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COVID-19 AND ACUTE HEPATITIS B CO-INFECTION – A CASE SERIES AND SINGLE CENTER EXPERIENCE

COVID-19 I AKUTNA HEPATITIS B VIRUSNA KOINFEKCIJA – SERIJA SLUČAJA I ISKUSTVO JEDNOG CENTRA

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Case report
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Abstract

Introduction. The COVID-19 pandemic has demonstrated that COVID-19 is a systemic disease capable of causing various degrees of liver injury. However, the co-infection of COVID-19 and acute hepatitis B viruses has not been extensively studied in the literature. This study focuses on four cases of COVID-19 and acute HBV co-infections admitted to our institution. **Case Report.** This case series includes four patients - three male and one female - aged 35-44. Three patients were initially hospitalized and treated for acute hepatitis B infection, with COVID-19 co-infection diagnosed at least three weeks into their hospital stay. One patient tested positive for both COVID-19 and hepatitis B viruses upon admission. All patients received antiviral therapy for acute hepatitis B. Only one patient presented with respiratory symptoms and early-stage COVID-19 pneumonia, for which glucocorticoid therapy was administered. All four patients achieved full recovery from COVID-19 and complete resolution of hepatitis B, confirmed by virological tests during follow-up examinations. **Conclusion.** Although literature on this subject is limited, our observations suggest that co-infection with COVID-19 and acute hepatitis B virus generally results in mild clinical manifestations, without complications related to COVID-19. During hospitalization, sudden fever or worsening of serum transaminase levels may indicate a potential COVID-19 infection, particularly during epidemic periods. Further research is warranted to explore antiviral therapy of acute hepatitis and the clinical course of mild COVID-19 infection.

Key words: Hepatitis B; COVID-19; SARS-CoV-2; Coinfection; Pandemics; Treatment Outcome; Antiviral Agents

Sažetak

Uvod. Tokom pandemija izazvane virusom korone 19 (COVID-19) pandemije, dokazano je da je COVID-19 sistemska bolest koja na više načina može uzrokovati različit stepen oštećenja jetre. Koinfekcija virusima COVID-19 i virusom akutnog hepatitisa B u literaturi nije često istraživana, te se u ovoj studiji fokusiramo na jedina četiri slučaja koinfekcije kovida i akutnog hepatitisa B koja su hospitalizovana u našoj ustanovi. **Prikaz slučaja**. U ovom prikazu slučajeva, tri pacijenta su muškarci a jedna žena, od 35 do 44 godine. Od njih, tri pacijenta su inicijalno lečena pod dijagnozom akutne infekcije hepatitisom B, a kovid koinfekcija je nastala nakon najmanje tri nedelje hospitalizacije, dok je jedan pacijent od početka bolesti bio pozitivan na oba virusa. Svi pacijenti su lečeni antivirusnom terapijom za akutnu infekciju hepatitisom B, a samo jedan pacijent je imao respiratorne tegobe i incipijentnu COVID-19 pneumoniju i lečen je prema protokolu kortikosteroidnom terapijom. Svi pacijenti su imali potpun oporavak i od COVID-19 infekcije, kao i kompletnu rezoluciju infekcije hepatitisom B, što je nakon hospitalizacije na kontrolnim pregledima potvrđeno virusološkim ispitivanjima. **Zaključak**. Iako u svetu postoji vrlo mali broj studija sa ovom temom, možemo da zaključimo da koinfekcija ova dva virusa ima blagu kliničku sliku, bez komplikacija COVID-19 virusne infekcije. U toku hospitalizacije, iznenadni porast telesne temperature ili pogoršanje laboratorijskih vrednosti transaminaza bi moglo da ukaže na moguću infekciju COVID-19 u doba epidemije. Potrebno je još istraživanja o povezanosti antivirusne terapije akutnog hepatitisa B i blage kliničke slike COVID-19 infekcije.

Ključne reči: hepatitis B; COVID-19; SARS-CoV-2; koinfekcija; pandemija; ishod lečenja; antivirusni lekovi

Introduction

Since December 2019, the coronavirus disease 2019 (COVID-19) pandemic has rapidly spread worldwide. By January 2023, over 600 million cases of COVID-19 and more than 6 million deaths have been reported globally [1, 2]. In Serbia, more than 2 million cases and over 17,000 deaths were estimated by the same period [2]. While diffuse alveolar damage and acute respiratory failure are the primary features of COVID-19, the disease has been recognized as systemic, affecting multiple organs [3]. The mechanisms through which SARS-CoV-2 affects hepatocytes are well documented, with evidence suggesting that COVID-19 can lead to liver damage. Elevated serum levels of alanine aminotransferase (ALT) were observed in 28% of patients, and aspartate aminotransferase (AST) levels increased in 35% in previous studies [4].

