folia medica

Folia Medica 65(2):343-347
DOI: 10.3897/folmed.65.e79869

Case Report

When Two Viruses Collide: Coronavirus Disease after Hepatitis B Virus Reactivation

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Received: 28 Dec 2021 ♦ **Accepted:** 22 Feb 2022 ♦ **Published:** 30 Apr 2023

Citation: Komitova RT, Kevorkyan A, Vasilev P, Golgocheva-Markova E, Atanasova M. When two viruses collide: coronavirus disease after hepatitis B virus reactivation. Folia Med (Plovdiv) 2023;65(2):343-347. doi: 10.3897/folmed.65.e79869.

Abstract

The COVID-19 pandemic has exploded since the first cases were reported in Wuhan in December 2019, engulfing the globe. Many infected individuals are asymptomatic or have a mild or moderate disease. A subset of people with advanced age, the immunocompromised and those with chronic diseases, are prone to serious-to-critical illness. We report a fatal case of metastatic colorectal cancer survivor who developed COVID-19 after clinically reactivated hepatitis B virus (HBV) due to chemotherapy. The patient's COVID-19 illness was supposed to be related to her recent medical evaluation. Although being diagnosed with chronic HBV infection for decades, she was not treated with nucleotide analogue and the possibility to preclude HBV reactivation was missed. Moreover, infectious control practices must be draconian in order to save such a fragile population from infections.

Keywords

colorectal carcinoma, COVID-19, HBV infection, SARS-CoV-2, reactivation

INTRODUCTION

First identified in Wuhan, China, in December 2019, the coronavirus disease 2019 (COVID-19), caused by a novel coronavirus (SARS-CoV-2), is now a global pandemic. Most of the infected people, especially in the early phase of disease, experience asymptomatic infection or a mild disease. A subset of people who are elderly or have some underlying comorbidities, including those receiving immunosuppressive therapy, are prone to serious-to-critical illness.[1,2] We report a case of cancer survivor who developed COVID-19 after clinically reactivated hepatitis B virus (HBV) infection. The patient's condition rapidly deteriorated to the point of having to be intubated and placed on mechanical ventilation. She died a month after the disease onset.

CASE REPORT

A 60-year-old woman with metastatic colorectal cancer presented to the Emergency Department of St George University Hospital, Plovdiv, in late March 2021 with a 2-day history of fatigue and nausea. She consulted her general practitioner who diagnosed her with gastritis and sent her home on omeprazole. Over the following two days, her symptoms improved slightly, but her urine became dark colored. She was tested in a private laboratory, and the results showed elevated aminotransferase and bilirubin levels and viral hepatitis serology positive for IgM antibodies against hepatitis E virus (HEV) and hepatitis B surface antigen (HBsAg). She had known about the latter for a long time. Then she presented to the aforementioned emergency department.

On admission, her oxygen saturation was 97% while breathing ambient air among the other normal vital signs. The physical exam showed jaundiced skin and sclera and tender hepatomegaly. The remainder of her examination was unremarkable. She was admitted to the Infectious Disease Department of the same hospital with suspicion of viral hepatitis.

Seven months earlier, the patient had been diagnosed with colorectal cancer (cT3N1M1, PAS and BRAF wild type, MSS adenocarcinoma) with unresectable liver metastases after undergoing a colonoscopy for hematochezia. The procedure was done with a 6-month delay because of COVID-19 restrictions. Soon thereafter, she underwent a cancer-related operation. Due to the subsequent surge of COVID-19 cases, it was not until February and early March 2021 that the patient received two cycles of chemotherapy with FOLFOX/BEVA (oxaliplatin, fluorouracil, leucovorin, and bevacizumab) regimen. Her past medical history was notable for chronic hepatitis B virus (HBV) infection (referred to as HBsAg "carrier"), diagnosed more than 40 years ago without a follow-up in the last few years.

