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Case Series

Critical Illness Cholangiopathy in COVID-19 Long-Haulers

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On March 11, 2020, the World Health Organization declared COVID-19 a pandemic, and as of May 11, 2022, there were over 516 million confirmed cases of COVID-19 and more than 6.2 million deaths.¹ COVID-19 has affected all age groups, and risk factors for severe illness or death include older age and comorbid chronic illnesses such as respiratory illnesses, diabetes, obesity, and hypertension.² Although respiratory illness and pneumonia are defining features and determinants of morbidity and mortality in COVID-19 patients, the virus has the capability to affect multiple organ systems, including the gastrointestinal tract. COVID-19 is frequently associated with abnormal liver tests, with no disease-specific features on biopsy.³ The incidence of abnormal serum liver biochemistries in hospitalized patients have been reported to range from 14%-58%.⁴ There have been increasing reports of long-term sequelae of COVID-19, and the term “long-haulers” has been used for patients who have recovered from the acute phase of illness but have persistent symptoms, including chronic respiratory, neurologic, and psychiatric effects.^{5,6} Faruqui et al described a syndrome in patients recovering from severe COVID-19 infection, characterized by abnormal liver tests, with marked elevation in serum alkaline phosphatase and abnormal appearance of the biliary tract on imaging, frequently with strictures similar to secondary sclerosing cholangitis seen in critically ill patients.^{3,7} The mean time to recognition of this syndrome was over 3 months after admission, and all patients had been critically ill and required intensive care. This syndrome has also been reported by other authors and appears to have important consequences for long-term morbidity, patient recovery, need for liver transplantation, and mortality after recovery from other manifestations of COVID-19.⁸⁻¹⁰

Cases

Here, we present 2 cases of severe COVID-19 infection requiring intensive care and prolonged hospitalization, subsequently developing cholestatic liver injury indicative of cholangiopathy 3 to 4 months after primary hospital discharge.

Case 1

A 73-year-old male with past medical history of asbestos-related lung injury, coronary artery disease, congestive heart failure, diabetes mellitus, and hypertension presented with cough, generalized weakness, and dizziness. He had no known history of liver disease. He was noted to be hypoxic with oxygen saturation of 90% on room air. Chest CT showed ground glass infiltrates in the right upper lobe and bilateral lung bases concerning for COVID-19 pneumonia. A respiratory viral panel confirmed COVID-19 infection. He developed acute respiratory distress syndrome shortly after admission and was admitted to the ICU for ventilator support for 4 days. He was treated with remdesivir, azithromycin, dexamethasone, and furosemide. He was also treated for presumed superimposed bacterial pneumonia and developed paroxysmal atrial fibrillation during hospitalization. Overall, he had good recovery and was discharged to a rehabilitation facility after 10 days of hospitalization.

Despite no specific abdominal symptoms, laboratory tests on routine follow-up 4 months after initial presentation showed abnormal liver tests: aspartate aminotransferase (AST) of 223 U/L (normal range: 17-59 U/L), alanine aminotransferase (ALT) of 223 U/L (normal range: 0-50 U/L), alkaline phosphatase of 1325 U/L (normal range: 38-126 U/L), total bilirubin of 1.5 mg/dL (normal range: 0.2-1.3 mg/dL), and gamma-glutamyl transferase of 1704 U/L (normal range: 15-73 U/L). Further serological workup was largely unrevealing, with a negative acute viral hepatitis panel, anti-nuclear antibodies, anti-smooth muscle antibodies, and antimitochondrial antibodies. A subsequent magnetic resonance cholangiopancreatography showed multiple areas of narrowing of the central intrahepatic bile ducts with peripheral dilatation and beaded appearance. The patient underwent endoscopic retrograde cholangiopancreatography (ERCP), which showed a large extrahepatic bile duct cast (Figures 1 and 2), which was removed along with additional smaller stones and sludge (Video 1). There were diffuse fine irregularities of the intrahepatic biliary ducts.

On follow-up 6 months after ERCP, liver function tests improved but remained elevated with AST of 102 U/L, ALT of 70 U/L, alkaline phosphatase of 746 U/L, and total bilirubin of 0.9 mg/dL. Repeat MRCP showed no

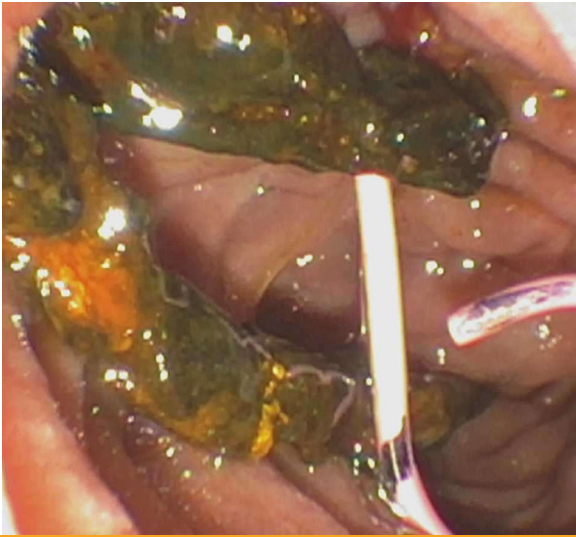


Figure 1. Biliary cast removed during ERCP. A pancreatic duct stent is also seen.