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Abbreviations

COVID-19 – coronavirus disease 2019
ALT – aminotransferase
AST – aminotransferase
ACE2 – angiotensin-converting enzyme 2
HBV – hepatitis B virus
Ag – antigen
PCR – Polymerase Chain Reaction
GGT – gamma-glutamil transferase
ALP – alkaline phosphatase

There are four proposed mechanisms for COVID-19-induced liver injury. The first is direct cytopathic damage, where SARS-CoV-2 directly affects hepatocytes and cholangiocytes via angiotensin-converting enzyme 2 (ACE2) receptors [5, 6]. The second is drug-induced liver injury from medications such as lopinavir/ritonavir, rececivir, chloroquine, tocilizumab, and mitifovir) [7]. The third mechanism involves a cytokine storm – a severe inflammatory reaction to the SARS-CoV-2 that can lead to multi-organ failure and secondary liver injury [6]. Lastly, underlying liver diseases – such as fatty liver disease, alcohol-related liver disease, and obesity may exacerbate liver damage. There have also been reports of chronic liver disease reactivation, such as hepatitis B virus (HBV), in COVID-19 patients treated with biological drugs such as tocilizumab, leading to liver function deterioration [6, 7].

The incidence rate of acute hepatitis B in Vojvodina in recent years is estimated at 1.2 per 100,000 and shows a declining trend, likely due to mandatory vaccination programs. Conversely, the incidence rates of chronic HBV infection are higher, ranging from 0.1 to 5.3 per 100,000 [8]. Hepatitis B infection (HBV) alone is associated with significant liver-related morbidity and mortality; however, co-infection with HBV and other viruses can accelerate liver disease progression [9].

Currently, it remains uncertain whether HBV infection predisposes patients to more severe COVID-19 or if COVID-19 exacerbates outcomes in HIV co-infected patients. While the impact of COVID-19 on chronic HBV infection has been well-documented, several studies have reported the risk of HBV reactivation during COVID-19 infection, irrespective of glucocorticoid use [4,10]. However, to our knowledge, few studies have documented cases of acute hepatitis B and COVID-19 co-infection [9]. This study presents a case series of patients co-infected with confirmed COVID-19 and acute HBV.

Material and Methods

During the COVID-19 pandemic, four patients at our institution were diagnosed with both acute HBV infection and COVID-19. These patients were selected for inclusion in this case series.

This study is a retrospective, single-center case series involving four patients who presented with acute hepatitis B and were infected with SARS-CoV-2. The patients were treated the University Clinical Center of Vojvodina, Clinic for Infectious Diseases, from March 2020 to May 2023. All patients were initially admitted to the Cohort Zone of the respective department, following the time standard protocol at the time. Upon admission to individual clinics within the University Clinical Center of Vojvodina, all patients underwent Real-Time SARS-CoV-2 PCR testing via nasopharyngeal swab and were confirmed negative prior to their transfer [11]. We reviewed medical records of these patients and collected demographic information, epidemiologic data, clinical characteristics, laboratory findings, treatment details, and outcomes of both acute HBV and COVID-19 infections. The study protocol was approved by the Medical Ethics Committee of University Clinical Center of Vojvodina. Statistical analysis was conducted using SPSS software, version 23.g.

Results

The age range of patient cohort was 35 to 44 years, with an average age of 39.7 years. The study included three male patients and one female patient. None of the patients had a prior history of chronic HBV infection, or any previous recorded underlying chronic liver diseases. All patients tested negative for secondary hepatotropic viruses. The average duration of hospitalization was 40.7 days. **Table 1** summarizes the clinical and laboratory characteristics observed during hospitalization.

Patient 1

A 35-year-old male presented with jaundice and abdominal pain lasting three days prior to admission to the Department of Abdominal Surgery with a diagnosis of acalculous cholecystitis. Laboratory results indicated acute liver injury, with transaminases significantly elevated (ALT 90x, AST 45x the normal range) and mixed hyperbilirubinemia, along with mild leucopenia. Further serologial testing confirmed acute hepatitis B with positive anti-HBc IgM, HBsAg and HbeAg. The patient was treated with Lamivudine, resulting in clinical and laboratory improvement. On the 22nd day of hospitalization, he developed a low-grade fever and showed an unexpected rise in transaminase levels. Per institutional protocols to prevent intra-hospital spread of COVID-19, an RT-PCR test and was performed, which confirmed COVID-19.

