



Severe Cholestatic Hepatitis Secondary to SARS-CoV-2

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ABSTRACT

Liver injury is a common manifestation of coronavirus disease 2019 (COVID-19), with most injuries manifesting as transient mild hepatocellular injury. Cholestatic injury occurs less commonly and is typically mild. Severe cholestatic injury is rare, with only 4 cases reported in the literature. We present a 70-year-old woman with no known liver disease who presented with severe COVID-19 and developed severe cholestatic hepatitis. A liver biopsy was performed demonstrating bile duct injury, uncommonly reported in patients with COVID-19. This complication needs greater awareness because it has been known to cause progressive liver disease requiring transplantation.

INTRODUCTION

Liver injury is a common manifestation of coronavirus disease 2019 (COVID-19), with data suggesting up to 78% of the patients exhibit liver enzyme abnormalities.^{1,2} The most common pattern of injury is mild transaminase elevation, with hyperbilirubinemia observed in 11–18% of the patients.¹ Although mild cholestasis has been reported, there were no published cases of severe cholestasis until 2021.^{2–4} Recently, 2 case reports, a total of 4 patients, have described severe cholestatic hepatitis attributed to COVID-19.^{5,6} Here, we present the fifth case of this newly emerging COVID-19 complication.

CASE REPORT

A 70-year-old woman without a history of liver or kidney disease presented to the emergency department with 2 days of nausea/vomiting, abdominal pain, diarrhea, hematochezia, and oliguria. She was afebrile, normotensive, tachycardic, and mildly tachypneic, with an oxygen saturation of 96%. An initial workup revealed lymphopenia, sodium 124 mmol/L, creatinine 4.86 mg/dL, alkaline phosphatase 277 U/L, alanine aminotransferase 370 U/L, aspartate aminotransferase 337 U/L, total bilirubin 5.0 mg/dL, direct bilirubin 4.3 mg/dL, and international normalized ratio 0.9. Abdominal computed tomography revealed small gallstones without intrahepatic or extrahepatic duct dilation and left-sided colonic wall thickening. Thoracic x-ray showed basilar opacities. Nasopharyngeal swab returned positive for COVID-19, and the patient was admitted for multiorgan failure secondary to severe COVID-19.

Stool pathogen testing was negative, and colon changes were attributed to ischemic colitis and treated with metronidazole and ceftriaxone over days 1–3. Serologic evaluation for infectious, autoimmune, and genetic causes of liver injury was negative. Blood culture, urine culture, and PCR for Epstein-Barr virus/cytomegalovirus/herpes simplex virus were negative. Ferritin, initially elevated at 550 ng/mL, peaked at 7,581 ng/mL. She received convalescent plasma on day 2 for severe COVID-19 per hospital protocol at the time and started renal replacement therapy for anuric renal failure.

Transaminases improved, but alkaline phosphatase and bilirubin increased dramatically, peaking at 3,010 U/L and 29.2 mg/dL, respectively, on day 24 (Figure 1). Magnetic resonance cholangiopancreatography on day 11 revealed normal hepatic echotexture, patent hepatic vasculature without biliary ductal dilation, or excretion of Eovist contrast into the biliary tree. Liver biopsy on day 14 revealed a normal sinusoidal pressure of 5 mm Hg, severe zone 3 hepatocanalicular cholestasis with focal necroinflammation, portal inflammation without interface lobular activity, prominent bile duct damage, and mild steatosis without ballooning hepatocytes or Mallory Denk bodies (Figure 2). This was consistent with cholestatic hepatitis, ultimately attributed to COVID-19. She remained hemodynamically stable. Other relevant medications included prednisone 40 mg daily for COVID-19 and ursodiol 600 mg twice

