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Hepatitis B virus associated with severe acute respiratory syndrome coronavirus 2 infection: a case report

Carmen-Elena Florea[1,2], Bianca Bălaş-Maftei[1,2*], Maria Obreja[2,3], Alexandra Rotaru[2], Erika-Raluca Irimie-Băluță[1,2] and Carmen Manciuc[2,3]

Abstract

Background After secondary respiratory failure, liver failure is often reported in the literature on coronavirus disease 2019 infection. Angiotensin-converting enzyme 2 receptors in hepatocytes make the liver directly susceptible to the severe acute respiratory syndrome coronavirus 2 virus. An exacerbated immune response, drug-induced hepatotoxicity, and hypoxia secondary to respiratory failure are further possible causes of hepatocytolysis in coronavirus disease 2019 patients. Pre-existing infection with the hepatitis B virus can aggravate coronavirus disease 2019 or be aggravated/reactivated by it. This case report describes unusually severe liver damage in a coronavirus disease 2019 patient with well controlled hepatitis B, where the evidence points to coronavirus disease 2019-related factors as the main causes of hepatic cytolysis.

Case presentation A 70 year-old patient of Romanian ethnicity with a 5-year history of chronic hepatitis B presented to the emergency department complaining of fever, chills, and marked physical asthenia with an onset of 2 weeks. Blood tests revealed an inflammatory syndrome and incipient liver cytolysis. Low-intensity opacities were visible on chest X-ray, and the severe acute respiratory syndrome coronavirus 2 polymerase chain reaction test was positive, so the patient was transferred to the infectious diseases hospital. His condition then aggravated atypically, with increasingly severe hepatic cytolysis that was not noted in other coronavirus disease 2019 patients with hepatitis B.

Conclusion The patient's history of well-controlled hepatitis B suggests that, in this case, liver dysfunction was secondary to coronavirus disease 2019 manifestations such as the cytokine storm, respiratory failure, and drug-induced hepatotoxicity. The patient eventually recovered, and there was no demonstrable reactivation of hepatitis B after discharge. Coronavirus disease 2019 can thus affect liver function severely and primarily, yet without necessarily interacting with adequately managed hepatitis B.

Keywords SARS-CoV-2, COVID-19, Hepatic cytolysis, Hepatitis B, Case report

*Correspondence:
Bianca Bălaş-Maftei
balasmafteibianca@gmail.com
Full list of author information is available at the end of the article

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, the causative agent of coronavirus disease 2019 (COVID-19), has greatly challenged health systems around the world. Although most reported cases have been mild to moderate, severe infection has been a significant driver of increased mortality, mainly due to acute respiratory failure secondary to alveolar damage. The systemic spread of infection involving multi-organ structures such as the liver and the digestive tract suggests that COVID-19 is both an infectious and a systemic inflammatory phenomenon [3].

Underlying chronic viral hepatitis may complicate both the expression and the management of acute COVID-19. In turn, the use of immunosuppressive therapy to address the SARS-CoV-2 viral infection can trigger a reactivation of the hepatitis virus, thereby adding an extra level of complexity to the treatment of hepatitis patients [2]. This may be the case in chronic infection with the hepatitis B virus (HBV), a member of the *Hepadnaviridae* family, which has a global prevalence of approximately 3.5% and is the main cause of liver cirrhosis and hepatocellular carcinoma, two very serious conditions in themselves without the added impact of COVID-19 [4].

Case description

A 70-year-old male Romanian patient with a 5-year history of chronic hepatitis B presented to the emergency department in August 2020 complaining of fever, chills and marked physical asthenia with an onset of 2 weeks. The patient had previously been attending regular checkups for hepatitis B, and he had been undergoing treatment with entecavir 0.5 mg/day due to positive HBsAg and negative anti-HBc-negative results on routine tests. His transaminases had been consistently within normal range, and viremia had been undetectable. Of note, 1 month prior to admission, a routine liver elastography with a FibroScan device had evidenced F2 liver fibrosis. The patient also had type 2 diabetes mellitus.

The biological investigations performed in the emergency department are summarized in the series of tables below, where the results can be compared across subsequent tests. The initial findings indicated thrombocytopenia, non-specific inflammatory syndrome, and low-grade hepatic cytolysis. Additionally, the patient's lactate dehydrogenase was high (336 IU/L), suggesting tissue damage, and he had hyperglycemia (fasting glucose level 259 mg/dL). A chest X-ray showed opacities of low intensity, imprecisely delimited in the middle half of the bilateral hemithorax. When the polymerase chain reaction (PCR) test came out positive for SARS-CoV-2, the patient was diagnosed with COVID-19, and he was subsequently transferred to our hospital specialized in infectious diseases.

On admission, the patient was afebrile, with mild general malaise, and he was conscious, cooperative, and hemodynamically stable. His peripheral oxygen saturation was 93% in normal room air. Basal crepitant rales could be heard bilaterally, along with dullness on bilateral basal percussion. The abdomen was depressed and painless; intestinal transit and urination were present. The skin and mucous membranes were normally colored.

