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Case report

Successful liver transplant in a patient with acute cholestatic liver failure due to COVID-19 infection: A case report

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The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an ongoing global pandemic that is known to target the pulmonary system but may also cause injury in the cardiovascular, gastrointestinal, liver, biliary tree, and neurologic systems [1]. The first infected patient was detected in December 2019 in Wuhan in China [2]. Hepatotropism of SARS-CoV-2, possibly relying on direct and indirect liver injury, remains poorly recognized [3]. In most cases, the authors reported a transient and slight elevation in liver chemistry. We report a case of SARS-COV-2 infection presenting as viral pneumonia with liver injury rapidly progressing to fulminant hepatitis with a cholesteric pattern, which eventually required liver transplantation.

Case report

A 42-year-old man with a body mass index of 28 kg/ m^2 presented to the emergency department with fever, cough, and shortness of breath in October 2020. On arrival, the patient had a respiratory rate of 36/min, a heart rate of 110/min; the temperature was 38.3 °C, blood pressure 115/80 mmHg, and oxygen saturation in room air 85%. Diffuse bilateral crackles were prominent on lung examination. He denied recent intake of any hepatotoxic drug or herbal and traditional products, the use of alcohol, or smoking. There was no history of underlying liver disease and no family medical history.

Laboratory investigation showed: white blood cell count 8.7×10^9 (N: 4.0–11.0), C-reactive protein (CRP) 98 mg/L (N: 0.0–8.0). Liver function, renal function, and biochemistries were otherwise in the normal range. Polymerase chain reaction (PCR) assay of the nasopharyngeal swab for SARS-COV-2 was positive. Spiral chest computed tomography (CT) scan revealed multilobular bilateral ground-glass opacifications, peripheral and prominent central, with a severity score estimated 19 (more than 75% of lung involved) (Fig. 1) [4]. The patient was isolated and received supplemental oxygen and dexamethasone, and remdesivir was started according to Massachusetts General Hospital COVID-19 treatment guidance [5]. The patient received 200 mg bolus dose remdesivir on the first day and then 100 mg on the second day, then remdesivir was discontinued since liver function tests worsened progressively. On day 2, slight scleral icterus was notable; the patient had no complaint of pruritus, abdominal pain, nausea, or vomiting. Liver function test raised from baseline: AST 73 IU/L ($N < 35$), ALT 62 IU/L ($N < 35$), alkaline phosphatase 546 ($N<150$) IU/L, total bilirubin 4.2 mg/dL (N: 0.2–1.2), conjugated bilirubin 2.1 mg/dL ($N < 0.4$), INR: 1, serum albumin 3.4 g/dL (N: 3.5–5.0), creatinine 0.6 mg/dL (N:0.5–1.2). Autoimmune markers, viral markers including hepatitis A, B, C, EBV, CMV, HSV 1, HSV2, and HIV were negative; serum ceruloplasmin and 24 h urine copper were within the normal range.

Transabdominal ultrasonography demonstrated heterogeneous liver patterns compatible with fatty liver grade I, and patent vascular permeability in Doppler. Transthoracic echocardiography revealed an ejection fraction of 55%, within the normal range. Abdominal CT showed no abnormality other than pleural effusion (Fig. 2).

Given the rapidly progressive liver failure and unremarkable etiology, a liver biopsy was performed. Histologic examination showed severe inflammation, intrahepatic cholestasis, few apoptotic bodies, no piecemeal necrosis, bile duct proliferation, and no other specific lesion was identified in HES and trichrome staining. There was no iron deposition and no signs of NASH (Fig. 3 Figure 4–5).

Severe icterus and mild encephalopathy developed. Continued elevation in total and conjugated bilirubin, worsening in coagulation studies, and continued increase in transaminase levels (Fig. 6) suggested acute liver failure. In accordance with the liver transplant department of our hospital, liver transplantation was proposed if spontaneous resolution after cessation of all drugs was not achieving and at least two weeks after the PCR test was negative and the chest CT scan was normalized.