Figure 2. Multiple extrahepatic filling defects on fluoroscopy during ERCP.

residual common bile duct stones but persistent multiple foci of intrahepatic ductal stricturing with mild dilatation, creating an irregular beaded appearance of the intrahepatic ducts.

Case 2

A 66-year-old male with a history of diabetes mellitus, pancreas transplant, and chronic kidney disease presented with progressive dyspnea and nonproductive cough for 4 days. He was found to be COVID-19 positive via a nasopharyngeal swab. He developed acute respiratory distress syndrome requiring mechanical ventilation. He was treated with dexamethasone and diuretics. He was also treated with piperacillin-tazobactam for presumed superimposed bacterial pneumonia. He had a prolonged course in the medical intensive care unit with septic shock, bacteremia, and renal impairment. While in the ICU, he developed a cholestatic pattern of liver function test abnormalities; his liver enzymes were normal on admission, but on day 33 of his hospital

stay, his labs were notable for an AST of 83 U/L, ALT of 72 U/L, alkaline phosphatase of 857 U/L, and total bilirubin of 1.3 mg/dL. An abdominal ultrasound showed mild intrahepatic bile duct dilatation and a CBD diameter of 6 mm. It was negative for choledocholithiasis. His clinical status slowly improved, and he was discharged from the ICU to a long-term acute care hospital on day 49.

On routine follow-up 6 months after hospital discharge, despite a paucity of abdominal symptoms, the patient's follow-up laboratory tests were notable for a cholestatic pattern of liver function test abnormalities: AST of 50 U/L, ALT of 56 U/L, alkaline phosphatase of 1819 U/L, and total bilirubin of 1.9 mg/dL. Endoscopic ultrasound showed a long, continuous filling defect in the common bile duct. A subsequent ERCP showed multiple biliary strictures in the left and right intrahepatic ducts (Figure 3). The biliary tree was swept, and multiple large, pliable linear stones/biliary casts were removed from the biliary system (Figure 4). The lower third of the



Figure 3. Segmental biliary strictures in the left and right intrahepatic ducts.

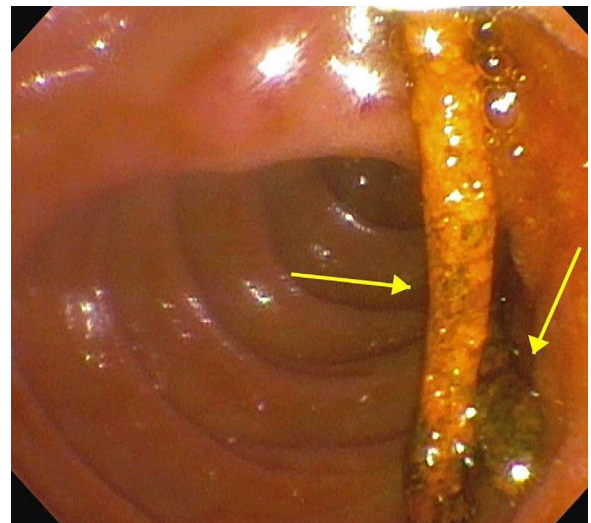


Figure 4. Biliary cast removal during ERCP.

main bile duct contained a single localized stenosis and was treated with placement of a covered metal stent. On follow-up 2 months after ERCP, he was noted to be doing well clinically but continued to have persistent abnormal liver function tests with AST of 83 U/L, ALT of 60 U/L, alkaline phosphatase of 1418 U/L, and total bilirubin 2.1 mg/dL.

Discussion and Conclusion

Biliary cast formation is a complication reported in 2.1%-3.6% of patients after liver transplantation.¹¹ It has been defined as hardened material molded to the bile ducts and contains fragments of biliary epithelium, leading to obstructive jaundice and cholangitis.^{12,13} It has been hypothesized that biliary cast formation is caused by ischemic biliary injury. Therapeutic options include cast removal during endoscopic retrograde cholangiopancreatography and stent placement.¹¹ In both cases presented, the clinical picture was consistent with biliary cast syndrome with secondary sclerosing cholangitis, related to severe COVID infection leading to critical illness. It is plausible that COVID-associated cast-forming cholangiopathy is a manifestation of critical illness cholangiopathy, which has previously been described.⁷ Purported pathogenetic mechanisms could include bile duct ischemia related to COVID-19-associated thrombosis or direct biliary epithelial viral infection.^{3,7} It is plausible that the resultant hypoxic injury to biliary epithelium leads to biliary cast formation and biliary strictures. Little is known about the natural history of such patients, but in our case, we believe that endoscopically clearing large casts with ERCP could help to prevent further ongoing worsening of secondary sclerosing cholangitis. The ultimate optimal management for such patients is not known. In conclusion, cholangiopathy with biliary cast formation is an important late complication of COVID-19 infection that requires further study to elucidate the underlying pathogenesis, natural history, therapeutic options, and long-term outcomes.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.tige.2022.05.006](https://doi.org/10.1016/j.tige.2022.05.006).

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The authors disclose no conflicts.

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Ethical Statement

The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.