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CASE REPORT

COVID-19-associated secondary sclerosing cholangitis — A case series of 4 patients

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Available online 5 November 2022

KEYWORDS
COVID-19; Secondary sclerosing cholangitis; Cholangiopathy; Case series

Abstract We report a case series of four patients diagnosed with COVID-19-associated secondary sclerosing cholangitis (SSC), a recently described rare late complication of severe COVID-19. Following prolonged stays in the intensive care unit, these patients developed marked sustained cholestasis and jaundice despite clinical improvement. Cholangiography showed beaded appearance of intra-hepatic bile ducts and bile casts were removed in one patient. None of the patients reached normalization of liver enzymes and at least one progressed to liver cirrhosis (follow-up time of 11 to 16 months). COVID-19-associated SSC has a dismal prognosis with rapid progression to advanced chronic liver disease.

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Abbreviations: (ALT), Alanine aminotransferase; (ALP), alkaline phosphatase; (ANA), antinuclear antibodies; (AST), aspartate aminotransferase; (cACLD), compensated advanced chronic liver disease; (CT), computed tomography; (COVID-19), coronavirus disease 2019; (ERCP), endoscopic retrograde cholangiopancreatography; (GGT), gamma-glutamyl transferase; (H&E), hematoxylin and eosin; (HBV), hepatitis B virus; (ICU), intensive care unit; (IMV), invasive mechanical ventilation; (MRCP), magnetic resonance cholangiopancreatography; (PEEP), positive-end expiratory pressure; (SARS-CoV-2), severe acute respiratory syndrome coronavirus 2; (SSC), secondary sclerosing cholangitis; (SSC—CIP), secondary sclerosing cholangitis in critically ill patients; (ULN), upper limit of normal.

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https://doi.org/10.1016/j.clinre.2022.102048
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Introduction

Coronavirus disease 2019 (COVID-19)-associated secondary sclerosing cholangitis (SSC) is a recently described cholestatic liver disease.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been linked to altered liver enzymes in up to 69% of hospitalized patients, particularly aspartate aminotransferase (AST) dominant aminotransferase elevation. This appears to reflect hepatic injury but is usually self-limited [1].

Nonetheless, some patients develop a rapidly progressive cholangiopathy, sometimes requiring liver transplantation.

Until now, about 30 cases of this severe cholestatic liver disease have been described in the literature [2, 3]. Common reported features were severe COVID-19 pneumonia requiring long intensive care unit (ICU) stay, invasive mechanical ventilation (IMV) with high positive-end expiratory pressure (PEEP), periods of prone position, circulatory support with vasopressors and administration of multiple other drugs. Patients had no prior liver disease or had liver steatosis at most.

Early in the course of the disease, an increase of AST and alanine aminotransferase (ALT) was observed, followed by a decrease soon afterwards. Then, there was a rise in alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and total bilirubin that persisted despite overall clinical recovery [2]. Magnetic resonance cholangiopancreatography (MRCP) common findings included mild dilatations and strictures of intrahepatic bile ducts with beaded appearance and biliary casts [2, 3]. Most patients underwent liver biopsy, which mainly revealed inflammatory infiltrate in portal tracts, portal and periporal fibrosis, bridging fibrosis, necrosis, degenerative and regenerative changes of cholangiocytes, cytokeratin 7 immunostain positivity indicating ductular reaction, and vascular damage such as hepatic artery endothelial swelling and hepatic veins endophlebitis [2, 3].

Case series presentation

We present a case series of four patients who developed SSC complicating the course of severe COVID-19. Written informed consent was obtained from all patients and this project was approved by our local ethics committee.

COVID-19 course

Patient A is a 64-year-old female of African descent, with a personal history of arterial hypertension and overweight (body mass index 29 kg/m²). Patient B is a 55-year-old male of African descent, with unremarkable medical history. Patient C is a 78-year-old white male, with medical history of arterial hypertension, atrial fibrillation, type 2 diabetes, dyslipidemia, stage 3a chronic kidney disease and cholecystectomy. Patient D is a 63-year-old white female, with type 2 diabetes and dyslipidemia.