Because of stabilization in general condition and liver function test, the patient was discharged on 30 days. On day 13 after the last

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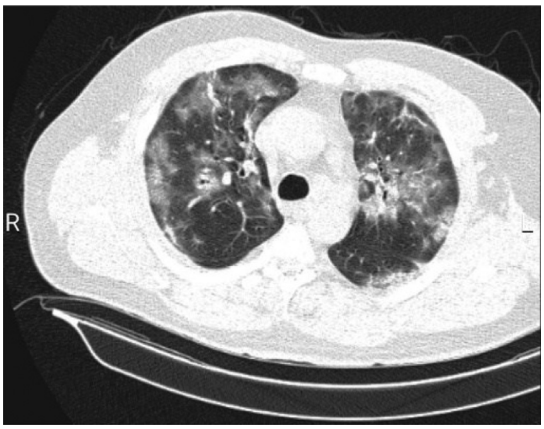

Fig. 1. Chest CT scan without contrast showing COVID-19 pneumonia.

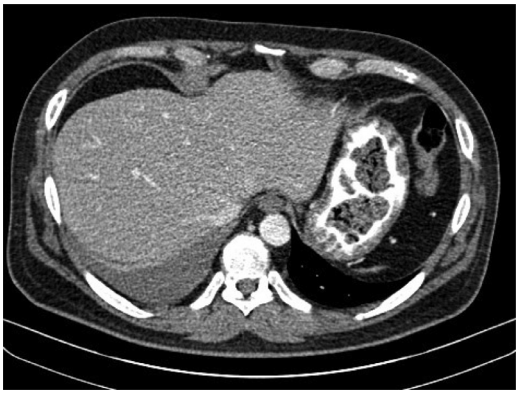

Fig. 2. Abdominal CT scan.

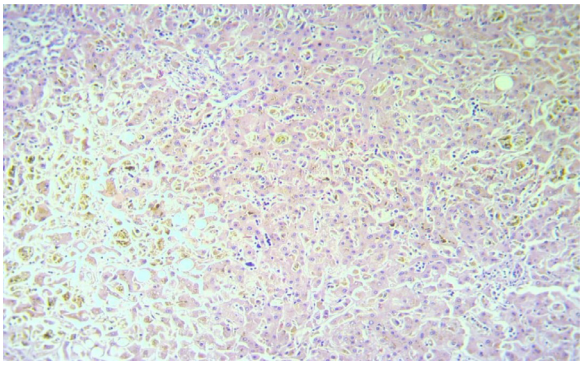

Fig. 3. Histological analysis of the liver. Many inspissated bile casts were seen in canaliculi and hepatocytes. HE, original magnification × 40.

admission, the patient came back to the clinic with disorientation. The biological results were: AST 350 IU/L, ALT:358 IU/L, alkaline phosphatase 1303 IU/L, total bilirubin 52 mg/dL (Fig. 6), creatinine 0.8 mg/dL. (N:0.5–1.2). COVID-19 PCR was negative and the thoracic CT scan near-normal. The MELD score was 33.

The patient underwent ortho-topic liver transplantation in December 2020. Due to a lack of reduction in the liver enzymes, a liver biopsy was performed on the third day, showing acute rejection and Banff score was moderate (RAI: 5), the patient received three pulses of 1 g methylprednisolone. The enzymes decreased, and the patient was discharged with near-normal enzyme values on the Fifteenth day. His-clinical and biological status is normal after a follow-up of 30 days.

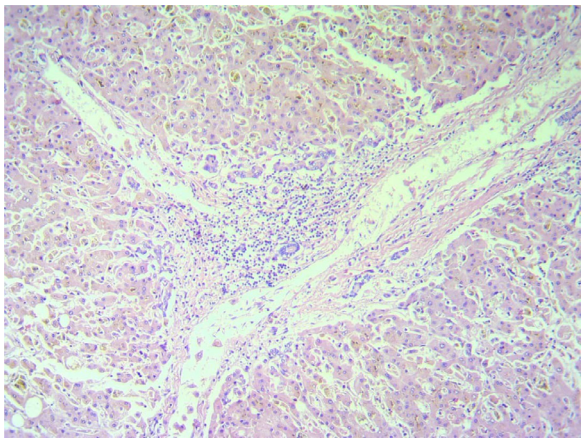

Fig. 4. Histological analysis of the liver. Portal tract showed mild to moderate mononuclear inflammation but no evidence of bile duct damage. HE, original magnification × 40.

