Chapter

SARS-CoV-2 Vaccine-Related Liver Failure: Active Hepatitis B and Comprehensive Literature Analysis

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Abstract

SARS-CoV-2 infection or vaccination is closely associated with liver injury, and autoimmune hepatitis episodes have been described, but liver failure has not been reported. Here, we report the case of a 41-year-old man, presenting with fatigue, anorexia after activity, greasy, decreased intake, yellow urine, and occasionally acid reflux in the stomach, occurring 2–3 weeks after receiving the first dose of inactivated SARS-CoV-2 vaccination, thought to be associated with his underlying chronic hepatitis B and fatty liver condition. The patient took the drug irregularly and did not achieve viral conversion to negative and appear rtA181T-resistant HBV mutation. Recently, the laboratory results showed abnormal liver function with high alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transferase (GGT), and there was no improvement in liver function after hepatoprotective therapy, and the serum hepatitis B virus (HBV) concentration was greater than 2.0×10^6 IU/mL. Later, after being admitted to our hospital, it was found that he was in, malaise, jaundice, his eyes and sclera were yellow, his lungs were coarse breath sounds, his liver function was abnormally elevated, and his HBV virus developed a drug-resistant mutation. He has no history of autoimmune disease and tests negative for autoimmune antibodies. He became severely ill after intermittently stopping HBV treatment, worsened liver injury after inactivated SARS-CoV-2 vaccination, and was diagnosed with acute-on-chronic liver failure (ACLF). By summarizing the case report, it will provide important information on the vaccine safety assessment of vaccine components, immunization routes, and dosage for people with underlying liver disease.

Keywords: liver failure (LF), SARS-CoV-2, vaccine, genetic mutation, hepatitis B

1. Introduction

A proportion of coronavirus disease 2019 (COVID-19) patients develop severe disease with multiple organ injuries after infecting severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2), including liver injury and autoimmune diseases [1–3]. Autoimmune hepatitis (AIH) episodes have been described following vaccination [4–6] or infection for SARS-CoV-2 [1, 7], possibly because a similarly

robust immune reaction is involved in both conditions. Histological findings have been reported that AIH is one of the adverse events after vaccination with two messenger RNA (mRNA)-based SARS-CoV-2 vaccines—BTN162b2 (Pfizer-BioNTech, New York, NY, USA/Mainz, Germany) and mRNA-1273 (Moderna, Cambridge, MA, USA), which were granted emergency use authorization by the U. S. government in December 2020 [1, 8]. All reported patients showed spontaneous resolution or responded well to corticosteroid therapy [4, 5].

Liver injury is also a common syndrome in some virus-infected diseases and vaccination. The most prominent pathogenic viruses that have been proposed in the trigger and initiation of liver injury include human cytomegalovirus (HCMV), Epstein-Barr-virus (EBV), influenza A virus, Hepatitis A to E, dengue virus, etc. [9–14]. Liver injury caused by SARS-CoV-2 mRNA vaccines (Pfizer-BioNTech, Oxford-AstraZeneca, and Moderna) has also been reported in many countries [6, 8, 15]. A small number of vaccinated cases have developed liver damage or liver failure (LF) and even require liver transplantation, but so far, vaccination-generated liver damage has responded well to therapy [8, 16]. As described in healthy individuals and patients with underlying disease, there were significant individual differences in strong SARS-CoV-2 adaptive immune responses [17]. Adverse reactions to SARS-CoV-2 vaccine responses should be similar. This may be related to the vaccine's gene that activates the interferon signaling pathways in the vaccinated person [8]. However, the knowledge of the adverse effects in patients with different underlying diseases is limited.

This chapter aims to describe the use of inactive SARS-CoV-2 vaccination as an inducer for liver injury progression in patient with active hepatitis B. In the case reported, the patient was treated for abnormal liver function and fatigue for more than half a month and was eventually diagnosed with acute-on-chronic liver failure (ACLF). There have been few reports of a link between ACLF disease and inactivated SARS-CoV-2 vaccine use. ACLF suggests poor prognosis and high mortality, and experts often recommend liver transplantation [18].

2. Case report

The publication of the patient's information was permitted after discussion by the hospital ethics committee (No. 2021–004–1).

In February 2021, a 41-year-old male hepatitis B patient was admitted to an ICU ward with fatigue 2–3 weeks after receiving the first dose of inactivate SARS-CoV-2 vaccine. It is characterized by hepatitis B surface antigen positive for more than 20 years, and he was treated with interferon for 1 year in 2000, with poor efficacy. In 2001, he took lamivudine for about 2 years, after which his serum HBV DNA came back negative and then stopped taking the anti-viral medicine. Subsequently, the HBV virus turned positive, and he began taking adefovir dipivoxil in 2013, but HBV DNA did not turn negative and considered possible resistance. He switched to entecavir 1 year later, and his HBV DNA copies was reduced from the 10^6 to the 10^3. He took entecavir intermittently from the beginning of 2018 until December, and he did not check the liver function and HBV DNA. In December 2020, blood tests from routine physical examinations revealed abnormal liver function and HBV DNA beyond the upper limit of the detection. In February 2021, the hepatitis B patient was admitted to an ICU ward with fatigue 2–3 weeks after receiving the first dose of inactivated SARS-CoV-2 vaccine.