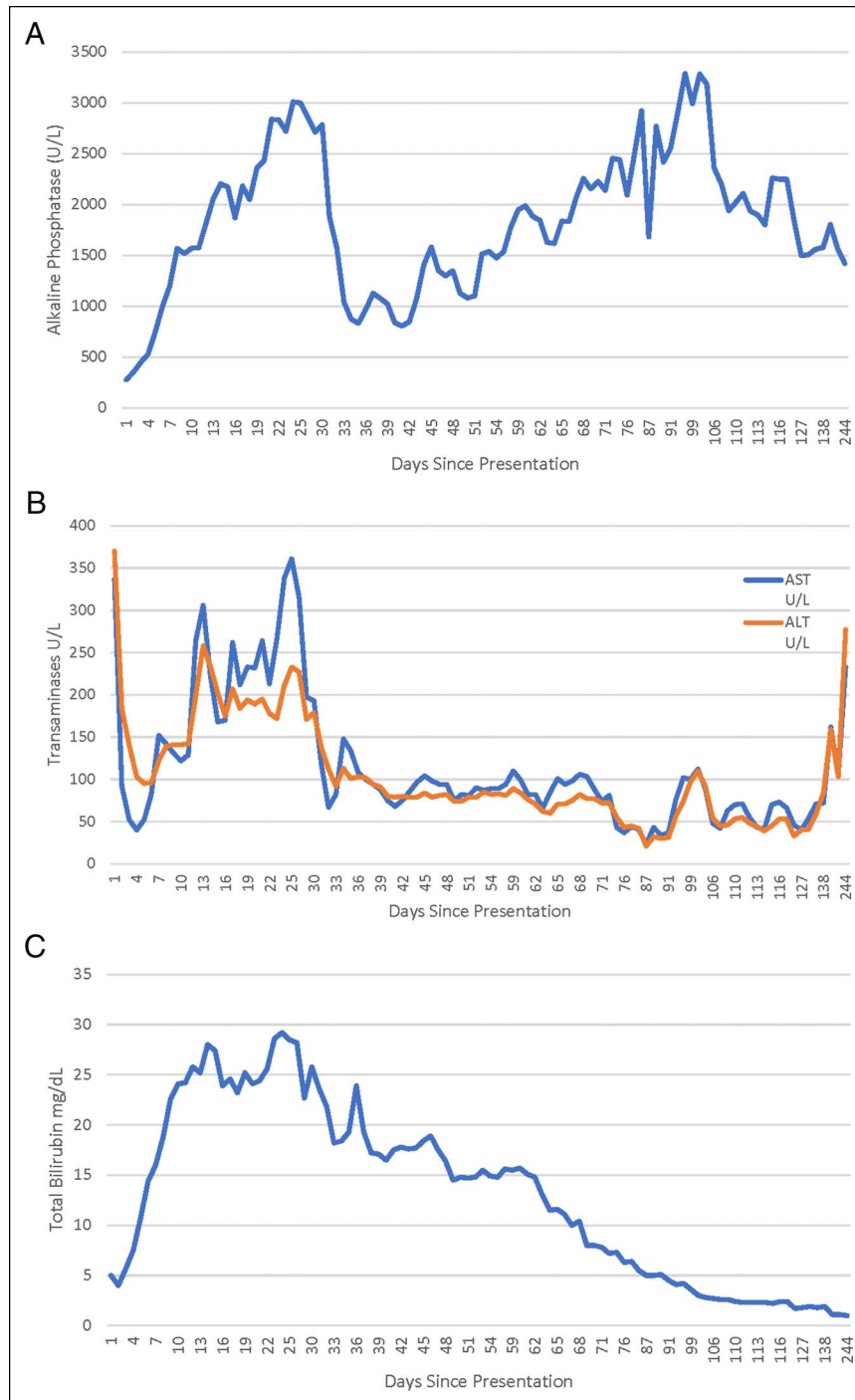


Figure 1. Trend of liver chemistries of the patient from presentation. Presentation is day 1. (A) Alkaline phosphatase (U/L), (B) aspartate aminotransferase (AST) (U/L) and alanine aminotransferase (ALT) (U/L), and (C) total bilirubin (mg/dL).

daily for cholestasis given on days 7 and 8. No other COVID-19-directed medications were administered. Outpatient medications included an herbal supplement containing stramonium she had taken for 20 years and acetaminophen, cyclobenzaprine, glucosamine with chondroitin, hydrocodone, ibuprofen, polyethylene glycol, and a probiotic; none continued on admission. Magnetic resonance cholangiopancreatography 95 days after presentation revealed mild hepatic steatosis without

biliary ductal pathology; liver tests were continued to be monitored.