However, the patient did not develop respiratory symptoms, and there was no need for antiviral, antibiotic, or corticosteroid treatment. The chest radiograph showed no signs of viral pneumonia. The transaminase levels gradually decreased, and there were no signs of liver failure. The patient was discharged after 32 days with significantly improved liver enzyme levels. At the follow-up examination, the patient tested negative for HBsAg and positive for anti-HBs antibodies, indicating complete resolution of acute HBV infection.

Patient 2

A 41-year-old female was admitted to the Clinic for Infectious Diseases in the second week of symptoms, which included jaundice, nausea, vomiting, malaise, and pruritus. Initial lab results showed elevated transaminase levels (ALT 25x, AST 16x) and mixed hyperbilirubinemia. Acute HBV infection was confirmed by positive IgM anti-HBc. The patient was treated with Lamivudine and supportive therapy. In the fourth week, she developed a fever with a subsequent rise in previously improved transaminase levels. A PCR test confirmed COVID-19. The patient did not develop any respiratory symptoms, and the chest radiograph was normal; therefore, there was no need for oxygen support or specific COVID-19 treatment. She was discharged after 39 days with significantly improved transaminase levels. At the follow-up examination, she tested negative for HBsAg and positive for anti-HBs antibodies, indicating complete resolution of the acute HBV infection.

Patient 3

A 39-year-old male was admitted in the second week of symptoms, presenting with jaundice, nausea, vomiting, malaise, and pruritus. Initial laboratory results indicated elevated transaminase levels and mixed hyperbilirubinemia, suggesting acute hepatitis. Further testing confirmed positive HBsAg and anti-HBc IgM. The patient was started on Tenofovir but showed minimal clinical improvement. After 30 days of persisting high transaminase levels and jaundice, he was tested for COVID-19 due to possible exposure, following institutional protocols for preventing intra-hospital COVID-19 spread. The RT PCR test was positive for SARS-CoV-2. The patient remained asymptomatic for respiratory symptoms, and the chest radiograph showed no signs of pneumonia, so no specific treatment for SARS-CoV-2 was administered. After 44 days, he was discharged with improved laboratory findings and without any symptoms of hepatobiliary disease. At the follow-up, he tested negative for HBsAg and positive for anti-HBs antibodies, indicating complete resolution of the acute HBV infection.

Patient 4

A 44-year-old male was admitted with symptoms of high fever, jaundice, nausea, and abdominal pain lasting five days prior to admission. He tested positive for COVID-19 and had positive HBsAg and later positive anti-HBc IgM. Initial laboratory results revealed elevated transaminase levels, mixed hyperbilirubinemia, and elevated infection markers. The

Table 1. Demographic information, clinical presentation, laboratory, and radiology findings of the examined patients

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age	35 years	41 years	39 years	44 years
Sex	Male	Female	Male	Male
Clinical presentation				
Jaundice	Yes	Yes	Yes	Yes
Fever	No	No	No	Yes
Abdominal pain	Yes	Yes	No	Yes
Nausea and vomiting	No	Yes	Yes	No
Laboratory tests				
WBC	5.6	6.6	5.0	9.2
Lymph	29%	26.1%	17.9%	21.3%
PLT	210	203	334	230
CRP	3.8	4.0	8.9	4.3
ALT	3428	921	2092	1756
AST	1622	577	820	604
Tbil	142.5	246.4	319.5	68.6
PT	1.06	1.30	1.16	1.06
Chest radiograph	Normal	Normal	Normal	Incipient pneumonia
USG of the abdomen	Perihepatic free fluid, periportal edema, cholecystitis	Focal changes in the liver parenchima, follow up is needed	Normal	Normal

Legend: WBC - white blood cells; Lymph - lymphocytes; PLT - platelets; CRP - C-reactive protein; ALT - alanine aminotransferase; AST - aspartate aminotransferase; GGT - gamma-glutamyl transferase; TBIL - total bilirubin; PT - prothrombin time

initial chest radiograph indicated suspected incipient viral pneumonia. The patient was started on Tenofovir, which showed a favorable initial response in treating acute hepatitis B. However, due to worsening respiratory symptoms and a chest radiograph confirming viral pneumonia, corticosteroid treatment (Dexamethasone) was administered according to the National COVID-19 treatment protocol. There was no indication for oxygen support, and follow-up chest radiographs showed significant improvement. The patient's clinical signs and laboratory results continued to improve, and he was discharged after 48 days. At the follow-up, he tested negative for HBsAg and positive for anti-HBs antibodies, indicating complete resolution of the infection, similar to the other patients.

