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Post-COVID-19 cholangiopathy: Current understanding and management options

Veerankutty FH *et al*. Pathophysiology and management of post-COVID-19 cholangiopathy

Abstract

Post-coronavirus disease 2019 (COVID-19) cholangiopathy (PCC) is a rare but life-threatening complication of COVID-19 infection. PCC typically presents when patients recovering from the contagion and manifests as cholestasis in patients with no history of pre-existing liver disease. The pathogenesis of PCC is little understood. Hepatic injury in PCC could be mediated by the predilection of severe acute respiratory syndrome coronavirus 2 for cholangiocytes. Though PCC shows some resemblance to secondary sclerosing cholangitis in critically ill patients, it is considered as a separate and unique entity in the literature. Various treatment options like ursodeoxycholic acid, steroids, plasmapheresis, and endoscopic retrograde cholangiopancreatography guided interventions have been tried but with limited success. We have noticed significant improvement in liver function with antiplatelet therapy in a couple of patients. PCC can progress to end-stage liver disease necessitating liver transplantation. In this article, we discuss the current knowledge of PCC focusing on its pathophysiology, clinical manifestations, and management strategies.

Key Words: COVID-19; Liver; Post-COVID-19 syndrome; Long haulers; Cholangiopathy; Cholestasis

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Core Tip: Post-coronavirus disease 2019 (COVID-19) cholangiopathy (PCC) is a rare complication of COVID-19 infection with gruesome prognosis. There is no proven treatment for this entity and patients often end up in liver transplantation. This review focusses on pathophysiology, clinical manifestations and management strategies of PCC along with our experience with antiplatelets in managing patients with PCC.

INTRODUCTION

World health organization declared coronavirus disease 2019 (COVID-19) as a global pandemic in March 2020[1]. Though severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) mainly affects the respiratory system, studies have demonstrated that organotropism of the virus can cause multisystem inflammation[2,3]. Hypercoagulability associated fatal cardiovascular, cerebrovascular, and gastrointestinal complications have been reported. Derangements in liver function tests (LFT) are the most frequent hepatic manifestation of COVID-19, and its incidence among hospitalized COVID-19 patients varies between 14% to 83%[4-10]. However, the spectrum of liver injury due to COVID-19 extends beyond just abnormalities in LFT. Other attributed hepatic effects of this contagion include vascular thromboses, cholangiopathy, and COVID-19 vaccine-related auto-immune hepatitis[11-13]. Remarkably, 'Long haul COVID' or 'post-COVID syndrome' (a collective term used to denote the persistence of symptoms or development of delayed complications beyond four weeks after the initial presentation of COVID-19) has also been known to adversely affect the liver[14,15].

Although COVID-19 results most commonly in a hepatocellular pattern of liver injury, severe cholestasis has also been occasionally noted[16-20]. Roth *et al*[13] labeled this unique entity of severe cholestasis as post-COVID-19 cholangiopathy (PCC)[21]. PCC typically presents when patients recover from COVID-19 and manifests as cholestasis in patients with no history of pre-existing liver disease. PCC is diagnosed in less than 1% of patients hospitalized for COVID-19[22]. Literature regarding this newly described entity is sparse, and the natural course of the disease remains unknown. We searched PubMed, *Reference Citation Analysis* (RCA), and Web of Science using Mesh words such as "post-Covid-19 cholangiopathy", "COVID-19 sclerosing cholangiopathy", "Covid-19 and liver", and "COVID-19 and liver transplantation". The data on pathogenesis, histology, imaging findings, clinical features, management, and outcomes were collected. This review summarizes the current knowledge of PCC, focusing on its pathophysiology, clinical manifestations, and management strategies.

PARTHENOGENESIS

SARS-CoV-2 utilizes angiotensin converting enzyme 2 (ACE2) receptor to enter the host cell and the internalisation process is aided by the host cell transmembrane serine protease 2. ACE2 receptors are expressed in various human organs including lung, liver, intestine, kidney, and heart[23,24]. The binding of SARS-CoV-2 to ACE2 receptor impairs ACE2 activity leading to the enhanced effect of angiotensin-2 resulting in an inflammatory and hypercoagulable state. In the liver, ACE2 receptors are more intensely expressed on cholangiocytes (59.7%) than on hepatocytes[24]. Cholangiocytes modify hepatocyte-derived bile acids, and the tight junction between these cells is essential for bile acid accumulation and excretion. Experimental studies using liver ductal organoid culture showed that SARS-CoV-2 can cause dysregulation of genes engaged in tight junction formation and bile acid transportation, thereby resulting in an impaired barrier and defective bile acid transportation. This mechanism of injury has been purported as the cause for direct cholangiocytic injury and consequent bile acid accumulation, resulting in severe and prolonged hepatic damage caused by COVID-19[25].

