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HIGHLIGHTS

- Post-COVID-19 cholangiopathy is a variant of secondary sclerosing cholangitis.
- Post-COVID-19 cholangiopathy can lead to progressive severe liver injury.
- We report the first case of liver transplantation for post-COVID-19 cholangiopathy.

ABSTRACT

Liver injury is one of non-pulmonary manifestations described in COVID-19. Post-COVID-19 cholangiopathy is a special entity of liver injury, which has been suggested as a variant of secondary sclerosing cholangitis in critically ill patients (SSC-CIP). In general population, the outcome of SSC-CIP has been reported to be poor without orthotopic liver transplantation (OLT). However, the role of OLT for post-COVID-19 cholangiopathy is unknown. We present a case report of a 47-year-old man who recovered from acute respiratory distress syndrome from COVID-19, and subsequently developed end stage liver disease from post-COVID-19 cholangiopathy. The patient underwent OLT and is doing well with normal liver tests for seven months. To our knowledge, this is the first case report of a patient who underwent successful liver transplantation for post-COVID-19 cholangiopathy.

INTRODUCTION

Severe acute respiratory syndrome coronavirus (SARS-COV)-2 was first identified in December 2020 in Wuhan City, China and was declared a global pandemic by the World Health Organization (WHO) on March 11th, 2020. The disease is termed Coronavirus Disease 2019 (COVID-19). COVID-19 is typically characterized by fever, fatigue, dry cough, anosmia and headache, which may evolve to respiratory failure [1]. Liver test abnormalities have been identified as one of a growing spectrum of non-pulmonary manifestations described in COVID-19, which may potentially be attributable to hepatic expression of the main viral entry receptor of the RNA virus, angiotensin converting enzyme II (ACE2) [2, 3].

The incidence of abnormal liver tests in patients with COVID-19 ranges from 14% to 76%, and most of them are aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The aminotransferases are mildly elevated on admission in most of cases (less than two times the upper limit of normal), and total bilirubin levels can modestly increase early in the disease process. Although most of liver damage in COVID-19 infection is hepatocellular type, severe cholestasis can also occur, and 12% of patients showed total bilirubin levels elevated to more than three times the upper limit of normal [4, 5]. A recent study revealed an association between abnormal liver tests and severe COVID-19, including ICU admission, mechanical ventilation, and death [6].

The unusual entity of Secondary Sclerosing Cholangitis in Critically Ill Patients has now been recognized as a novel entity in patients after COVID-19 infection [7] and recently named Post-COVID-19 Cholangiopathy [8]. It is characterized by marked cholestasis associated with ongoing jaundice that persists long after pulmonary and renal recovery. We report a case of a patient that developed post-COVID-19 cholangiopathy requiring a liver transplant. To our knowledge, this is the first case report of a patient developing post-COVID-19 cholangiopathy whom underwent successful liver transplantation. This case is being reported to provide reference and guidance for possible long-term complications following COVID-19 pandemic including liver related consequences with liver transplantation as a viable treatment option.

CASE REPORT

Clinical Presentation and Diagnostic Tests

A 47-year-old male with class 3 (severe) obesity, BMI of 51, obstructive sleep apnea, hypertension, and hyperlipidemia with no prior history of liver disease presented to an outside facility with respiratory symptoms of dyspnea, cough, and fever. Chest x-ray showed diffuse patchy airspace opacities compatible with multifocal pneumonia, and he was subsequently found to be positive for SARS-COV-2 infection. The patient was treated with hydroxychloroquine (Plaquenil), azithromycin and high dose vitamin C. Laboratory findings were remarkable for elevated AST of 79 unit/L and ALT 52 unit/L with a total bilirubin of 0.3 mg/dL at the time of presentation. The patient experienced rapid clinical decline that included acute respiratory distress syndrome (ARDS) and acute kidney injury, and he required prolonged mechanical ventilation (29 days) and

continuous veno-venous hemofiltration (CVVH). While his pulmonary function subsequently improved and was weaned off mechanical ventilation, his acute kidney injury persisted and required regular hemodialysis.