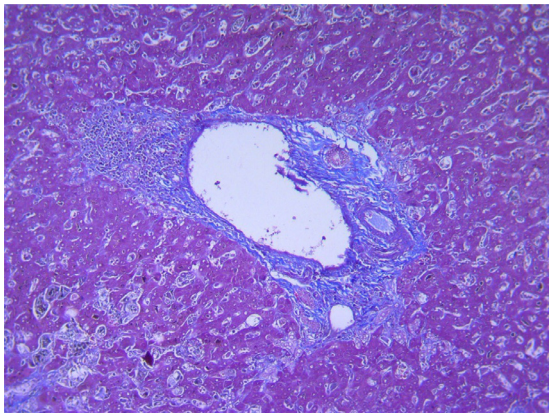

Fig. 5. Histological analysis of the liver. No specific fibrosis was seen. trichrome staining, original magnification × 40.

Discussion

Since December 2019, with the first case identified, SARS-CoV-2 killed millions of humans [6]. The respiratory system is the primary organ involved, with dyspnea, cough, and fever [1], and lung disease is the main cause of death. However, as for the previous coronaviruses- related Severe Acute Respiratory Syndrome (SARS) in 2003 and the Middle East Respiratory Syndrome (MERS) in 2012, SARS-CoV-2 also affects the liver [7]. Liver involvement has a wide spectrum ranging from a mild increase in liver function tests to severe liver disease. Qingxian Cai et al. found that 76.3% of covid-19 patients had impaired liver chemistry and 21.5% liver injury [8]. SARS-CoV-2 is an infrequent cause of acute liver failure and case reports are infrequent. Melquiest et al. reported a fulminant hepatic failure in a 35 years old woman with systemic lupus erythematosus with SARS-COV 2 infection [9]. Haji Esmaili Memar et al. reported an 11 years old boy with no history of hepatic disease that died following fulminant hepatic failure associated with SARS-COV 2 [10]. Numerous pathways of liver injury have been proposed. First, the Angiotensin-Converting Enzyme 2 receptor, which is a host cell target of the virus, is expressed on cholangiocytes and hepatocytes [11]. Second, the liver is a crucial organ for the detoxification of the body from internal and external toxin metabolites. Cytokines that enter the hepatic circulation may result in a transient elevation in the liver enzyme, a phenomenon called bystander hepatitis [12]. Third, sepsis-related to covid-19 may disturb liver perfusion and cause ischemic hepatitis or cholestasis [12]. Fourth, medication prescribed during the treatment