All four patients presented with severe COVID-19 with acute respiratory failure requiring long ICU stays (21 to 69 days). They underwent IMV with high PEEP and periods of prone positioning. Ventilator weaning was difficult and culminated to tracheostomy in three patients. During their stay in the ICU, these patients required circulatory support with vasopressors and administration of multiple other drugs, including antibiotics, sedatives and high dose steroid therapy. None of the patients required renal replacement therapy or extracorporeal membrane oxygenation.

Demographic and clinical characteristics of the four patients are summarized in Table 1.

Liver disease

All patients had normal liver tests before developing severe COVID-19. Patient C had liver steatosis, but none of the other individuals had a previously known liver disease.

In all patients, a significant rise in AST – 17x upper limit of normal (ULN) and ALT 12 – 34x ULN was initially observed with subsequent improvement. This was followed by marked cholestasis with ALP 8 – 23x ULN and GGT 40 – 99x ULN and jaundice (total bilirubin 2 – 7x ULN). Patients A, B and C also presented mild transient pruritus. Overall, cholestasis improved with time, but without complete normalization, despite clinical recovery (Fig. 1).

In patient A, we documented a previous hepatitis B virus (HBV) infection (negative HBs antigen, positive HBs and HBc antibodies). Antinuclear antibodies (ANA) were positive (title 1:320). Abdominal ultrasound showed mild hepatomegaly and minor dilatation of intra-hepatic bile ducts. After her liver tests started to improve, cholestasis worsened again around day 100, accompanied by elevated inflammatory markers. Antibiotic therapy with amikacin and ceftazidime/avibactam was started against multidrug-resistant Klebsiella pneumoniae identified in blood cultures and maintained for 21 days. Computed tomography (CT) identified obstructive content at the pancreatic portion of the common bile duct as well as a nodular lesion with 17 mm in liver segment VI suggestive of an abscess. She underwent endoscopic retrograde cholangiopancreatography (ERCP) with bile casts removal at day 107 and after an initial raise of cholestasis markers, there was a subsequent decrease and clinical improvement.

In patient B, we found chronic HBe antigen negative HBV infection with low viremia (307 UI/mL) for which entecavir was started because of high dose corticosteroid therapy. ANA were positive (title 1:160). Abdominal ultrasound revealed minor heterogeneous hepatomegaly.

In patient C, viral serologies and autoimmunity were unremarkable. Abdominal ultrasound showed mild liver heterogeneity and contrast enhanced CT demonstrated mild central intra-hepatic biliary dilatation with discrete hyper-enhancement of bile ducts walls.

Patient D had positive ANA 1:320, anti-soluble liver antigen and anti-sp100. Abdominal ultrasound revealed liver heterogeneity, but CT showed no liver nor biliary abnormalities. She initially stayed in the ICU for 69 days. Then, she was readmitted on day 81 for acute cholecystitis after being submitted to laparoscopic cholecystectomy complicated by right hepatic artery bleeding which was successfully controlled intraoperatively. On day 94, she was readmitted again to the ICU after cardiorespiratory arrest in relation to air embolism. She needed IMV and vasopressors for four days. During this period, liver tests worsened again and later improved.
Table 1  Demographic and clinical characteristics of the four patients.