Half a month ago, he developed fatigue, worsening after activity, anorexia and greasy, decreased food intake, yellow urine, no nausea and retching, occasional acid reflux, abdominal pain without bloating, no diarrhea, and no purulent bloody stool, and admitted to the hospital on February 20, 2021. In addition, the genetic test report indicated that the hepatitis B virus developed rtA181T genetic resistance mutation.

At the time of admission, the patient was conscious, mentally weak, and could cooperate with the physical examination, answer questions accurately, and have normal orientation and counting abilities. He appears with yellow staining of the skin and mucous membranes all over the body (**Table 1**), no liver palm, no spider angiomas, normal hair distribution, no skin petechiae ecchymosis, superficial lymph nodes of the whole body are not swollen, sclera appears yellow stain, eye conjunctiva is not hyperemia, bilateral pupils are as large and round, normal light reflection, no ulcers on the oral mucosa, no congestion in the throat, no swelling of the bilateral tonsils, and the tongue is in the center. He has no history of "typhoid fever," no history of "diabetes, high blood pressure, heart disease," history of drug and food allergies, trauma, or surgery. On January 20, 2021, he received his first dose of inactive SARS-CoV-2 vaccine, and the admission laboratory test results showed that his hepatitis B virus has rtA181T resistance mutation and liver fat attenuation (Fibertouch), suggesting fatty liver.

It has been reported that viral mutations, such as rtA181T, are often associated with advanced liver disease and increase the risk of hepatocellular carcinoma (HCC) [19]. Therefore, active hepatitis B with drug-resistant HBV mutants in patients is the main cause of nucleoside analogue treatment failure and also promotes the progression of liver disease, such as fatty liver, and obvious liver damage after inactivated SARS-CoV-2 vaccination.

The diagnostic criteria for new-onset LF are extreme fatigue, significant gastrointestinal symptoms, rapidly progressing jaundice, serum total bilirubin (Tbil) greater than 10 times the upper limit of normal or a daily rise of ≥17.1 μmol/L, and decompensated cirrhosis with ascites, possibly with or without hepatic encephalopathy [20]. Liver function tests before admission showed alanine aminotransferase (ALT) 937 U/L, glutaminase (AST) 258 U/L, γ-glutamyl transpeptidase (GGT) 195 U/L, albumin (ALB) 39.7 g/L, total bilirubin 10.9 μmol/L, direct bilirubin 4.5 μmol/L. Liver function did not improve after self-taking hepatoprotective drugs, and serum HBV virus was greater than 2.0 × 106 IU/ml. Patients come to our hospital for further treatment. When the patient was admitted, there were no obvious chills, fever, chest pain, cough, night sweats, hemoptysis, epistaxis and gum bleeding, no hematemesis, melena, chest tightness, shortness of breath, no obvious skin itching and clay-colored stool, night sleep, and no significant weight loss recently. The patient has no recent travel history to areas where the SARS-CoV-2 was endemic, and has not been in contact with a person infected with the SARS-CoV-2, and his SARS-CoV-2 nucleic acid was negative. The patient has no history of exposure to toxic substances, which excludes toxic liver disease. The patient has no history of taking drugs that cause liver injury before the onset of illness, and the basis for drug-induced liver injury is insufficient. The patient has no previous history of autoimmune diseases and no obvious manifestations of autoimmune diseases, and autoimmune antibodies have been checked on admission to the hospital to exclude further. The color ultrasound showed that his intrahepatic echo was thickened, cholecystitis, gallbladder polyps, splenomegaly, and no chest ascites, and the laboratory test results showed poor coagulation function [D-dimer and Activation of partial thromboplastin time (APTT), **Table 1**].

Day	1	7	14	25	33	58	63
ALT (10–49 U/L)	136.60	479.00	506.00	924.00	1477.00	53.00	47.00
AST (0–34 U/L)	122.60	199.00	241.00	925.00	1378.00	85.00	74.00
TBil (5–21 μmol/L)	63.00	108.00	224.00	282.00	450.00	160.00	110.00
Procalcitonin (0–0.05 ng/mL)	0.55	0.86	0.63	1.23	2.35	0.52	0.43
Antithromboplastin III (60–120%)	52.00	34.00	35.00	33.00	56.00	32.00	35.00
D-dimer (0–0.5 μg/ml)	0.28	1.02	0.58	0.83	0.74	0.66	0.62
APTT(26–40 s)	46.50	45.20	35.60	110.30	>180.0	42.80	41.20
HBV DNA (0–20 IU/mL)	9.65×10^6	3.33×10^8	—	9.66×10^5	4.57×10^4	—	1.70×10^3
Blood ammonia (11–20 μmol/L)	—	23.00	50.00	43.00	66.00	36.00	—
Complexion	Yellow	Yellow	Yellow	Yellow	Yellow	Dark	Dark
Disease condition	Chronic active hepatitis B	Chronic active hepatitis B	Pre-liver failure	ACLF	ACLF	Symptom reduction	Symptom reduction

Notes: ALT: alanine aminotransferase, AST: aspartate aminotransferase, TBil: Total bilirubin, APTT: Activation of partial thromboplastin time, ACLF: acute-on-chronic liver failure, normal reference values are indicated in brackets.