Discussion

Hepatitis B virus (HBV) infection is a significant global health concern, capable of causing acute, fulminant, or chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma [12]. In Vojvodina, the incidence of acute HBV is currently 1.2 per 100,000, with a declining trend attributed to compulsory vaccination [8]. In non-endemic countries, where the prevalence is below 1%, HBV infection primarily affects adults and in high-risk groups, such as men who have sex with men, intravenous drug users, and an increasing number of immigrants from hyperendemic regions [13].

As mentioned previously, COVID-19 can cause liver injury even in individuals without pre-existing liver disease [14]. Several patophysiological mechanisms have been proposed to explain liver damage in COVID-19. Patients with COVID-19 often exhibit elevated markers associated with liver injury, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamil transferase (GGT), and alkaline phosphatase (ALP). While the prognostic significance of elevated liver injury markers in COVID-19 patients remains debated, some studies have shown that increased AST and ALT levels are associated with a worse prognosis [15].

Few studies have examined the co-infection of viral hepatitis and COVID-19, making it challenging to determine the impact of HBV on COVID-19 severity. A Chinese study reported HBV in 12.2% of COVID-19 patients, and it remains the only study to suggest an association between HBV and increased COVID-19 severity and mortality rates [16]. Other studies, however, have found no evidence of worsening liver injury or prolonged hospitalization in HBV/COVID-19 co-infected patients [15].

Our findings are consistent with previous studies. The patients presented in our study experienced mild COVID-19 symptoms and a generally benign disease course. Only one patient (Patient 4) required corticosteroid treatment. This patient was also the only one who appeared to be co-infected with COVID-19 before the onset acute hepatitis B symptoms. Although fever in acute HBV could indicate a high risk of acute liver failure, in this case, it may have pointed out to an infection of a different etiology, possibly SARS-CoV-2 co-infection [17, 18]. In Patients 1 and 3, persistent lymphopenia was among the clinical signs that raised suspicion of a COVID-19 co-infection. Studies have shown that SARS-CoV-2-induced lymphopenia may pose a risk for patients with active HBV infection and may be associated with increased COVID-19 severity and mortality [19]. However, in our study, these patients did not experience COVID-19 progression and did not require immunosuppressive therapy or oxygen therapy.

In Patient 2, clinical suspicion of a possible COVID-19 infection arose after a sudden increase in serum transaminase levels and the development of fever. Previously, this patient had an uncomplicated clinical course and steady resolution of acute hepatitis B. Despite the co-infection, the patient did not develop any COVID-19 symptoms or viral pneumonia, and there was no need for specific COVID-19 treatment. This case highlights the need for clinicians to consider COVID-19 co-infection in the differential diagnosis of unexpected serum transaminase elevation or fever during the management of acute HBV infection.

It is noteworthy that Patients 1, 2, and 3 had already begun antiviral treatment for acute HBV infection and the time of their COVID-19 diagnosis. These patients had normal chest radiographs, required no specific COVID-19 therapies, and did not experience any clinical exacerbation of COVID-19. During the study period, antiviral drugs for COVID were not available to us, and these patients did not exhibit severe COVID-19 symptoms.

Our study suggests that the timing of HBV superinfection may determine the severity of COVID-19. In Patient 4, there appeared to be a superinfection of SARS-CoV-2 during the prodromal period of the HBV infection. This patient had the most severe clinical presentation compared to other patients, who acquired COVID-19 as a nosocomial infection with a mild course. Unlike the other patients, Patient 4 developed viral pneumonia and required corticosteroid therapy, and had the longest hospitalization. To our knowledge, this finding has not been reported in the literature, and it raises intriguing questions for further research.

Conclusion

In conclusion, cases of co-infection with acute hepatitis B and COVID-19 appear to have mild clinical manifestations. In this case series, three out of four exhibited no COVID-19 symptoms, had normal chest radiographs throughout hospitalization, and did not require specific SARS-CoV-2 treatment regimens. Further studies are needed to determine whether the use of antiviral agents, such as Lamivudine or Tenofovir, may be associated with a milder clinical course of COVID-19. Additionally, a sudden elevation in serum transaminase levels or an unexpected onset of fever in hospitalized patients could indicate a nosocomial COVID-19 infection during a SARS-CoV-2 epidemic. Physicians should be vigilant in monitoring serum transaminase levels in COVID-19 patients, as these could provide early indicators of disease progression or secondary infections.

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