|                | Patient A | Patient B | Patient C | Patient D |
|----------------|-----------|-----------|-----------|-----------|
| **Age (years)**| 64        | 55        | 78        | 63        |
| **Gender**     | Female    | Male      | Male      | Female    |
| **Race/Ethnicity** | African descent | African descent | White   | White |
| **Comorbidities** | Arterial hypertension, overweight | No | Arterial hypertension, atrial fibrillation, type 2 diabetes, dyslipidemia, stage 3a chronic kidney disease, cholecystectomy | Type 2 diabetes, dyslipidemia |
| **Previously known liver disease** | No        | No        | Liver steatosis | No |
| **ICU stay**   | 41        | 43        | 21        | 69        |
| **Days on mechanical ventilation** | 24        | 38        | 12        | 55        |
| **Prone position** | Yes       | Yes       | Yes       | Yes       |
| **Tracheostomy** | Yes       | Yes       | No        | Yes       |
| **Complications of ventilation** | Pneumothorax and pneumomediastinum 3 days | Antibiotics: amikacin, azithromycin, ceftazidime, ceftriaxone, meropenem, vancomycin; Sedatives: ketamine for 22 days, propofol, fentanyl; Corticosteroids. | Antibiotics: amikacin, azithromycin, ceftazidime, ceftriaxone, meropenem, vancomycin; Sedatives: ketamine for 22 days, propofol, fentanyl; Corticosteroids. | |
| **Medications** | Antibiotics: amikacin, amoxicillin/clavulanic acid, ampicillin, azithromycin, ceftriaxone, meropenem, piperacillin/tazobactam vancomycin; Sedatives: ketamine for 19 days, propofol, fentanyl; Corticosteroids. | Antibiotics: amikacin, amoxicillin/clavulanic acid, azithromycin, ceftazidime, ceftriaxone, daptomycin, linezolid, piperacillin/tazobactam; Sedatives: ketamine for 8 days, propofol, fentanyl; Corticosteroids. | Antibiotics: amikacin, azithromycin, ceftazidime, ceftriaxone, meropenem, vancomycin; Sedatives: ketamine for 22 days, propofol, fentanyl; Corticosteroids. | |
| **MRCP findings** | Slight dilatation, duct wall thickening and hyper-enhancement of intra-hepatic bile ducts with restricted diffusion. Thickening and hyper-enhancement of distal common bile duct. Single 13 mm abscess in liver segment VI. Removal of bile casts. Rarefaction, stenosis and focal dilations of intra-hepatic bile ducts. | Multiple high-grade short strictures of intra-hepatic bile ducts with cystic dilatations. | Multiple short high-grade strictures of intra-hepatic bile ducts. Hyper-enhancement of duct walls with restricted diffusion. Some abscesses up to 8 mm with peripheral ring enhancement. | Multiple high-grade short strictures, some high-grade long strictures (>1 cm) and some small dilations of intra-hepatic bile ducts. Discrete hyper-enhancement in some locations coincident with slight restricted diffusion. |
| **ERCP** | No | No | No | No |
| **Histology findings** | Edema and mixed inflammatory infiltrate of portal spaces, ductulitis, intra-hepatic cholestasis, interface hepatitis, low grade fibrosis, small-medium vessel with marked intima edema and inflammatory infiltrate with partial reduction of lumen. | Edema and mixed inflammatory infiltrate of portal spaces, ductulitis, intra-hepatic cholestasis, interface hepatitis and low-grade fibrosis. | No | Mild marginal ductular proliferation and slight inflammatory infiltrate of ductular epithelia, with no fibrosis. |

ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit; MRCP, magnetic resonance cholangiopancreatography.
Fig. 1  Variation of liver enzymes since hospital admission.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIL, total bilirubin; GGT, gamma-glutamyl transpeptidase; ULN, upper limit of normal. ULN:

- ALP 130 U/L
- ALT 41 U/L
- AST 40 U/L
- BIL 1.20 mg/dL
- GGT 60 U/L
Serum IgG4 levels were within the reference interval in all patients.

Cholangiographic findings

MRCP was performed in all patients (Fig. 2).

In patients B, C and D, cholangiographic findings were quite similar, with multiple high-grade strictures and cystic dilatations of intra-hepatic bile ducts, accompanied by hyper-enhancement of duct walls with restricted diffusion in patients C and D (Figs. 2a and 2c). The common bile duct was normal.

In patient A, MRCP showed slight dilatation, duct wall thickening and hyper-enhancement of intra-hepatic bile ducts with restricted diffusion, as well as thickening and hyper-enhancement of distal common bile duct (Fig. 2b). A CT scan performed later identified calculi in the intra-pancreatic common bile duct. Hence, an ERCP was performed with removal of bile casts and revealed rarefaction, stenosis and focal dilations of intra-hepatic bile ducts (Fig. 2d).