Treatment for COVID-19 was initiated with ceftriaxone 3 g/day, lopinavir/ritonavir 4 tablets/day, dexamethasone 8 mg/day, and enoxaparin sodium (Clexane) 0.6 mL/day. Additionally, the patient received symptom-relief medication and liver protectors (silymarin 600 mg/day and intravenous arginine 250 mL/day). All the doses were calculated based on the patient's weight.

On the second day, the patient's general condition deteriorated. Peripheral oxygen saturation decreased to 88% in normal room air, which is why oxygen therapy was initiated, and tocilizumab 400 mg/day (in two doses) was added to the treatment. On day 5 of treatment, the patient was still dependent on oxygen, and his general condition remained unsatisfactory. Repeat laboratory tests and imaging were ordered. Relative to admission, the leukocyte count was now higher (9740/mm^3); neutrophils rose to 88.1%, while platelets decreased to 54,000/mm^3. The antibiotic treatment appeared to reduce inflammation: C-reactive protein dropped to 5.56 mg/dL, and the erythrocyte sedimentation rate and fibrinogen level almost halved. Liver cytolysis was noted in the doubling of alanine transaminase (ALT; from 71 to 141 IU/L), while decreasing aspartate transferase (AST) was still too high (43 IU/L). At the same time, on the repeat chest X-ray, the patient's lungs did not appear to have any more active bilateral lesions.

After 3 more days, the patient was in stable condition, and another round of tests were performed. The results showed that the inflammatory syndrome was again rising despite the antibiotic therapy; the interleukin-6 marker was excessively high (985.8 pg/mL), suggesting an unfolding cytokine storm. Moreover, liver cytolysis continued to aggravate, with ALT now 649 IU/L and AST 122 IU/L. Considering the ongoing hepatocytolysis syndrome, arginine was maintained, and lopinavir/ritonavir therapy was stopped (after 9 days of administration in total).

A total of 13 days into the patient's hospitalization for COVID-19 and 4 days after withdrawing lopinavir/ritonavir, new bloodwork showed a slowing increase in leukocytosis (21,090/mm^3), as well as neutrophilia (87.6%) and thrombocytopenia (51,000/mm^3), while inflammatory markers were now normalizing. Most notably, although AST had gone down to 57 IU/L, ALT was still

rising substantially (1485 IU/L) (Table 1). Such exacerbated liver cytolysis was unique to this case compared with other patients with chronic hepatitis B whom we had been treating in our hospital during the COVID-19 pandemic.

The patient's history of hepatitis B justified serology testing for anti-hepatitis D virus (HDV) antibodies to exclude related complications, that is, hepatitis D viral co-infection. The result to that was negative. Considering the increase in transaminase values, the antibiotic treatment was changed to ampicillin 4 g/day. The patient's condition improved sufficiently, and on discharge, after 20 days of hospitalization, the levels of liver enzymes were finally showing a favorable, decreasing trend (ALT 290 IU/L, AST 30 IU/L, bilirubin 0.64 mg/dL).

Discussion

Infection with the SARS-CoV-2 virus in association with chronic HBV infection has the potential to cause or aggravate hepatic dysfunction via direct viral action on hepatocytes, hypoxia, and/or drug-induced hepatotoxicity [6]. Infection with the SARS-CoV-2 virus and the ensuing COVID-19 illness are typically associated with respiratory symptoms, yet liver damage can sometimes become the main concern. Acute respiratory failure induces hypoxia, with damaging effects on various tissues including liver cells, but the SARS-CoV-2 virus can also enter hepatocytes and cholangiocytes directly via the angiotensin-converting enzyme 2 (ACE2) receptors, causing the destruction of these cells and the release of liver enzymes in the bloodstream. Concurrently, the body's inflammatory response can facilitate hepatic cytolysis, and thrombocytopenia is yet another factor that can contribute to it. Additionally, the antivirals and the immunomodulators used in the treatment of COVID-19 can have toxic effects on the liver. (Fig. 1).

In the case presented herein, successive laboratory findings of liver injury included increasing liver enzymes (ALT and AST), gamma glutamyl transferase, and total bilirubin in a pattern of exacerbation not seen in the other COVID-19 patients with hepatitis B treated at our hospital. Prior to admission, the patient had normal transaminases and was not on any treatment that could have hepatotoxic effects. Therefore, the hepatocytolysis

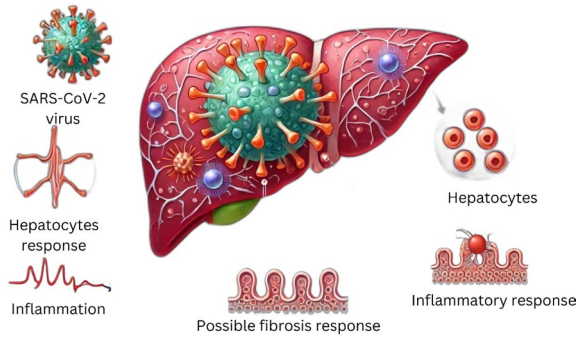

Fig. 1 Liver lesions secondary to severe acute respiratory syndrome coronavirus 2 virus infection

