



Ischaemic Sclerosing Cholangitis Post COVID-19: A Case Report

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Abstract

Coronavirus disease 2019 (COVID-19) primarily presents with respiratory symptoms. However, it is increasingly recognized as a multisystem condition involving extra-pulmonary complications, including hepatic involvement.

Objective: We report a case of hepatic injury in the form of ischemic sclerosing cholangitis secondary to SARS-CoV-2 infection.

Case Report: A 71-year-old female patient was admitted to the intensive care unit for two months due to COVID-19 viral pneumonia complicated by acute respiratory distress. During the course of her hospitalization, she developed abnormal liver tests suggestive of cholestasis. A diagnosis of post-COVID-19 ischemic cholangitis was established. She was treated with ursodeoxycholic acid combined with bezafibrate. The clinical course was unfavorable, marked by the development of secondary cirrhosis complicated by edema-as-cites decompensation. Given her age, liver transplantation was not considered.

Conclusion: Post-COVID-19 ischemic cholangitis is a rare but serious complication. It should be considered in the presence of persistent cholestasis following severe COVID-19 pneumonia.

Keywords: COVID-19 Pneumonia; Cholestasis; Ischemic Cholangitis

Introduction

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, mainly presents with respiratory symptoms. However, it is increasingly recognized as a multisystem disorder, involving extrapulmonary complications, particularly at the hepatic level.

Liver involvement related to COVID-19 typically manifests, in the early stages of the disease, as a hepatocellular injury often associated with a minor elevation in liver enzymes. However, in more advanced stages, some patients may develop severe cholestatic liver injury.

We report a case of hepatic involvement in the form of ischaemic sclerosing cholangitis secondary to SARS-CoV-2 infection.

Medical Case Report

This concerns a 71-year-old female patient, hypertensive and diabetic under treatment, followed since 2017 for a low-grade non-Hodgkin lymphoma initially treated with rituximab and bendamustine, then rituximab and chloraminophene, in complete hematologic remission. She was hospitalized in intensive care for 2 months for a COVID-19 viral pneumonia associated with septic shock and

paroxysmal atrial fibrillation. Her respiratory status deteriorated rapidly, requiring invasive ventilation just hours after admission, which had to be maintained for 42 days.

During her hospitalization, she initially developed an increase in gamma-GT to 246 U/L with no other liver-function abnormalities (initial liver panel was normal), then one month later a progressive icteric cholestasis appeared: alkaline phosphatase 259 U/L ($N < 120$), gamma-GT 328 U/L ($N < 36$), with bilirubin 29 $\mu\text{mol/L}$ (predominantly conjugated) and a mild transaminasaemia ($< 2\times$ the upper limit of normal). Three months later there was a marked increase with alkaline phosphatase 1429 U, gamma-GT 1699 U, bilirubin 47 $\mu\text{mol/L}$, AST 40 U/L, ALT 27 U/L. The etiological work-up found no viral cause (neither HBV nor HCV), no signs of autoimmunity.

Abdomino-pelvic CT scan showed no morphological argument for chronic liver disease, no focal hepatic lesion, no portal thrombosis. MRCP (magnetic resonance cholangiography) found a pattern compatible with sclerosing cholangitis, showing upstream dilations and narrowed/stented intra-hepatic bile ducts mainly in the right liver lobe without nodular lesion on contrast injection. Ileocolonoscopy, searching for a chronic inflammatory bowel disease, was unremarkable.

Serum IgG4 levels were within normal range, and HIV serology was negative. FibroScan revealed increased hepatic stiffness at 23.5 kPa, though this finding was interpreted with caution given the presence of cholestasis.

Upon review of the MRCP (Images 1, 2), the findings were considered not suggestive of primary sclerosing cholangitis. A thorough review of all therapeutic agents administered during the patient's ICU stay, compared with data reported in the literature, did not identify any drug known to be associated with cholangiopathy. The final diagnosis retained was post- ICU ischemic cholangitis. Treatment with ursodeoxycholic acid at 20 mg/kg/day was initiated, along with cholestyramine to manage the onset of pruritus.

The subsequent course was initially marked by persistent cholestasis with disabling pruritus. Follow-up MRCP (Images 3, 4) revealed worsening of tight, stepwise strictures affecting the intrahepatic bile ducts and the upper biliary confluence, sparing the main bile duct. It also showed dilatation of the intrahepatic bile ducts and marked enlargement of lymphatic vessels, suggesting ischemic cholangitis. Addition of a PPAR agonist (bezafibrate) was then proposed.

Over a three-year follow-up, the disease progressed to secondary cirrhosis with edematous-ascitic decompensation unresponsive to diuretics, requiring repeated ascitic drainages.

Considering the patient's age, liver transplantation was not deemed an appropriate option.