Ischemia injury, especially to the cholangiocytes has also been implicated in the causality of PCC. ACE2 receptors are expressed on vascular endothelial cells and SARS-CoV-2 can lead to uncontrolled inflammation through the interleukin (IL)-6 signaling pathway. Endothelitis results in hypercoagulability and thrombosis of the peribiliary vascular plexus aggravating biliary ischemia. Shreds of evidence in favor of this hypothesis include endothelial swelling with luminal narrowing of the hepatic arterioles and portal venous endophlebitis reported on histological examination of PCC specimens. Furthermore, improvement in liver function on treatment with antiplatelets in two of our patients (detailed below) also implicates the role of microvascular events in the pathogenesis of PCC[26].On the contrary, a few studies noted no significant microvascular thrombi in their patients' livers with PCC[22,27,28].

Due to their similar clinicopathological features, many researchers believe that PCC is a variant of secondary sclerosing cholangitis in critically ill patients (SSC-CIP). SSC-CIP

is a rare form of secondary sclerosing cholangitis which occurs in patients with no history of hepatobiliary disease after a long intensive care unit stay for various conditions requiring prolonged mechanical ventilation and high-dose vasopressors. SSC-CIP was first described by Scheppach *et al*[29]. The pathogenesis of SSC-CIP is not fully elucidated, but the main mechanism appears to be bile duct ischemia. Other proposed causes include changes in the composition of the bile and biliary infection[30]. Ischemia leads to necrosis and sloughing of biliary epithelium resulting in biliary cast formation. Ischemia can also damage hepatobiliary transporters involved in the protective barrier mechanism of cholangiocytes from toxic bile salts. Progression to cirrhosis may occur over several months[31,32]. SSC-CIP has a mortality of over 50% in severe cases and up to a fifth of patients require a liver transplant (LT)[33,34]. Damages to extra and intrahepatic biliary ducts, cholangiocyte necrosis and biliary epithelial destruction, ductular reaction, and progressive fibrosis portal tracts are features common to PCC and SSC-CIP. Though PCC is typically described in patients with severe COVID-19 who required prolonged mechanical ventilation, few authors have reported cases of severe cholestasis in patients with mild to moderate COVID-19[17,18]. In contrast to acquired immunodeficiency syndrome cholangiopathy, the opportunistic infection has not been implicated as an etiological factor of PCC.

Some authors attributed PCC to ketamine related hepatobiliary damage, a condition called Ketamine induced cholangiopathy. Ketamine is metabolised in the liver and is used for sedation of patients with respiratory distress. Two recent articles reported patients with severe COVID-19 developed cholestatic liver disease with features of sclerosing cholangitis after exposure to ketamine. Nonetheless, a majority of other reports of PCC do not mention the use of ketamine. Antiviral drugs, particularly remdesivir and immunomodulatory agents like tocilizumab (IL-6 receptor antagonist) used in the management of COVID-19 are known to cause hepatic injury. The use of these agents has not been uniformly reported in any of the published cases of PCC. Moreover, there is insufficient evidence to prove that these medications may cause cholangiopathy.

CLINICAL, BIOCHEMICAL & IMAGING FEATURES

Patients with PCC are predominantly males (80%) and their median age at presentation is over 50 years[13,23,35-37] (Table 1). Patients typically present with jaundice with or without pruritus several weeks or months after the initial admission in intensive care units for severe COVID-19[13,37]. Significantly, these patients have no prior history of liver disease. Diabetes mellitus is the most common comorbid condition reported[37]. LFTs at the time of admission following COVID-19 diagnosis are almost always near-normal. In a cohort of 24 patients with PCC from various German centers, the median serum total bilirubin level at admission was 0.6 mg/dL (N: 0.6-1.2 mg/dL), while at the time of diagnosis of PCC it was 11.9 mg/dL[37]. The highest serum total bilirubin level reported in a patient with PCC was 42.4 mg/dL[16]. Gross elevation of serum alkaline phosphatase (ALP) levels, with peak levels above 1000 U/L (N: 20-140 U/L) have been commonly reported[13,22,27]. Remarkably, these biochemical changes in PCC are similar to that observed in patients with SSC-CIP[37].

