths worldwide.[1] Although COVID-19 primarily affects the lungs, it can also affect other organs in the body. Approximately 60% of patients with COVID-19 had a liver injury.[2] Viral binding to angiotensin-converting enzyme 2 (ACE2) in hepatobiliary cells is believed to mediate liver inflammation.[3] Patients with liver disease are at greater risk of liver injury and mortality.[4] The relationship between hepatitis B virus (HBV) infection and COVID-19 is poorly understood. However, immunosuppressive therapy used for COVID-19 puts these patients at greater risk of HBV reactivation (HBVr).[5] We present a case of a patient with HBVr because of COVID-19 in the absence of any immunosuppressive treatment, leading to fulminant liver failure and subsequent requiring liver transplantation.

CASE REPORT

A 72-year-old woman with newly discovered positive HBV serologies presented with jaundice and myalgias. She had no known previous diagnosis of hepatitis B. She was hemodynamically stable, with normal mentation. Laboratory workup was significant for alanine transaminase 2,922 U/L, aspartate aminotransferase 5,423 U/L, alkaline phosphate 274 U/L, total bilirubin 19.7 mg/dL with conjugated bilirubin 13.3 mg/dL and unconjugated bilirubin 2.7 mg/dL, and international normalized ratio 2.81. She denied the use of any new medications, including any immunosuppressants. Serum acetaminophen levels were <10 μg/mL. Workup was unremarkable for antinuclear antibodies, anti-smooth muscle antibody, liver kidney microsome type 1 antibodies, anti-mitochondrial antibody, ferritin, alpha-1 antitrypsin, and ceruloplasmin. Hepatitis serologies were significant for HBsAg+/Ab−, HBc IgM−/IgG+, HBeAg −ve, anti-HBe–positive, and HBV viral load of 276,737,089 IU/mL and 8.44 log IU/mL, suggestive of HBVr (Table 1).

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Correspondence: Muhammad Mushtaq, DO (mamushta@utmb.edu).

Table 1 Patient's hepatitis serologies: HBsAg–positive and anti-HBc–positive with an HBV log of 8.44, suggestive of HBr

Hepatitis B Serology	
HBsAg	Positive
HBsAb	Negative
HBc IgM	Negative
HBc IgG	Positive
HBeAg	Negative
Anti-HBe	Positive
HBV NAAT	276,737,089 IU/mL 8.44 log IU/mL

HBsAB, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

The patient was also found to be COVID-19–positive; however, she had no respiratory symptoms, and therefore was not treated to avoid further immunosuppression. The right upper-quadrant ultrasound with Doppler was remarkable for coarsened hepatic parenchymal echotexture with gall bladder wall thickening and small-volume ascites but negative for portal vein thrombus. Computed tomography of the abdomen and pelvis with contrast showed similar findings with the addition of ground glass opacity in the right lower lobe indicative of infection/inflammatory process.

She was provided supportive therapy, including entecavir, N-acetyl cysteine (NAC), lactulose, rifaximin, and vitamin K; however, throughout hospitalization, the patient became increasingly lethargic with acute change in mentation (AO × 0–1) with worsening international normalised ratio (>13) concerning for fulminant liver failure. The patient was transferred to a transplant facility, where she underwent successful liver transplantation. After transplantation, the patient was continued on emtricitabine-tenofovir and entecavir along with immunosuppressants, including prednisone, tacrolimus, and mycophenolate mofetil.