At 58th day from his initial presentation, his pertinent laboratory blood tests included AST of 384 unit/L, ALT of 175 unit/L, alkaline phosphatase of 1,644 unit/L and total bilirubin of 19.0 mg/dL. Initial abdominal ultrasound showed severe fatty liver and innumerable gallstones throughout the gallbladder without biliary dilation or gallbladder wall thickening. A computerized tomography (CT) scan of the abdomen and pelvis without contrast showed normal liver size and contour without focal hepatic lesions or evidence of biliary ductal dilatation. At 73rd day, his follow up blood tests were AST of 236 unit/L, ALT of 121 unit/L, alkaline phosphatase 970 unit/L, and serum total bilirubin of 10.9 mg/dL. A liver biopsy demonstrated mechanical bile duct obstruction presumably related to sepsis, drug induced liver injury less likely. An endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy was performed and retrieved a small pigment stone. Noteworthy is the finding of diffuse intrahepatic biliary strictures or cholangiopathy (**Figure 1**).

On the 81st day from his initial presentation, the patient was hospitalized for hypotension during hemodialysis. Pertinent laboratory tests were ALT of 130 unit/L, AST of 491 unit/L, alkaline phosphatase of 2,730 unit/L and marked hyperbilirubinemia with total bilirubin of 19 mg/dL. An abdominal ultrasound showed cholelithiasis without evidence of acute cholecystitis while magnetic resonance cholangiopancreatography (MRCP)

demonstrated mild intrahepatic biliary ductal dilatation with multifocal strictures or beading without extrahepatic biliary dilatation. ERCP confirmed findings of secondary sclerosing cholangitis: short segments of strictures and dilatations of the intrahepatic ducts while no pathology noted in the common hepatic and common bile ducts.

Preoperative Treatment Planning and Management

The patient was evaluated and enlisted for liver transplantation with a Model for End Stage Liver Disease (MELD) score of 37. While the patient met criteria for a combined liver and kidney transplantation, the multidisciplinary liver and kidney transplantation team pursued a single organ liver transplantation as a life-saving treatment. Wait listing for renal transplantation was deferred due to co-morbidity that included morbid obesity and post-COVID-19 infection pulmonary dysfunction: restrictive ventilatory defect with low-expiratory volume and reduce diffusion capacity and evidence of post inflammatory state with mild interstitial edema. As such, staged renal transplantation is planned once the patient has recovered from his severe illness.

Orthotopic Liver Transplantation and Explant Histopathology

On the 108th day from his initial presentation, the patient received and an orthotopic liver transplantation (OLT) with a whole hepatic allograft from a deceased donor. OLT was performed with intraoperative renal replacement therapy as well as total peripheral and mesenteric veno-venous bypass. A staged choledochocholedochostomy was performed the following day [9]. Noteworthy are findings on the native liver: 4,000 grams in weight with histologic findings of severe sclerosing cholangitis with hepatic abscesses (**Figures**

2–6). There was no histologic evidence of IgG4 or other causes of secondary sclerosing cholangitis.

Post-operative care

The induction immunosuppression regimen consisted of basiliximab (Simulect) on the post-OLT days 0 and 4, solumedrol taper, and everolimus (Zortress) followed by maintenance therapy with tacrolimus and everolimus. His hepatic allograft function normalized within 8 days after OLT, and the patient was weaned off from the mechanical ventilation on the post-OLT day 13. The patient continued his recuperation in the acute rehabilitation unit beginning the post-OLT day 46, and subsequently discharged home on the post-OLT day 55.

At 7 months after OLT, the patient's hepatic allograft function remains normal: ALT of 27 units/L, AST of 28 units/L, alkaline phosphatase of 123 units/L, and total bilirubin 0.2 mg/dL. He did not experience any episode of acute cellular or antibody mediated rejection during his post-OLT period. Regarding his renal function, he continues to require regular hemodialysis. Following a successful weight loss of 50 kg in our weight loss management program, the patient is currently undergoing a comprehensive evaluation for enlisting for renal transplantation.