In a series of 12 cases reported by Faruqui *et al*[22] mean interval between the initial diagnosis of COVID-19 and the diagnosis of PCC by magnetic resonance cholangiopancreatography (MRCP) was 118 d. All 12 patients in their series, showed some structural changes in the biliary system on MRCP[35]. Intrahepatic bile duct strictures and the beaded appearance of intrahepatic bile ducts were the most commonly noted findings[13,22]. Ghafoor *et al*[35] studied magnetic resonance imaging/MRCP of 17 patients with PCC, and noted that none of the patients had cirrhosis or vascular thrombosis. Strictures in the form of beading of intrahepatic bile ducts were seen in 14 (82.3%) patients and biliary casts were seen in 2 (11.8%) patients. In addition to biliary abnormalities, liver contour irregularities and signal intensity changes in PCC livers can also be ascertained on MRCP.

HISTOPATHOLOGY

On macroscopic examination, the PCC livers are described to have a greenish discoloration[13,38,39] (Figure 1A). Brightfield microscopy may show portal/periportal fibrous expansion with bile ductular proliferation, degenerative cholangiocyte injury accompanied by leucocytes[13,39]. Loss of interlobular bile ducts has been described in PCC (Figure 1B). Ductular bile plugs and bile lakes are reported. Lobular disarray, hepatocanalicular bilirubinostasis with rosetting, and patchy lobular inflammation may be seen. Hilar bile ducts with inflammation and fibrosis have been described. Portal veins may show fibrin thrombi (Figure 1C). A case from the authors' series also showed Mallory Denk bodies along with patchy sinusoidal dilatation and congestion with hepatocyte atrophy (Figure 1D). In late cases, bridging fibrosis and cirrhosis have been reported[13,38]. Immunostaining with CK7 may show biliary metaplasia of hepatocytes (Figure 1E). Pathognomonic findings of PCC on immunohistochemistry include a granular cytoplasmic positivity for SARS-CoV-2 within hepatocytes and sinusoidal macrophages (Figure 1F).

TREATMENT

Given that PCC is a recently described disease arising out of the COVID-19 pandemic, little is known about its natural history. Anecdotal evidence of various treatment modalities is present in the literature, and currently, there is no well-defined treatment algorithm. Though universally used for PCC, medical treatment with ursodeoxycholic acid and cholestyramine does not seem to offer much clinical or biochemical improvement. Antiplatelet medications have serendipitously shown benefits (two patients from the authors' series). However, the exact indication, timing, dose, and duration of this regimen remain unknown. Franzini *et al*[40] recently published a video demonstration of their experience with cholangioscopy (SpyGlass@) to assess bile duct changes and removal of biliary casts. In patients with biliary casts or cholangitis, interventions using endoscopic retrograde cholangiopancreatography may offer transient improvement of the clinical condition, but abnormal liver functions are likely to persist even after an anatomical clearance of the extrahepatic ducts[13,36].

LIVER TRANSPLANTATION FOR PCC

In most patients, the disease causes progressive biliary injury with worsening cholestasis and recurrent infections[16,22]. The first successful LT for PCC was reported by Durazo *et al*[27]. A 47-year-old man with PCC and worsening liver and renal function underwent deceased donor liver transplantation on day 108 from the initial presentation with COVID-19. Histopathology of the explanted liver showed features of severe sclerosing cholangitis with hepatic abscesses. The patient improved well and graft function was normal at 7 mo after LT. Subsequently, various authors reported their experience with LT for patients with PCC[16,22,38]. Our team reported a living donor auxiliary right lobe LT (APOLT) in a 50-year-old patient at 12 wk after the initial diagnosis of COVID-19. The patient underwent a right trisectionectomy with caudate lobectomy. The right lobe was retrieved robotically from a related donor and implanted orthotopically. Interestingly, hepatobiliary scintigraphy at six months follow-up showed 90% and 10% in the graft and native livers respectively, reflecting some native liver recovery[16]. The authors' premise was that since the natural course of PCC is unknown, there remains the possibility of spontaneous liver recovery. Thus, the allograft in APOLT potentially acts as a bridge till native regeneration occurs, providing the patient with a realistic possibility of becoming immunosuppression-free. While LT is an effective curative option for patients with PCC, it is naïve to offer it to every patient with PCC. It is also sobering to realise that several variables of this management continue to be undefined. These include vital data to define which cohort of patients are likely to recover without an LT. It is likely that these questions will have answers as experience grows with this disease entity.