DISCUSSION

The American Association for the Study of Liver Diseases (AASLD) defines HBVr in patients who are positive for HBsAg and anti-HBc as any one of the following: (i) a ≥2-log (100-fold) increase in HBV DNA compared with the baseline level; (ii) HBV DNA ≥3 log (1,000) IU/mL in a patient with a previously undetectable level, given that HBV DNA levels fluctuate; or (iii) HBV DNA ≥4 log (10,000) IU/mL if the baseline level is not available. For patients who are HBsAg-negative but anti-HBc–positive, HBVr is reasonable if HBV DNA is detectable or if reverse HBsAg seroconversion occurs.[6] In our case, our patient was HBsAg–positive and anti-HBc–positive with an HBV log of 8.44, suggestive of HBVr per AASLD guidelines. Several risk factors have been identified for reactivation, including male sex, HBsAg-positive, HBeAg-positive status, and immunosuppressant therapies, including corticosteroids.[7]

Treatment for patients with COVID-19 who are hospitalized currently involves antiviral drugs such as remdesivir, which directly targets the virus, and immunosuppressants that target the immune response to the virus. Immunosuppressive therapy duration for symptomatic COVID-19 disease is limited to less than 2 weeks. However, there have been cases reported where the COVID treatment has resulted in the reactivation of chronic hepatitis B (CHB), with fewer reports of liver failure.[8–11] In rare instances, COVID-19 infection without immunosuppressive treatment may lead to reactivation of hepatitis B and liver failure, such as in our case.[12,13] It is not yet fully understood how COVID-19 infection, without using an immunosuppressant, directly affects the pathophysiology of HBVr because of a lack of data. Reportedly, 33%–96% of patients with COVID-19 experience lymphopenia, which could potentially lead to an increase in viral load and ultimately cause HBVr.[14] More research is required to understand the relationship between COVID-19 and HBVr.

Although COVID-19 and COVID-19–related treatments are reported to cause HBVr, the risk is low. To date, there are 2 prospective studies. Rodriquez-Tajes et al followed 600 patients with CHB with a final cohort of 61 patients (HBsAg-negative, anti-HBc–positive, and HBV DNA undetectable) who received immunosuppressive therapy with tocilizumab, baricitinib, or corticosteroids.[11] Thirty-eight patients received entecavir daily for 1 month, and 23 remained untreated. HBV DNA became detectable in serum in 2 (8.7%) of the 23 patients in the nonprophylaxis group and none of the 38 who underwent entecavir prophylaxis. This suggests that HBVr was preventable by adequate prophylaxis. However, Foo et al followed 157 with a final cohort of 54 patients with CHB and COVID-19 treated with baricitinib or tocilizumab and corticosteroids.[15] These patients were followed for 24 weeks without any case of HBVr, which raises questions about using antiviral prophylaxis and monitoring. However, none of these studies included patients with HBsAg-positive status.

Given inconsistent data from current studies as mentioned above, low incidence, and no direct guidelines for patients with CHB and COVID-19 regarding HBVr and management, further studies are needed to assess the benefit and cost-effectiveness of anti-HBV prophylaxis. Meanwhile, AASLD guidance for patients with CHB and immunosuppressive can be considered on case-by-case basis. AASLD recommends patients with HBsAg-positive patients on immunosuppressants should receive anti-HBV prophylaxis, given the substantial risk of HBVr, especially if their HBV DNA levels are elevated.[6] Anti-HBV prophylaxis should be continued for 6 months after the completion of immunosuppressive therapy, which in our patients could be 6 months after COVID-19 infection.

Meanwhile, another alternative could be on-demand anti-HBV therapy, especially for patients with HBsAg-negative, anti-HBc–positive patients, given they are at lower risk of HBVr.[6] HBV DNA could be monitored every 1–3 months for up to 12 months.[6]

COVID-19 testing should still be performed in patients presenting with viral hepatitis, even without respiratory symptoms, as infection incurs a greater risk of reactivation and decompensation. Although there are no current guidelines for managing patients with CHB and COVID-19 for risk of HBVr, AASLD guidelines for CHB and immunosuppressants can be considered for anti-HBV prophylaxis on a case-by-case basis.

DISCLOSURES

Author contributions: All authors made substantial contributions to the conception or design of the work; acquisition, analysis, or interpretation of data; drafting or reviewing it critically for important intellectual content; and gave final approval for the version to be submitted. M. Mushtaq is the article guarantor.

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