DISCUSSION

We report a rare, newly recognized complication of severe COVID-19 manifesting as severe, persistent cholestasis with associated bile duct injury. To date, there have been 4 other cases

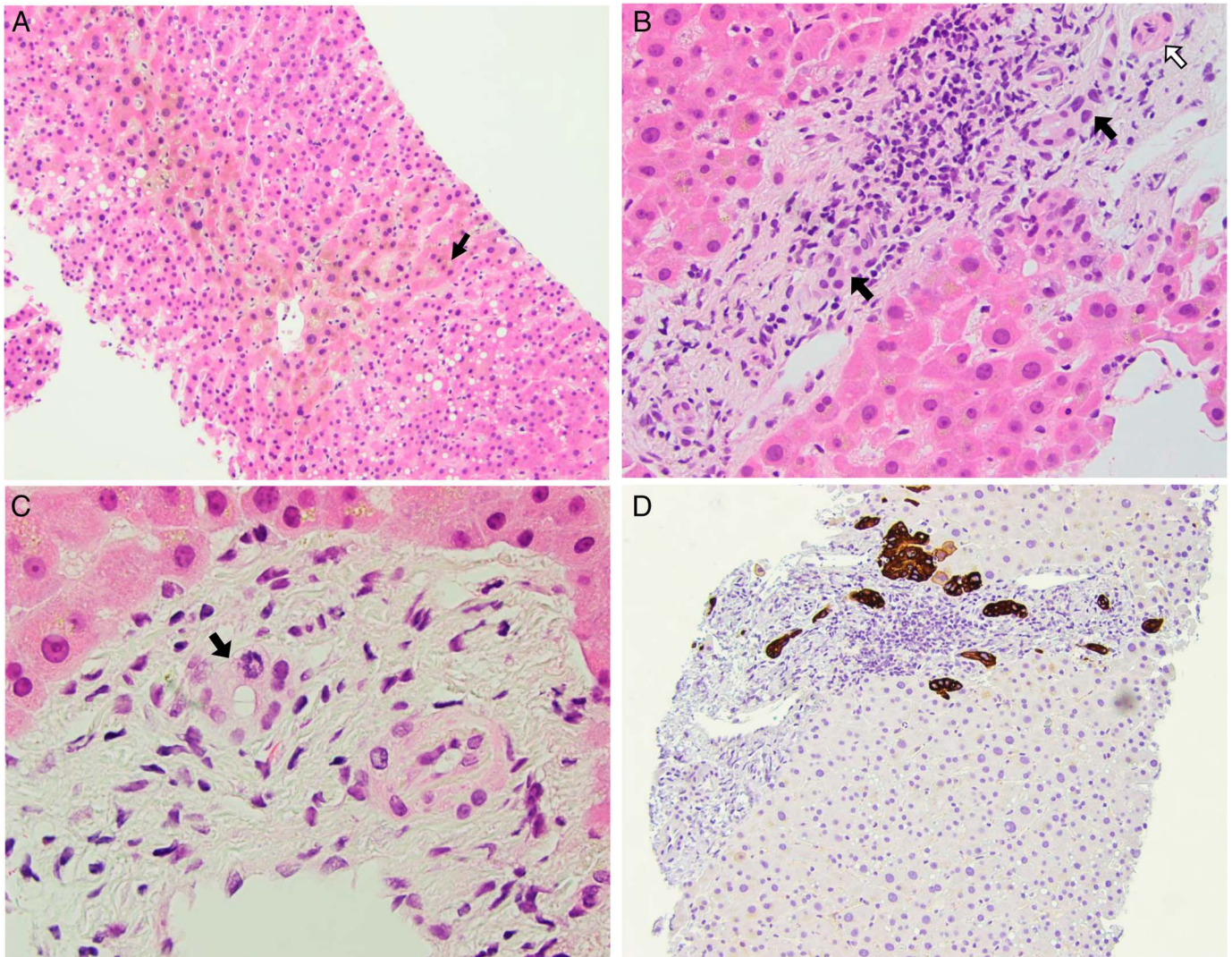


Figure 2. The histopathologic findings of cholangiopathy in the liver biopsy (hospital day 14). (A) Hepatocanalicular cholestasis in zone 3 (10× magnification). The background liver parenchyma shows mild steatosis and minimal lobular inflammation. Arrow indicates bile plug. (B) Portal inflammation with prominent bile duct damage (20× magnification). The injured cholangiocytes (black arrows) show eosinophilic cytoplasm, nuclear pleomorphism, and irregular spacing. An adjacent hepatic artery (white arrow) shows endothelial injury manifested as endothelial cell swelling and lumen obliteration. (C) At high power, the injured cholangiocytes show cytoplasm vacuolization, degenerative changes, and mitosis (40× magnification). (D) CK7 immunohistochemical stain highlights ductular reaction at the periphery of the portal tract (20× magnification).

published.^{5,6} The frequency of this injury is not yet established. Like previously published cases, our patient had no underlying liver disease. Because this entity becomes more commonly recognized, it may become easier to determine whether preexisting liver disease changes the prevalence or severity of this complication. Our case differs from most of the reported cases because our patient did not require mechanical ventilation, pressor support, or have biliary pathology on imaging. However, she required renal replacement therapy as did 3 of the published cases.

Despite high rates of liver injury in COVID-19, few studies have presented histopathological findings.^{5–9} Most findings are from autopsy and include microvesicular steatosis, mild sinusoidal dilatation, mild lobular lymphocytic infiltration, and patchy hepatic necrosis in the periportal and centrilobular areas. A

recent study by Lagana et al⁹ described the major histopathological findings of 40 postmortem livers of patients who died of COVID-19, finding lobular necroinflammation, portal inflammation, lobular apoptosis, and steatosis. Cholestasis was described in 38% of the explanted livers. There were no reported bile duct injuries.