A nasopharyngeal swab for SARS-CoV-2 antigen testing on admission established for all hospitalized patients returned negative. Initial laboratory results revealed elevated aminotransferase and bilirubin levels. Serological tests for viral hepatitis did not confirm her outpatient result for anti-HEV IgM but showed previous exposure to HEV and active HBV infection ***(Table 1)****. An abdominal ultrasonography visualized liver enlargement with steatosis without intra- or extrahepatic dilation and several scattered lesions suspected of being metastatic. Over the next few days, her clinical condition gradually improved.*

Table 1. Laboratory findings at days 0, 12 and 23

Variable	On admission	Day 12 Covid-19	Day 23 transfer, ICU	Reference range
Hemoglobin, g/l	126	114	100	140-160
Lc $\times 10^9$/l	6.6	5.7	6.2	3.5-10.5
Tc $\times 10^9$/l	148	156	185	150-350
INR	1.07	1.7	1.31	<1.2
Bilirubin, μmol/l	137	91.5	56.5	5-21
ALT, U/l	425	186	106	01-50
AST, U/l	513	177	61	10-60
Protein, g/l	65	65.7	64	60-82
Albumin, g/l	34	32	30	33-52
Glucose, mmol/l	5.7	5.1	4.5	3.4 -6.1
Ferritin, μg/l	-	-	>2000	13-150
CRP, mg/l	4.0	69.6	94.6	<10
LDH, U/l	654	780	956	134-214
HBs Ag	reactive			
HBe Ag	nonreactive			
HBe Ab	nonreactive			
HBc IgM	reactive			
HBc Ab	reactive			
HBsAb	nonreactive			
HEV IgM	nonreactive			
HEV IgG	reactive			
HCV Ab	nonreactive			
HAV IgM	nonreactive			
HDV Ab	Nonreactive			
HBV DNA*	342 IU/ml			

AST: aspartate aminotransferase; ALT: alanine aminotransferase; INT: international ratio; CRP: C-reactive protein; LDH: lactate dehydrogenase; HCV: hepatitis C virus; HEV: hepatitis E virus; HBV: hepatitis B virus; HAV: hepatitis A virus; HDV: hepatitis D virus; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis Be antigen; HBcAg: hepatitis B cor antigen; HBcIgM: IgM antibody to HBcAg; HBcAb: antibodies to HBcAg; HBsAb: antibodies to HBsAg; HBeAb: antibodies to HBeAg; HAVIgM: IgM antibody to HAV; HCV Ab: antibodies to HCV; HEVIgM: IgM antibody to HEV; HEVIgG: IgG antibody to HEV; HDVAb: antibodies to HDV; *HBV DNA was tested at day 15

On hospital day 12, she developed a temperature of 38°C, sore throat, and dry cough. Her oxygen saturation was 96% while breathing ambient air and the lung auscultation was clear. A portable chest X-ray (CXR) revealed no abnormalities in the lung parenchyma. A nasopharyngeal swab testing became positive for SARS-CoV-2 RNA and she was referred to a designated ward for treatment as a confirmed case. The patient had not been vaccinated against COVID-19. She was started on ceftriaxone and levofloxacin. Remdesivir was not applied due to contraindication.

Eight days later (day 20 post admission), the patient experienced shortness of breath, desaturated to 85% at room air, and required supplemental oxygen by nasal cannula. Methylprednisolone (80 mg i.v.) and convalescent plasma were added. Over the following three days, the patient's condition continued to decline. She was transferred to the intensive care unit, necessitating endotracheal intubation and mechanical ventilation. Methylprednisolone (80 mg i.v.) for seven days with a taper to 20 mg and convalescent plasma were continued. Laboratory findings revealed elevated inflammatory markers (ferritin and C-reactive protein) and improved liver biochemical results ***(Table 1)****. Repeat CXR on day 23 demonstrated bilateral intestinal opacities with peripheral distribution in the lower fields* ***(Fig. 1)****. COVID-19-associated acute respiratory distress syndrome was assumed. Her repeat nasopharyngeal swab testing remained positive for SARS-CoV-2 RNA until day 20.*

The condition of the patient further deteriorated as she developed ventilator-associated pneumonia (blood culture and tracheal aspirate grew both multi-resistant A. baumannii and Kl. pneumoniae), septic shock with multiorgan failure and expired 18 days after admission to the intensive care unit.