Table 1.
Key indicators of liver function before and after hospitalization.

When he was admitted to the hospital for 15 days, he had aggravated fatigue, yellow urine, obvious yellow staining of the skin sclera, coarse breathing sounds in both lungs, and aggravated liver function damage, and was given magnesium isoglycyrrhizinate on the same day to protect the liver, hepatocyte auxin to promote hepatocyte regeneration, acetylcysteine detoxification, and yellowing, Bacillus licheniformis to regulate the intestinal flora and albumin support. On the 16th day, the urine was dark yellow and has low potassium, and on the 19th day, he was given blood purification treatment (artificial liver), and on the 20th day, he developed mild tenderness in the gallbladder area and was positive for Murphy's sign. The patient has severe hepatic necrosis, and artificial liver technology was used for intervention. The patient had hypoproteinemia, continuous hemofiltration acute plasmapheresis adjuvant therapy for several days, the patient's liver function deteriorated on the 24th day after admission, and transaminases rebounded, suggesting that inflammation reappeared. Patients with hepatitis B virus activity in the body, co-infection, and pleural ascites need to be closely monitored for biochemical indexes and continue artificial liver therapy to clear inflammatory mediators. On day 26, the patient's transaminases were significantly elevated, and bilirubin rebounded, indicating severe liver damage slow recovery of liver function, and experts suggested that there may be a poor prognosis. After hepatoprotection and yellowing treatment, he was transferred to Shanghai Hospital for treatment.

He was treated in Shanghai from day 35 to day 57, and was treated with polyene phosphatidylcholine, reduced glutathione, compound glycyrrhizin hepatoprotective, adenosylmethionine, and ursodeoxycholic acid exchange, tenofovir alafenamide fumarate tablets (TAF) anti-HBV treatment, torasemide combined with spironolactone diuresis, daily virus inactivated frozen plasma 200 ml to improve coagulation function, with Tienam (imipenem and cilastatin sodium) 1 g × 3 times per day plus voriconazole 200 mg × 2 times per day anti-infective treatment. The patient returned to our hospital after his condition improved. The biochemical, coagulation, and highly sensitive hepatitis B virus DNA test results during treatment in our hospital are shown in **Table 1**.

3. Discussion

Acute decompensation from an acute injury is poorly recoverable; acute liver injury caused by hepatotropic virus infection mainly has HBV reactivation or superinfection. HBV reactivation is still the leading cause of acute injury in Eastern countries, and reactivation can be spontaneous [20]. The patient is chronically active with hepatitis B, previously irregularly taking antiviral drugs, now detected that HBV has appeared with rtA181T mutation, has been in tenofovir propofovir antiviral therapy, now with entecavir combined with tenofovir antiviral to prevent the re-emergence of viral resistance, the antiviral load will usually decline after antiviral treatment. Patients with LF have an inflammatory response and immune activation. The virus is not used as the main evaluation index, and clinical treatment is mainly artificial liver removal of inflammatory factors and jaundice. Patients with acute liver damage based on chronic hepatitis generally have a good prognosis if liver function recovers rapidly.

HBV gradually cleared after the patient was admitted to the hospital to improve the medication, but the continuous aggravation of liver function, hepatitis activity, and LF tendency, may be related to the injection of inactivated SARS-CoV-2 vaccine during the active hepatitis period and the aggravation of the liver disease and progressive damage of liver cells occurred in the case of passive immunization. However, it is

not excluded that the patient will have ACLF due to liver injury after self-interruption or discontinuation of the medication. The patient did not respond well to using artificial liver, and liver transplantation was considered prior to transfer.

It has been described that SARS-CoV-2 can trigger autoimmune responses through cross-reactivity with host cells [1, 7]. Autoantibodies as markers of autoimmune disease have been excluded during the examination of this patient. Therefore, this case suggests that injection of inactivated new coronavirus vaccine in patients with chronic active hepatitis B is at risk of inducing LF.

4. Conclusions

It has been shown that the second dose of the Pfizer-BioNTech vaccine produces more severe liver injury than the first shot [8]. In China, most people with adverse reactions will not receive the second dose, and some people show significant adverse reactions when receiving the second dose of inactivated vaccine. Side effects of inactivated SARS-CoV-2 vaccine-induced LF are rarely reported, and this chapter provides case information on the association or coincidence.

Acknowledgements

This work was supported by the Wuxi Key Medical Talents Program (ZDRC024), the Top Talent Support Program for Young and Middle-Aged People of Wuxi Health Committee (BJ2020094), Chinese Public Health Alliance (ZGLM202005), and National Natural Science Foundation of China (81701550).

Conflict of interest

The authors declare no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.112706

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