All 4 previously reported cases underwent liver biopsy. The case series presented by Roth et al⁵ described varying degrees of ductular reaction, cholangiocyte swelling, cholangiocyte regenerative change, zone 3 hepatocanalicular cholestasis, and fibrosis. Similar, although milder, changes were seen in our patient's liver biopsy, which was taken on day 14 compared with days 96, 151, and 178 in the 3 case series, possibly highlighting the histologic progression of the syndrome.

Our patient had no other identifiable causes for her cholestatic hepatitis. The only potentially offending medication before hospitalization was an herbal supplement containing stramonium. This has caused mild hepatocellular injury in rats, but cholestasis has not been reported and would not explain her other systemic symptoms.¹⁰ The patient received convalescent plasma; however, this has not been associated with liver injury in the thousands of patients who have received it.^{11,12} This therapy was also administered to one of the earlier 4 patients, although the timing is unclear. The only other COVID-related therapy our patient received was 2 days of prednisone, which has not been associated with cholestasis. It has been observed that some patients with COVID-19 suffering from acute respiratory distress syndrome receiving ketamine for sedation have developed progressive cholestasis; however, our patient did not receive this therapy.¹³

Many mechanisms have been proposed to describe liver injury associated with COVID-19, including direct infection of hepatocytes and/or cholangiocytes through the ACE2 receptor, inflammatory cytokine storm, and drug-induced liver injury (DILI) associated with COVID-19 therapies. Recent reports have suggested direct hepatic injury from SARS-CoV-2. SARS-CoV-2 DNA has been isolated from postmortem livers, and electron microscopy has demonstrated viral particles within hepatocytes with viral cytopathic effects.^{9,14} Furthermore, ACE2 is expressed primarily on cholangiocytes, which has been suggested as the entry point for hepatobiliary damage.^{15,16} Direct polymerase chain reaction testing for SARS-CoV-2 DNA was not performed on our patient's liver biopsy. More research is warranted regarding this syndrome because it has been implicated in ongoing liver damage severe enough to warrant liver transplantation.⁶

DISCLOSURES

Author contributions: All authors contributed equally to this article. KE Daniel is the article guarantor.

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Informed consent was obtained for this case report.

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