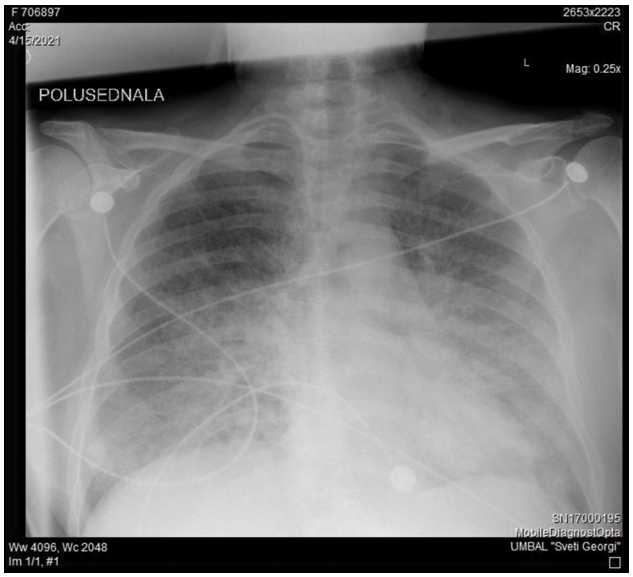

Figure 1. Repeat chest-X-ray, day 23, bilateral intestinal opacities with peripheral distribution in the lower fields.

DISCUSSION

We report a case of metastatic colorectal cancer survivor with fatal COVID-19 after reactivation of HBV infection as a result of chemotherapy. It is likely that she acquired the infection during her recent medical evaluation.

Immunocompromised and cancer patients in particular are not only at high risk for acquiring COVID-19 but are also more likely to have a worse outcome. These with hematologic malignancies and lung cancer as well as with advanced stage of the disease, appear to have the worst prognosis.[3,4] To reduce the risk of disease progression, treatment with monoclonal antibodies targeting SARS-CoV-2 is recommended for the patients with early symptomatic COVID-19.[5] Unfortunately, at the time of the patient's hospitalization, these medications were not available in the country.

It is not possible to determine the exact place and time the patient contracted the infection. Given the date of her SARS-CoV-2 positive test (hospital day 12), transmission during her recent medical evaluation seems the likely possibility. Notably, immunosuppressed patients can present with COVID-19 far outside of the typical 2-to-14-day incubation period.[6] She might have been infected by an asymptomatic case as an outpatient or during the latest hospitalization. Asymptomatic cases ("overt transmitters") are a crucial problem of COVID-19 propagation.[7] No staff member taking care of this patient got infected with COVID-19. However, none of the staff had been tested after receiving her positive result. Some severely immunocompromised patients keep shedding the virus for a long time as our patient did, and thus continue to be infectious. [2] This highlights the ongoing infectious risk in hospital settings and the need for meticulous infection control.

Hepatitis B virus is another virus with a worldwide distribution. Currently, 3.5% of the global population is chronically infected.[8] As both SARS-CoV-2 and HBV challenge liver function, the question raises of how they might interact. So far, there is limited evidence that HBV increases the risk of severity and outcome of COVID-19 unless patients present with end-stage liver disease.[9]

Initially, during the pandemic, a very low prevalence of chronic HBV was reported in hospitalized patients with COVID-19 in China. It seems unexpected, as this country has an intermediate-high prevalence of chronic HBV infection. The impact of host immune dysfunction on SARS-CoV-2 might be an explanation. Decreased virus-specific T-cell reactivity to produce adequate cytokines is a well-known feature of chronic HBV infection.[10] This altered response of the "exhausted" T-lymphocytes to other viruses, including SARS-CoV-2, may result in reduced degree of "cytokine storm", leading to less severe COVID -19.[11]

Corticosteroids and tocilizumab, which are used in the therapy of severe COVID-19, may cause reactivation of HBV. Antiviral prophylaxis should be considered when initiating these therapies.[12] On the contrary, HBV reactivation in our patient was probably a result of her

recent chemotherapy and resolved without specific therapy. Nevertheless, her evaluation required a number of examinations and tests with subsequent contacts and probable exposures to the virus in an outpatient setting and then in a hospital. All this turned out to be fatal. Cancer patients, such as the case presented, are vulnerable to COVID-19 with an inevitably worse prognosis.