Therefore, cholangiographic findings of these four patients were of sclerosing cholangitis (Fig. 2).

Two patients developed liver abscesses. In patient A, a 13 mm abscess contiguous to intra-hepatic bile ducts was identified in liver segment VI (Fig. 2e). This lesion disappeared after antibiotic treatment. Patient C had some abscesses up to 8 mm with peripheral ring enhancement throughout the liver (Fig. 2e), although without clinical repercussion.

Histopathology

Liver biopsy was performed in three patients (A, B and D).

In patients A and B, liver biopsy was performed 2 months after initial presentation and revealed similar aspects in both patients — edema and mixed inflammatory infiltrate of portal spaces, degeneration and mixed inflammatory infiltrate of ductular epithelia (Fig. 3a), intra-hepatic cholestasis (Fig. 3b), interface hepatitis and low-grade fibrosis (Fig. 3c). In patient A, immunohistochemistry with cytokerin-7 was also performed (Fig. 3d), suggesting marginal ductular proliferation. Additionally, a small-medium vessel with marked intima edema and inflammatory infiltrate with partial reduction of lumen was identified (Fig. 3e).

Patient D underwent liver biopsy 12 months after initial presentation and histopathology showed less severe features — mild marginal ductular proliferation and slight inflammatory infiltrate of ductular epithelia, with no fibrosis.

Detection of SARS-CoV-2 by immunohistochemistry was negative in all liver biopsies.

Follow-up

Patients were followed for 11 to 16 months. They were all started on ursodeoxycholic acid, but none of them reached normalization of liver enzymes.

After 16 months, patient A maintained altered liver enzymes (AST 116 U/L, ALT 136 U/L, GGT 789 U/L, ALP 516 U/L, GGT 789 U/L) with normal total bilirubin (0.89 mg/dL) and developed low platelet count (129 x 10^9/L). Repeat MRCP showed macronodular cirrhosis, splenomegaly and mild ascites. Transient elastography showed a liver stiffness of 75 kPa. Upper endoscopy revealed small esophageal varices and portal hypertensive gastropathy. She was referred to a liver transplant center.

Patient B also maintained altered liver tests after 15 months (AST 67 U/L, ALT 69 U/L, ALP 445 U/L, GGT 473 U/L and total bilirubin 1.79 mg/dL). Repeat MRCP was similar to the first one, without features of liver cirrhosis. He was also referred to a liver transplant center. He maintained entecavir treatment with suppressed viral load.

After 11 months, patient C maintained abnormal liver tests (AST 48 U/L, ALT 52 U/L, ALP 526 U/L, GGT 526 U/L and total bilirubin 1.2 mg/dL). Transient elastography showed a liver stiffness of 24 kPa. Repeat MRCP revealed liver dysmorphism and mild splenomegaly, but upper endoscopy showed no varices. Because of his age and comorbidities, he was not a candidate for liver transplant.

Patient D maintained altered liver enzymes after 16 months of follow-up (AST 69 U/L, ALT 62 U/L, ALP 750 U/L, GGT 908 U/L) with normal bilirubin (0.41 mg/dL). Repeated imaging showed no signs of cirrhosis, and the patient hasn’t yet been referred for liver transplantation.

Discussion

These four patients developed similar features to other COVID-19-associated SSC described in the literature [2].

The pathogenesis of this disease is uncertain, but some authors suggest that this entity is a form of secondary sclerosing cholangitis in critically ill patients (SSC—CIP) [2].