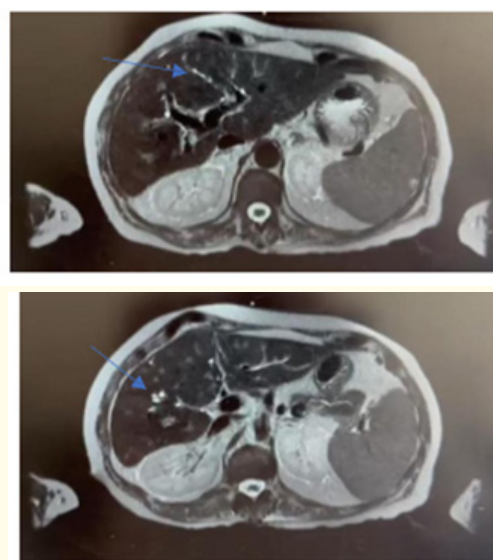


Figure 1 and 2: MR cholangiography slices (2020) showing dilations of the intra-hepatic bile ducts (arrows).

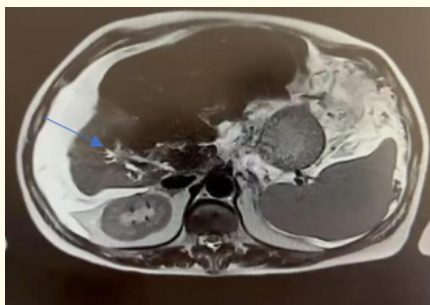


Figure 3: MR-cholangiography slice (2025): persistent dilatation of the right intra-hepatic bile ducts with a dysmorphic signs of portal hypertension.

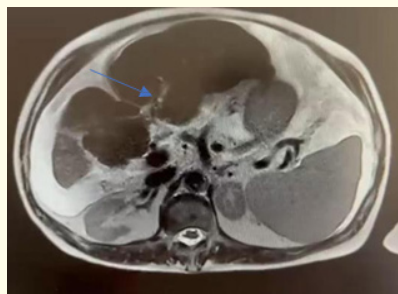


Figure 4: MR cholangiography slice (2025): a very tight stricture of the confluence of the intra-hepatic bile ducts.

Discussion

Considered a variant of secondary sclerosing cholangitis in critically ill patients, ischemic cholangitis associated with SARS-CoV-2 infection (post-COVID-19 ISC) is an emerging disease. It occurs particularly in patients who have undergone prolonged management in intensive care units [1-7]. It is characterized by ischemic lesions of the bile ducts caused by respiratory failure, systemic hypotension, or vasopressor administration [1,8].

A German study conducted by Christoph R. Werner, *et al.* in 2020 reported an incidence of 7.8% (5 out of 64) confirmed cases of CSI-post COVID-19 among ventilated patients with ICU stays longer than 20 days [9].

In January 2021, Roth, *et al.* reported three similar cases. Faruqi, *et al.* published a case series in 2020 of 12 patients with persistent cholestasis after severe COVID-19, consistent with a diagnosis of CSI [10,11].

The pathophysiology of post-COVID-19 ischemic sclerosing cholangitis (post-COVID-19 ISC) appears to be multifactorial, involving several interconnected mechanisms. It partly results from direct cholangiocyte injury caused by ischemia or hypoxia due to respiratory distress, but also from bile toxicity resulting from altered bile composition, or even direct viral infection. Severe hypotension observed in ICU patients can induce ischemic injury of the bile ducts and contribute to the pathogenesis by altering hepatobiliary transporters. Moreover, sepsis and microcirculatory disturbances are also implicated in this functional alteration [12].

Additionally, hepatic injury associated with SARS-CoV-2 has been widely reported throughout the pandemic. Numerous studies have highlighted elevated liver enzymes from the early stages of infection, as well as parenchymal liver damage. These findings are explained by overexpression of the angiotensin-converting enzyme 2 (ACE2) receptor, particularly in cholangiocytes, which facilitates direct cellular destruction by the virus [13-15].

Furthermore, microvascular changes, including hepatic steatosis and intrahepatic thrombosis, resulting from the thrombogenic properties of the virus, also contribute to parenchymal lesions [14,15]. Finally, Kaltschmidt, *et al.* showed that SARS-CoV-2 can replicate in the liver parenchyma and be secreted into the bile ducts. This replication, combined with platelet activation and inflammatory lesions of the parenchyma, appears to cause direct damage to the biliary system. Biliary necrosis, accompanied by the development of bile duct stenosis, is a determining factor in the onset of sclerosing cholangitis [16].

The main clinical manifestations of post-COVID-19 ischemic sclerosing cholangitis (CSI-post COVID-19) are jaundice and pruritus, with a biological cholestasis characterised by elevated serum alkaline phosphatase, gamma-glutamyl transferase and bilirubin levels. They typically occur at a later stage of the disease, gener-

ally after recovery from acute respiratory illness. The average time between initial infection and diagnosis of CSI-post COVID-19 is reported to range between 90 and 118 days [3,8]. Among other systematically reported findings are male predilection, a median age over 50 years [17,18], and comorbidities such as hypertension or diabetes mellitus [3,8,19,20].