HBV reactivation is characterized by increased levels of HBV DNA. Clinically, it may be silent or manifest with overt hepatitis, like this patient, and even with fulminant hepatitis.[13] In order to prevent HBV reactivation, the European Association for the Study of the Liver[14] and most other guidelines recommend antiviral prophylaxis in some category patients. Any patient on prolonged immunosuppressive or cytotoxic chemotherapy should be screened for HBsAg and anti-HBc and, if required, triaged to an appropriate treatment with nucleotide analogues such as tenofovir or entecavir. However, a review of HBV screening patterns at one cancer center showed low screening rates[15], illustrating a discrepancy between the ideal and "real-world" HBV screening practices.

Although our patient case was diagnosed with chronic HBV infection for decades, she was not placed on tenofovir and thus the opportunity to preclude HBV reactivation was missed. Nevertheless, had the patient been treated with tenofovir, HBV would probably not have been reactivated. Subsequently, it would not have been necessary to evaluate her new-onset hepatitis in a hospital setting and thus put her at risk of infection during a pandemic.

Another point merits consideration is liver metastases. Usually, they cause obstructive jaundice with a compatible clinical and imaging picture, which our patient did not have. Moreover, liver metastases almost never resolve spontaneously, contrary to the case presented.

Last but not least are the COVID -19 vaccines. The immunogenicity and effectiveness of COVID-19 vaccines appear to be lower in cancer patients than in the general population. Nonetheless, the potential for severe COVID-19 in this population outweighs the uncertainty. Immunocompromised individuals should receive a three-dose primary mRNA vaccine series.[16] COVID-19 vaccines have been available since late December 2020 in Bulgaria. However, elderly people aged 65 and over and people with concomitant chronic diseases, including these with cancers, were planned for vaccination in May-June 2021 - at least one month after the patient's death.

CONCLUSIONS

Cancer patients, including these with colorectal cancer, are vulnerable to COVID-19 with an increased risk of mortality. They should receive a COVID-19 vaccine, although it may be less effective for them. In addition, infection control practices must be draconian to save them from infection. Finally, for these cancer patients with chronic HBV infection, antiviral drugs should prevent reactivation of HBV to further reduce exposure to infections if this condition does occur.

Author contributions

R.K. is responsible for the study design, manuscript writing, and the literature review. E.G. and M.A. were responsible for the microbiological investigations, and data analysis. P.V. was responsible for the data acquisition and analysis. A.K. edited and reviewed the manuscript. All the authors have approved the final manuscript.

Acknowledgements

The authors have no support to report.

Funding

The authors have no funding to report.

Competing Interests

The authors have declared that no competing interests exist.

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При столкновении двух вирусов: коронавирусное заболевание после реактивации вируса гепатита B

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Дата получения: 28 декабря 2021 ♦ **Дата приемки:** 22 февраля 2022 ♦ **Дата публикации:** 30 апреля 2023

Образец цитирования: Komitova RT, Kevorkyan A, Vasilev P, Golgocheva-Markova E, Atanasova M. When two viruses collide: coronavirus disease after hepatitis B virus reactivation. Folia Med (Plovdiv) 2023;65(2):343-347. doi: 10.3897/folmed.65.e79869.

Резюме

Пандемия COVID-19 разразилась с тех пор, как в декабре 2019 года в Ухане были зарегистрированы первые случаи заболевания, охватившие весь земной шар. У многих инфицированных лиц заболевание проявляется либо бессимптомно, либо в лёгкой или средней степени. Подмножество людей пожилого возраста, с ослабленным иммунитетом и с хроническими заболеваниями, склонны к серьёзному и критическому протеканию заболевания. Мы сообщаем о смертельном случае выжившего после метастатического колоректального рака, у которого развился COVID-19 после клинически реактивированного вируса гепатита B (HBV) в результате химиотерапии. Предполагалось, что заболевание пациентки COVID-19 связано с её недавним медицинским обследованием. Несмотря на то, что в течение десятилетий у неё диагностировали хроническую инфекцию HBV, её не лечили аналогами нуклеотидов, возможность предотвратить реактивацию HBV была упущена. Более того, методы инфекционного контроля должны быть строжайшими, чтобы спасти столь уязвимую часть населения от инфекций.

Ключевые слова

колоректальный рак, COVID-19, HBV-инфекция, SARS-CoV-2, реактивация