SSC—CIP is thought to result from ischemic cholangiopathy, bile toxicity, biliary infection and drug-induced liver injury. Invasive mechanical ventilation with high PEEP and prone position, hemodynamic instability and microcirculatory disturbances contribute to cholangiocyte necrosis, which is further promoted by bile toxicity stimulated by systemic inflammation [4]. Indeed, all of our patients had long stays in the ICU (21 to 69 days) with IMV (12 to 55 days), high PEEP and periods of prone position, and required circulatory support with vasopressors. Differences in intra-hepatic and extra-hepatic bile ducts’ blood supply make the latter less susceptible to ischemia, which explains why common bile duct is usually spared in SSC—CIP [4]. In fact, common bile duct was normal in all our patients, except for the presence of obstructive bile casts in patient A. The formation of bile casts in SSC—CIP is a pathognomonic finding, thought to result from necrosis of cholangiocytes that induces obliteration of intra-hepatic bile ducts. Bile duct obstruction promotes biliary infection that worsens cholangiocyte lesion. Indeed, two of our patients developed liver abscesses probably in relation to infectious cholangitis, which was overt in patient A and presumably present in patient C but not clinically evident. Drug-induced liver injury is also thought to contribute to the pathogenesis of the disease [4]. Several drugs commonly used in the ICU setting have been implicated, including antibiotics and anesthetics such as ketamine [4]. In fact, multiple drugs were administered to our patients including various antibiotics in all patients and ketamine in three of them.

The cytokine storm and hypercoagulability state induced by SARS-CoV-2 infection are thought to exacerbate all these pathogenic mechanisms. Furthermore, SARS-CoV-2 may...
Fig. 2  Magnetic resonance imaging with cholangiopancreatography and endoscopic retrograde cholangiopancreatography findings. ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.
Fig. 3  Histopathology findings in liver biopsies.
H&E, hematoxylin and eosin.
exert a direct cytopathic effect on cholangiocytes and endothelial cells, that highly express angiotensin-converting enzyme-2 receptors unlike hepatocytes [5].

The prognosis of SSC—CIP is dismal, with 50% mortality during ICU stay and rapid progression to advanced chronic liver disease over a period of months, strongly affecting life expectancy (mean survival 17–10 months) [6]. The only effective treatment in advanced stages is liver transplantation. Therapeutic options include antibiotic treatment of bacterial cholangitis and endoscopic removal of biliary casts [6]. UDCA (10–15 mg/kg/day) may be used, although controlled trials are lacking to allow a firmer recommendation [6]. Medical treatment with proven efficacy is still lacking, so referral for liver transplantation should be considered early in the course of the disease [4].

This recently described cholangiopathy in association with severe COVID-19 seems to have the same risk factors, clinical features and disease course as SSC—CIP. Therefore, it may be reasonable to consider them as the same disease, which is presenting more frequently because of an increased number of patients needing ICU treatment in the pandemic context.

Three of our patients had positive autoantibodies, ANA being the most common. ANA are frequent autoantibodies in general population. Their prevalence is increased in patients with recent COVID-19 (43.6% after 12 months); however, it is not clear if they are important contributors to severe disease or an epiphenomenon of marked inflammation [7]. Autoantibodies are also more prevalent in liver diseases such as drug-induced liver injury (DILI) in which ANA are present in 67% and anti-mitochondrial antibodies (AMA) in 10% of the patients, probably resulting from acute liver injury with cell destruction and release of intracellular antigens [8].

One of the patients (patient A), who showed no signs of liver disease initially, progressed to compensated advanced chronic liver disease (cACLD) with clinically significant portal hypertension in about 12 months. Likewise, patient C seems to be progressing to cACLD. This rapid fibrosis progression is a striking feature of SSC—CIP [4] and COVID-19-associated SSC [2], which seems to be unparalleled in other liver diseases (with the notable exception of fibrosing cholestatic hepatitis) [9].

Therefore, as the cohort of survivors of severe COVID-19 increases, it is likely that end-stage liver disease requiring liver transplantation emerges as a late consequence of the disease. Reports of successful liver transplantation after COVID-19 associated SSC have already been published [10].

By sharing these four cases, we hope to contribute to gather more knowledge about the natural history of this uncommon but potentially life-threatening disease.

Conflicts of interest and source of funding

None declared.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing 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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