DISCUSSION

Secondary sclerosing cholangitis in critically ill patients (SSC-CIP) is a recently recognized form of cholestatic liver disease occurring in patients without prior history of hepatobiliary disease, after receiving treatment in the intensive care unit in different settings, including cardiothoracic surgery, infection, trauma, and burns.[10, 11].
The pathophysiology of SSC-CIP is not completely understood. The presence of critical illness and its treatment in an intensive care unit seem to play an important role in the development of the disease, but the main pathogenic mechanism seems to be a combination of bile duct ischemia, changes in bile composition, and biliary infection [12, 13]. The diagnosis is made by endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography revealing diffuse strictures and dilatations of the intrahepatic bile ducts with filling defects due to the presence of biliary casts [13, 14].

Among the various pathophysiologic events associated with critical illness, biliary ischemia seems to play a major role in the etiology of SSC-CIP. While the hepatocytes receive dual blood supply from the portal vein and the hepatic artery, the biliary epithelium receives blood supply solely from the peribiliary plexus. As such, the cholangiocytes are more susceptible to ischemia than the hepatocytes. When ischemia of the biliary epithelium takes place, blood supply to the bile ducts is reduced, resulting in necrosis and sloughing of the biliary epithelium resulting in bile cast formation [12, 15]. Deltenre et al. demonstrated that the degree of ischemic cholangiopathy was inversely proportional to the caliber of the supplying occluded artery [16].

Toxic bile may also play a role in the pathogenesis of SSC-CIP. Destruction of the protective mechanisms for the cholangiocytes, i.e., secretion of phospholipids from the hepatocytes and biliary secretion of bicarbonate, will cause their lipid membrane to be susceptible to the detergent properties of the hydrophobic bile acids [12]. Biliary secretion of bicarbonate, via the transporter ion exchanger 2 (AE2) forms a protective alkaline bicarbonate film on the apical cholangiocyte membrane as part of a defense strategy [17]. A disturbance in the fine balance between bile acids and protective mechanisms can lead to damage to the biliary epithelium leading to sclerosing cholangitis. A heightened inflammatory response through the release of proinflammatory cytokines will also add to the development of toxic bile and contribute to cholangiocyte necrosis [12].

Multi-modal treatments for critically illness have been associated with the development of SSC-CIP. Prolonged hypotension and vasopressors administration are common in patients with SSC-CIP. All the patients experienced an episode of severe hemodynamic instability with a decrease in mean arterial blood pressure <65 mm Hg for at least 60 minutes and often longer [12, 18]. Vasopressor administration is also very common before the development of SSC-CIP. Epinephrine, norepinephrine, dopamine, and dobutamine all increase systemic blood pressure but do not have the same effect on hepato-splanchnic blood flow. Dopamine has a positive effect on liver perfusion [19], contrary to epinephrine and norepinephrine that are believed to have a negative effect on splanchnic blood flow [20].

Mechanical ventilation with high positive end-expiratory pressures (PEEP) greater than 10 cm H_2O has also been shown to contribute to microcirculatory ischemia within the hepato-splanchnic vascular plexus [21]. Additionally, excessive use of prone positioning of mechanically ventilated patients has been linked to the development of SSC-CIP [22]. SSC-CIP has a mortality up to 50% in patients during an ICU admission. Adverse prognostic factors include associated renal failure, a high model for end-stage liver disease (MELD) score and rapid deterioration to liver cirrhosis [23]. In another study of SSC-CIP patients, 60% survived ICU, 40% developed stable biliary cirrhosis, and 20% required a liver transplant [24]. Without liver transplant, and the median survival in such patients is 12–44 months [25].

Post-COVID-19 cholangiopathy has been recently described [7, 8], and refers to SSC-CIP in patients that recovered from severe COVI-19 infection. All the patients described in the case reports had no preexisting liver disease, all had a prolonged hospitalization because of acute hypoxemic respiratory failure requiring mechanical ventilation and additional complications from COVID-19. All the patients developed marked cholestasis with associated jaundice that persisted long after pulmonary and renal recovery. None of the imaging studies was suggestive of cirrhosis.