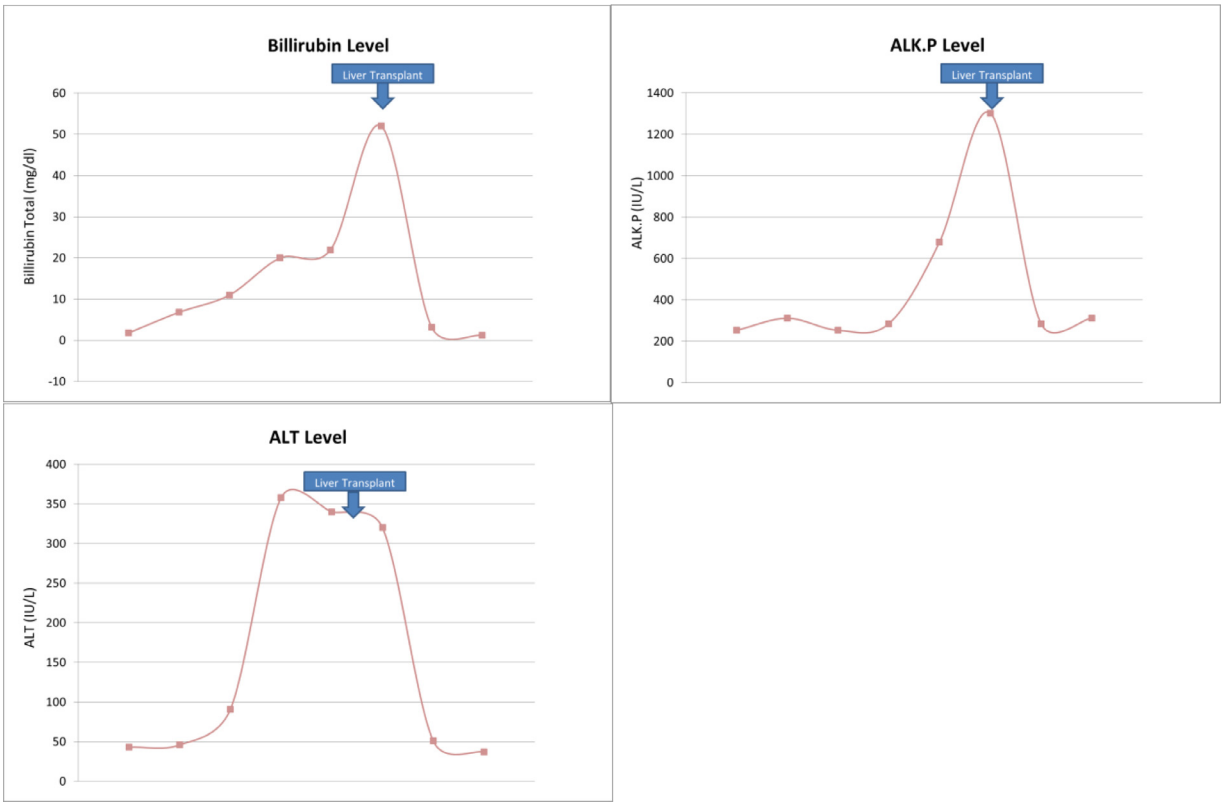

Fig. 6. Dynamic liver enzyme changes during hospitalization.

of covid-19 such as antibiotics (azithromycin, hydroxychloroquine), acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), antiviral drugs (remdesivir, lopinavir, ritonavir), and consumption of herbal products may cause drug-induced liver injury (DILI) or herbal induced liver injury (HILI) [13]. Prognosis of DILI and HILI are varied and severe injury may lead to liver transplantation [14].

According to histopathologic changes, one of the main differential diagnoses in this patient was DILI. Our patient did not receive NSAID, hydroxychloroquine, or anticough drugs and received only 1 g of paracetamol on the first day of admission. Remdesvir is a nucleotide analog product that exhibits effective antiviral activity against a broad spectrum of RNA viruses including Covid-19 [15]. Remdesvir causes multiple adverse effects including diarrhea, anemia, rash, renal impairment, and hypotension [16]. Several studies found an increase in AST, ALT, and bilirubin with a rapid return to normal values after discontinuation of the drug [17,18]. No case of severe liver failure has been described so far. Our patient received only briefly remdesivir, then the drug was discontinued, although the biological parameters deeply worsened, excluding a major role of this drug in the pathogenesis of liver failure.

We thus hypothesized that covid-19 infection was mainly responsible for liver disease. In a German case series, the pattern of liver disturbance was an elevation in AST in 70%, raised in ALT in 15.8%, and cholestatic liver injury only in a minority of patients [19]. In our patient, the pattern of liver biological abnormalities was an increase in conjugated bilirubin and alkaline phosphatase while transaminases were moderately elevated. Intrahepatic cholestasis was confirmed by liver biopsy. In the series from Wuhan, Chu H et al. showed that hepatocellular injury induced by hypoxemia was not a risk factor for mortality but that cholestatic and mixed patterns were associated with increased mortality risk [20]. Our patient is the first case with cholestatic hepatic failure which eventually led to liver transplantation in SARS-COV-2 infection.

Many pitfalls still exist with understanding covid-19 and physicians should be aware of cholestatic liver damage and its poor prognosis and instigate monitoring of liver tests.

Statement of informed consent

No statement was reported.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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