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Case Report

Liver transplantation for favipiravir-induced cholestasis and alcohol consumption - A case report and literature review

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Abstract.

This case details a unique presentation of severe cholestasis progressing to acute liver failure in an adult patient following treatment with favipiravir for mild coronavirus disease 2019 (COVID-19). The patient was a 26-year-old man (height, 170 cm; weight, 45 kg) with COVID-19 in May 2021. Two days after the onset of the disease, he presented with complaints of fever, cough, sore throat, malaise, headache, and myalgia, but without shortness of breath, dyspnea, or chest imaging abnormalities. He only had a history of occasional alcohol consumption. Favipiravir was administered at a loading dose of 1600 mg twice daily on the first day of treatment, followed by 600 mg twice daily for the next five days. Complete clinical improvement then occurred. Two months later, the patient underwent liver transplantation with severe jaundice and a MELD score of 39. This case shows that if drug-induced liver injury is suspected, the drug's potential effect on the liver and other influencing factors, such as alcohol consumption, should be considered.

Introduction

Clinical data indicate that patients with coronavirus disease 2019 (COVID19) often had abnormal liver function tests, such as aspartate transferase (AST) and alanine transferase (ALT) [1]. Acute liver injury is defined based on the upper limit of normal (ULN) serum concentration of ALT, AST, and total bilirubin as follows: Increased ALT more than 5-fold ULN or ALP more than 2-fold ULN (in the absence of bone pathology), or simultaneous increase of ALT ≥3-times ULN and total bilirubin concentration more than 2-times ULN [2].

COVID-19-associated liver injury is defined: as liver damage caused by the pathogenesis or treatment of the infectious disease [3], reported in 20-46.9% of COVID 19 patients [4].

Although the COVID-19 vaccine is being researched and developed, safe and effective drugs are still needed to control and treat the infection. Favipiravir is an antiviral used to manage influenza, and that has the potential to target other viral infections. The antiviral drug favipiravir emerged as; a promising treatment option for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, a case of favipiravir-induced cholestatic liver injury has been described in an individual with previous liver injury due to alcohol-associated liver disease [5].

Drug-induced Liver Injury (DILI) remains a clinical challenge and requires further clarification. Here, we describe the case of an adult patient with severe cholestasis and acute liver failure following treatment with favipiravir for mild COVID-19.

Case Report

A 25-year-old man (BMI, 15.6 kg/m2) presented with pruritus and severe progressive jaundice. In the past two months, he had been on favipiravir tablets for about a week due to mild COVID-19 illness. Favipiravir was administered at a loading dose of 1600 mg twice daily on the first day of treatment, followed by 600 mg twice daily for the next five days. Then, the complete clinical recovery from COVID-19 occurred. However, after that, jaundice and itching gradually developed. He had a significant medical history of occasional alcohol consumption but denied that to take any other medications or herbal supplements. On presentation, the patient had scleral icterus and severe jaundice without evidence of encephalopathy. His lung exam was unremarkable. Laboratory evaluation showed the cholestatic liver pattern as follows: total / direct bilirubin 29.8 / 21 mg / dL (N: 0.2–1.2/ <0.3), AST 200 U / L (N: 5- 40), ALT 352 U / L (N: 5- 40), ALP 606 U / L (N: 80-306), albumin 3.5 g / dL (N: 3.5 – 5.2), international sensitivity ratio 1.2.

The patient's serological tests of hepatitis A / B / C / E and Epstein-Barr / herpes simplex/cytomegalovirus were negative, as well as autoimmune markers, ceruloplasmin, and liver Doppler ultrasound were reported normal. In addition, on magnetic resonance cholangiopancreatography, no biliary filling defects were reported. After performing a liver biopsy, the patient finally underwent liver transplantation. Pre-transplant COVID-19 polymerase chain reaction (PCR) by nasopharyngeal sampling was negative for the disease. After the surgery, the patient's liver chemistries and coagulation tests significantly improved to the acceptable range, and the patient was discharged from the hospital one month later.