Patients with severe COVID-19 infection have several predisposing conditions for SSC-CIP such as hypotension and administration of vasopressors. The presence of COVID-19 associated coagulopathy with a high risk of arterial and venous thromboembolism

[26, 27]. Mechanical ventilation with the use of PEEP for prolonged periods due to the challenges of weaning [28] plus the use of prone positioning in such patients for up to 16 hours per day are relatively common [29]. Increased proinflammatory cytokines with the syndrome of uncontrolled immune activation leading to a cytokine storm [30] and contributing to the development of toxic bile contributing to cholangiocyte necrosis [12].

The histologic picture of the patients with post-COVID-19 cholangiopathy seems to differ from the histology seen in patients with SSC-CIP of other causes [8]. All the biopsies exhibited extensive degenerative cholangiocyte injury with extreme cholangiocyte cytoplasmic vacuolization and regenerative change, not previously described for SSC-CIP. The microvascular features of hepatic artery endothelial swelling, portal vein phlebitis, and sinusoidal obstruction syndrome are also unique, as well as the intrahepatic microangiopathy affecting all 3 microvascular compartments, as noted in autopsy findings in patients succumbing to COVID-19 [31]. These histologic changes suggest direct hepatic injury from COVID-19 in patients with underlying SSC-CIP.

The patient we describe in this report had similar findings, including destruction of the biliary epithelium characterized by vacuolar degeneration with cytoarchitectural disarray, anisonucleosis and even cholangiocyte necrosis. The extensive biliary injury was associated with marked cholestasis, ductular reaction and ductulocentric fibrosis. Furthermore, our patient demonstrated obliterative portal venopathy and microarteriopathy characterized by endothelial cell swelling with obliteration of the

arterial lumen. Many of these features have been previously described in post-COVID-19 cholangiopathy [8]. Therefore, post-COVID-19 seems to be a variant of SSC-CIP and further investigation is needed in regards the pathogenicity of COVID-19 in the biliary epithelium. A major concern for patients with post-COVID-19 cholangiopathy is that it may lead to progressive liver injury with the potential need for liver transplantation, as seen in our patient [8].

To our knowledge, this is the first report of a patient requiring liver transplantation due to fulminant post-COVID-19 cholangiopathy. Given the increased number of COVID-19 infections intensive care medical management, it is important to develop a practical approach in screening and evaluation of patients who are likely to develop post-COVID -19 cholangiopathy, particularly those who will progress to a fulminant course and require an expedited orthotopic liver transplantation.

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DISCLOSURE

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FIGURE LEGENDS

Figure 1. Endoscopic retrograde cholangiography showing a normal common bile duct with diffuse stricturing of the intrahepatic ducts.

Figure 2. Hilar bile duct with findings of inflammation and fibrosis (hematoxylin & eosin, 20×). Red and black inserts (100×) show increased collagen deposition with associated mononuclear inflammatory infiltration within the wall of the bile duct.

Figure 3. Liver abscess occupying the bottom left field (hematoxylin & eosin stain, 40×). One bile lake occupying top right field (Insert, 400× hematoxylin & eosin staining, showing neutrophil rich abscess contents).

Figure 4. Bile lake associated with bile duct injury with vacuolization and neutrophilia (400×, hematoxylin & eosin).

Figure 5. Microarteriopathy with endothelial cell swelling and obliteration of the lumen (400×, hematoxylin & eosin).

Figure 6. Obliterative portal venopathy (100×, hematoxylin & eosin).