COVID-19 VACCINATION AND PCC

In the current era of near-universal COVID-19 vaccination, it is important to re-evaluate the natural course of PCC. Vaccination has been shown to reduce the severity of COVID-19 and improve outcomes[41]. Kulkarni *et al*[17] compared 8 unvaccinated

patients with 7 vaccinated patients with post-COVID-19 cholestasis and showed that serum ALP and gamma glutamyl transpeptidase (GGT) were significantly lower in the vaccinated group. Furthermore, all patients in the vaccinated group improved with conservative management while a majority in the unvaccinated group required LT. Again, literature in this regard is scarce, but intuitively, COVID-19 vaccination is likely to play a positive role in preventing/attenuating the course of PCC.

OUR EXPERIENCE

Our experience with PCC is limited to four patients. All of them presented with severe cholestatic jaundice following initial recovery from COVID-19 illness[26] (Table 2). All were men in their 5th or 6th decade of life. Unlike other reported series, only half of our patients had a history of mechanical ventilation for their COVID-19 related respiratory illness. Clinical recovery from COVID-19 was complete and was discharged between 7 and 21 d. None of them had a history of any underlying liver disease. LFTs were uniformly unremarkable at the time of COVID-19. All these patients were readmitted with fatigue and jaundice four to six weeks following their COVID-19 and a couple of them developed pruritus. Peak enzymes were aspartate aminotransferase 4-8 times upper limit normal (ULN), alanine aminotransferase 3-10 ULN, ALP 4-6 ULN, and GGT 5-15 ULN. Peak bilirubin varied between 15 to 42 mg/dL (N: 0.6-1.2 mg/dL). Interestingly, none of them developed coagulopathy, ascites, or hepatic encephalopathy. Abdominal imaging in 3 patients was unremarkable. MRCP of one patient demonstrated mild prominence of central intrahepatic, common hepatic, and common bile ducts with minimal beading of the right posterior sectoral and segment 2 ducts. Liver biopsies showed loss of interlobular bile ducts, degenerative features in residual ducts, hepatocanalicular bilirubinostasis, and fibrin thrombi in some vessels.

Of the 4 patients, one died of worsening symptoms and sepsis. The second patient developed progressive jaundice and underwent APOLT (described above)[16]. He remains well on 9 mo follow-up and is due to have a hepatobiliary scintigraphy at 12 mo to reassess native liver regeneration. The third patient remained symptomatic with

worsening hyperbilirubinemia and was listed for LT. On evaluation, he was noted to have double-vessel coronary artery disease which required stenting. Following stent placement, he was commenced on aspirin and clopidogrel. Interestingly, there was a significant improvement in LFT within six weeks of initiating antiplatelet therapy. He was discharged home without the need for LT and his clinical improvement was attributed to anti-platelet drugs. With this experience, the fourth patient was commenced early on antiplatelet therapy and he too had a remarkable improvement in his clinical and biochemical status. Both these patients remain well on 6- and 7-mo' follow-up respectively. This finding underpins the theory of microvascular events in the pathogenesis of PCC.

CONCLUSION

PCC is a recently described entity of severe cholestasis that has been recognized in patients recovering from severe COVID-19 infection. While the exact etiopathogenesis remains unknown, purported theories include SSC-CIP, microthromboses, direct liver injury, and autoimmune etiology among others. Although relatively uncommon at present, it is likely that this disease will be more commonly encountered in the near future. Its natural course remains undefined, but with accumulating evidence several successful management strategies have been proposed. There remains a need for concentrated, multicenter studies to further elucidate this disease which can potentially have high morbidity if not identified and managed appropriately.

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