Although definitive criteria have not been established, the generally accepted definition of CSI-post COVID-19 includes the presence of severe cholestasis, as well as biliary-tract abnormalities on imaging or pathology that were not documented prior to COVID-19 [17,19,21].

The imaging findings of ischemic sclerosing cholangitis post-COVID-19 (CSI-post COVID-19) strongly resemble those seen in primary sclerosing cholangitis (PSC) and other secondary forms of sclerosing cholangitis. As in those conditions, one classically observes multifocal strictures of the intra-hepatic bile ducts, producing the characteristic “beaded” appearance [18,19,21]. These strictures may sometimes occur without upstream dilatation, making detection difficult on standard CT. Thus, magnetic resonance cholangiopancreatography (MRCP) is the diagnostic modality of reference, as it better visualises these abnormalities.

Imaging also reveals thickening of the bile-duct walls, often associated with contrast enhancement, as well as biliary stasis. Notably, the ductal abnormalities seen in post-COVID-19 cholangiopathy appear almost exclusively in the intra-hepatic bile ducts, with the extra-hepatic ducts generally spared. This particular topographic pattern was confirmed in a study of 17 patients, in which all patients had intra-hepatic involvement and only 5.9% had associated extra-hepatic duct involvement [18]. This distinctive distribution may help differentiate post-COVID-19 ischemic sclerosing cholangitis (CSI-post COVID-19) from primary sclerosing cholangitis (PSC), which typically affects both biliary territories [22].

Other authors have reported additional radiological abnormalities including the presence of gallstones, biliary sludge in the ducts or gallbladder, as well as hepatic abscesses [2,23].

Furthermore, morphological changes of the liver such as hepatomegaly or a cirrhotic appearance have been observed in nearly 20 % of cases [18].

On the histopathological level, post-COVID-19 ischemic sclerosing cholangitis is characterized by typical cholangiocyte lesions. These include degenerative alterations such as cytoplasmic vacuolization, necrosis and apoptosis. A ductular reaction is frequently observed, marked by variable proliferation of bile ducts, accompanied by a light to moderate mixed inflammatory infiltrate within the portal tracts. Portal and septal fibrosis are also noted, as well as concentric periductal fibrosis characteristic of the chronic evolution of bile-duct injury.

Microvascular changes add to this picture, particularly signs of microangiopathy. This manifests as endothelial edema associated with luminal narrowing of the hepatic arteries, as well as endophlebitis of the portal veins [2,24,25]. These alterations suggest an ischemic mechanism involved in the development of liver lesions. In this context, Tsutsumi., *et al.* reported a correlation between elevated fibrinogen levels and liver injury in COVID-19 patients, concluding that hepatic dysfunction could result from microvascular thrombosis [26].

The study by Shih., *et al.*, which to date represents the largest series of liver biopsies (seven cases), confirmed these characteristic lesions of post-COVID-19 cholangiopathy [27]. In contrast, the work of Esposito., *et al.*, conducted on patients with secondary sclerosing cholangitis not related to COVID-19, did not find similar results, which supports the hypothesis of a distinct pathological phenotype specific to post-COVID-19 SSC [28]. In our case, a liver biopsy was not performed following a collegial decision.

Treatment options for post-COVID-19 SSC remain limited and unstandardized. Most patients reported in the literature received ursodeoxycholic acid (UDCA). Similarly to the management of

patients with primary sclerosing cholangitis, UDCA could protect cholangiocytes from inflammation [29]. At the same time, endoscopic retrograde cholangiopancreatography (ERCP) has been suggested as a way of improving prognosis, particularly in patients with biliary obstruction [30,31]. However, the benefits of ERCP in this context remain unclear, and this invasive procedure carries significant risks, including pancreatitis and bacterial cholangitis.

Although some patients with post-COVID-19 SSC recover, many eventually progress to biliary cirrhosis or liver failure, requiring liver transplantation [17,21].

Liver transplantation is the only curative option for advanced cases of post-COVID-19 SSC. Several studies have reported that up to 22% of patients with ischemic sclerosing cholangitis require transplantation [1,2,24,32,33]. In another series, 50% of the 12 patients with post-COVID-19 SSC either underwent liver transplantation or were listed for it [3].

Without transplantation, the prognosis remains very poor: only 40.0% of patients were alive one year after the onset of post-COVID-19 SSC. Leonhardt, *et al.* [5] reported mortality rates of 60% during the first 12 months and 83% over a 24-month period. In the case of our patient, although the disease progressed to decompensated cirrhosis with ascites and edema, her age precluded consideration of liver transplantation.

Conclusion

Post-COVID-19 SSC is a rare but serious complication. Any prolonged cholestasis following severe COVID-19 pneumonia should raise suspicion for this diagnosis. Imaging with MRCP and/or ERCP, along with histopathological examination, are reliable and effective methods for diagnosis. Although observations have shown that UDCA can improve liver function tests, liver transplantation appears to be a salvage treatment in severe cases. The prognosis for these patients is often poor, with a high risk of complications in the absence of liver transplantation, as illustrated by the case of our patient.

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