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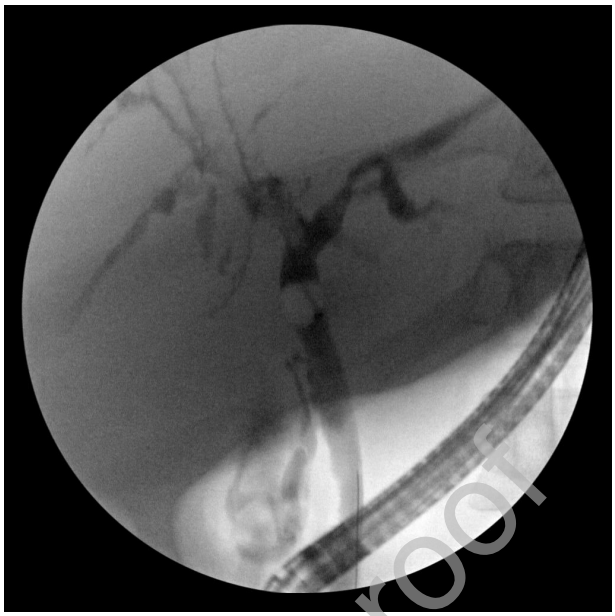
Figure 1.



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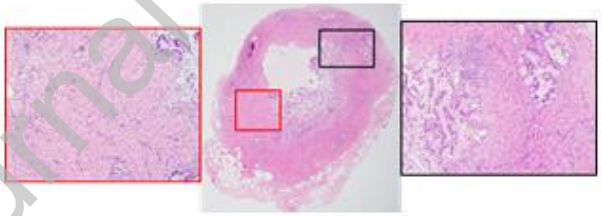

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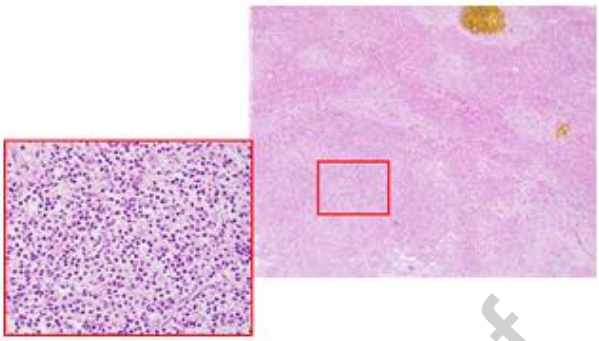

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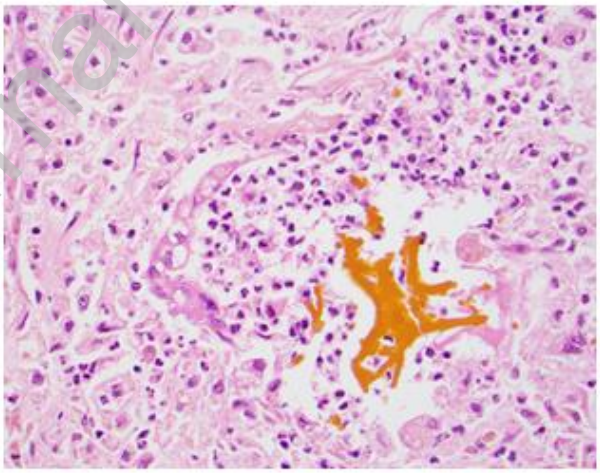

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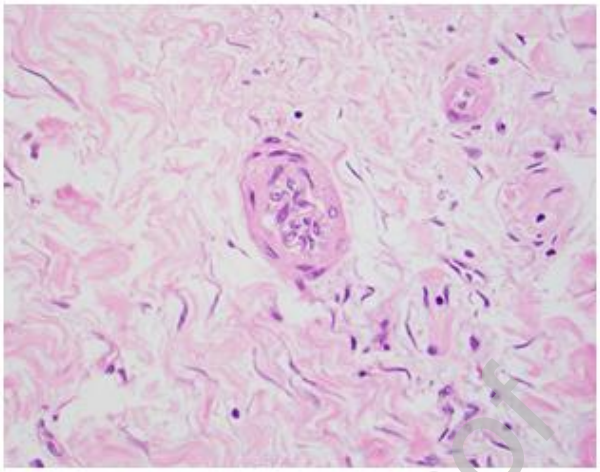

Figure 6.