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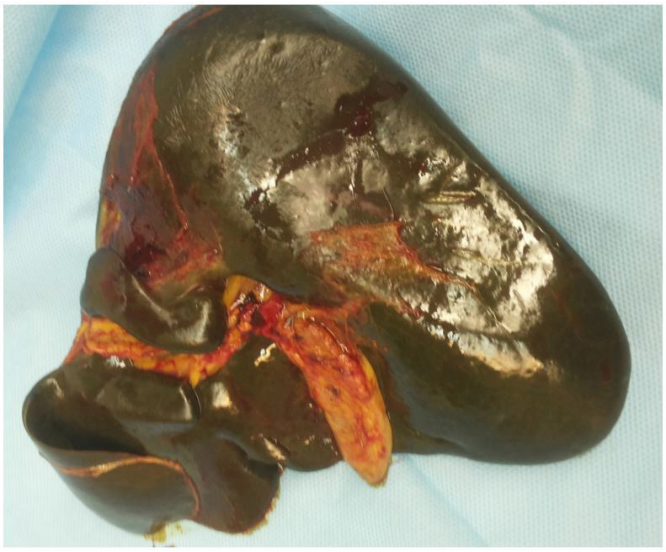

Figure 1: *Macroscopic appearance of the explanted liver*

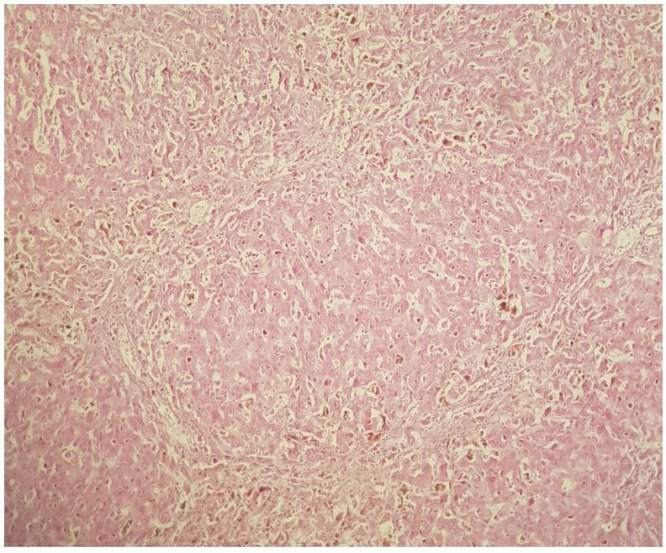

Figure 1: *The explanted liver biopsy reveals severe cholestasis with incomplete cirrhosis*

Figure 1 shows the macroscopic appearance of the explanted liver. The liver biopsy revealed severe cholestasis with incomplete cirrhosis (Figure 2).

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Discussion

The side effect profile of favipiravir is generally minor and acceptable, with mild reversible transaminase elevation being the most commonly reported adverse event [6]. We encountered an adult patient with severe cholestasis and acute liver failure following treatment with favipiravir for mild COVID-19.

Liver biochemical abnormalities are common in patients with COVID-19. Whether these abnormalities are directly related to hepatic SARS-CoV-2 infection and their prognostic significance are uncertain [7].

In patients with acute liver failure, DILI is a differential diagnosis [8]. In suspected cases of DILI, the potential hepatotoxic effect of the drug, and various contributing factors, should be considered. The study by Björnsson ES [9] described the contributing factors, including race, age, and sex. Although the incidence of DILI has been reported to be higher among elderly patients, data from large registries fail to support this hypothesis [10]. Advanced age can affect susceptibility to certain medications, leading to DILI. Also, gender is not a general risk factor for DILI [11]. An increasing number of studies point to genetic susceptibility as a potential factor in DILI, although evidence of genetic susceptibility for DILI is still limited. Further research is required to verify the topic.

The effect of existing liver disease on the risk of DIL has not yet been completely clarified. However, DILI patients with preexisting liver disease are at increased risk for more severe outcomes [12]. The recently published article from the Spanish DILI registry found that patients with pre-existing liver disease have an increased mortality risk compared to those without (7.5% vs. 1.8) [13].

To our knowledge, another case of favipiravir-related acute cholestatic liver injury has been reported. This case report described a patient with a history of alcoholic hepatitis and SARS-CoV 2 who developed a favipiravir-induced cholestatic liver injury [14]. However, according to the author's opinion, the administration of antimicrobial therapy caused liver damage, and high-dose favipiravir worsened liver function. As mentioned, our patient only received favipiravir as antimicrobial therapy, so the accuracy of the opinion is questionable.

Finally, the history of alcohol consumption in both cases is an important point. Evidence suggests that heavy alcohol consumption can lead to an increased risk of DILI caused by certain medications [15]. Our report indicates that alcohol consumption may increase risk of favipiravir- induced cholestatic DILI, but more research is needed to determine how favipiravir affects this condition.

Conclusion

This case details a unique presentation of favipiravir-induced cholestatic liver injury that underwent liver transplantation. It is noteworthy that in these cases, contributing factors such as alcohol consumption should be considered.

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