Table 1 Evolution of biological markers-4days after stopping lopinavir/ritonavir

Complete blood count (excerpts)			
	Leukocytes	**Neutrophils**	**Platelets**
Admission	6630/mm^3	75.1%	68,000/mm^3
Day 5	9,740/mm^3	88.1%	54,000/mm^3
Day 13*	21,090/mm^3	87.6%	51,000/mm^3
Day 20 (discharge)	12,000/mm^3	70%	90,000/mm^3
Inflamatory markers			
	C-reactive protein (CRP)	**Erythrocyte sedimentation rate (ESR)**	**Fibrinogen (Fb)**
Admission	16.93 mg/dL	95/min	4.61 g/L
Day 5	5.56 mg/dL	50/min	2.61 g/L
Day 13*	Normal	Normal	Normal
Liver function markers			
	ALT	**AST**	**Bilirubin**
Admission	71 IU/L	47 IU/L	0.61 mg/dL
Day 5	141 IU/L	43 IU/L	0.59 mg/dL
Day 13*	1485 IU/L	57 IU/L	0.62 mg/dL
Day 20 (discharge)	290 IU/L	30 IU/L	0.64 mg/dL

* A total of 4 days after stopping lopinavir/ritonavir

evidenced during his hospitalization was likely caused by SARS-CoV-2 viral action and/or COVID-19 treatment toxicity.

Research has shown that mild-to-moderate liver involvement is fairly common in COVID-19, yet only a small number of patients with SARS-CoV2 and HBV co-infection suffer severe liver injury. It is hypothesized that long-term HBV therapy with nucleoside analogues (entecavir and tenofovir) may play a protective role in combating SARS-CoV-2 infection, given the reduced SARS-CoV2 prevalence noted among HBV patients on nucleoside analogues [12, 13]. Another possible explanation is that chronic HBV infection leads to decreased anti HBV CD4 and CD8 cells due to the persistence of viral antigens [14, 15]. Clearance of specific HBV T cells leads to altered cytokine secretion (IL-2 and TNF-alpha), which progressively favors a reduced antiviral function [16]. The cytokine storm seen in SARS-CoV2 infection implies an overproduction of pro-inflammatory cytokines (IL-2, IL-6, TNF-alpha), an important risk factor associated with disease mortality.

However, in patients with chronic HBV infection, severe COVID-19 may increase the risk of hepatic virus reactivation, although this is debatable, as there is currently no standard notion of "reactivation." One way to define reactivation is as a sudden rise in HBV plasma levels in patients with and without previously detectable HBV DNA levels. Hepatocytolysis can occur as a result of therapy aimed at managing the cytokine storm, such as immunosuppressive therapy with IL-6 antagonists (but only rarely), IL-1 receptor antagonists, and high-dose corticosteroids, thereby inducing an imbalance between host immune status and viral replication [18–21]. In the presented case, the evidenced hepatocytolysis is less likely a reactivation of the hepatitis because the patient was treated with entecavir before, throughout, and after his hospitalization for COVID-19. The rise in transaminases occurred during the patient's COVID-19 illness and treatment, after which his transaminases decreased considerably. Moreover, the patient received just two doses of the IL-6 antagonist tocilizumab, so we would not attribute his exacerbated hepatic response to this therapeutic decision. Also, the combination of ritonavir and lopinavir can induce hepatocytolysis, but the patient already had elevated markers for liver damage prior to using these antivirals.

Conclusion

This case of a COVID-19 patient with pre-existing hepatitis B who manifested a particularly severe hepatic response contributes meaningfully to the ongoing discussion of COVID-19 severity and treatment implications. Based on successive tests, the patient's hepatitis B did not appear to either contribute to or be reactivated by COVID-19, suggesting that the viral infection processes and treatment were the probable causes of hepatocytolysis. Therefore, hepatocytolysis can be a relevant indicator of COVID-19 severity and treatment-related toxicity, highlighting the importance of monitoring liver function in COVID-19 patients. It also shows that pre-existing hepatitis B infection, when managed effectively, is not necessarily a complicating factor.

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Conceptualization: CM, CF, and BBM; methodology: AR and CF; software: AR; validation: CF, BBM, and CM; investigation: CF, EIB, and BBM; resources: AR; writing—original draft preparation: CF and BBM; writing—review and editing: CM, MO, and CF; visualization: MO and CM; and supervision: CF and CM. All authors have read and agreed to the published version of the manuscript.

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Data availability
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Declarations

Ethics approval and consent to participate
Approved by the ethics committee of the hospital for infectious diseases Saint Parascheva Iasi. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Not applicable.

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Competing interests
The authors declare that they have no competing interests.

Author details
[1]Doctoral School, "Grigore T. Popa" University of Medicine and Pharmacy, 16 Universității Street, 700115 Iași, Romania. [2]Department of Infectious Diseases, "Sf. Parascheva" Clinical Hospital of Infectious Diseases, 2 Octav Botez Street, 700116 Iași, Romania. [3]Department Medical Sciences II–Infectious Diseases, "Grigore T. Popa" University of Medicine and Pharmacy, 16 Universității Street, 700115 Iași, Romania.

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