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Letter to the Editor

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Post-COVID-19 Cholangiopathy: A Recent Indication for Liver Transplantation

Subhi Mansour[a], Rozan Marjieh[a], Yoram Kluger[a, b], Hayim Gilshtein[a, c], Safi Khuri[a, b, d]

To the Editor

Introduction

Since its discovery in the late 2019 in Wuhan city, China, coronavirus disease 2019 (COVID-19) rapidly became a major public health problem, with more than 5 million deaths at 2 years of follow-up [1, 2]. Furthermore, COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been associated with a considerable morbidity as well [3]. Although COVID-19 is known as a predominantly respiratory tract infectious disease, with fever, fatigue, cough and dyspnea being the most common presenting symptoms, SARS-CoV-2 has the ability to affect and damage other organ systems [4]. To gain cellular entry, this virus uses angiotensin-converting enzyme 2 (ACE2) as a cell receptor [5]. In addition to the lungs, the aforementioned receptors are highly expressed in the gastrointestinal (GI) tract, kidneys, liver and biliary tree, pancreas, arterial smooth muscle cells and vascular endothelial cells [5]. The expression of ACE2 receptors in the previously mentioned systems raises the possibility of COVID-19-induced multi-organ system [6]. When affected, they are referred to as extra-pulmonary complications of COVID-19. Extra-pulmonary complications post-COVID-19 infections are more common in critically and severely ill patients [4]. Liver and biliary complications following COVID-19 infection were firstly reported by Huang et al [7], when he noticed an elevated level of liver function tests (LFTs), especially in patients with critically ill COVID-19. Almost 20% of patients with COVID-19 infection have elevated liver enzymes, which can predict disease outcome [8]. The current literature has demonstrated that liver injury is more common in patients with critical COVID-19 and pre-existing chronic liver disease, such as cirrhosis, and in those who have other coexisting causes of liver damage, such as the use of potentially hepatotoxic therapies [9, 10]. The mechanisms by which COVID-19 causes damage to the liver are diverse and include, among others, direct hepatocellular injury (the main injury pattern) and cholestatic pattern, referred to as "post-COVID-19 cholangiopathy" (PCC) [11, 12]. PCC, previously known as secondary sclerosing cholangitis in critically ill patients due to severe COVID-19 infection, is a newly introduced entity gaining medical attention worldwide. It is characterized by severe cholestasis and ongoing jaundice that persist long after renal and pulmonary recovery. Although PCC is a well-known extra-pulmonary manifestation post-COVID-19 infection, data regarding this specific entity, mainly mechanism of injury and therapeutic options, are still vague and not clear.

Patient's characteristics and pathogenesis of PCC

About 30 cases of PCC have been reported, since the discovery of the COVID-19, to the English literature [13-15]. All patients were hospitalized in the intensive care unit (ICU) and required mechanical ventilation due to severe disease. The majority of patients diagnosed with PCC were men (> 80%) in their fifth decade of life. Most patients were diagnosed months (1 - 10 months) following recovery. The mean time from diagnosis of COVID-19 to PCC diagnosis was 2.5 months.

Although the exact pathogenesis for the development of PCC is yet to be known, several hypotheses regarding mechanism of injury have been suggested: 1) The ischemic hypothesis. PCC is more common to develop in patients with critically ill COVID-19. This group of patients endured hemodynamic instability and prolonged mechanical ventilation, which in turn lead to decreased blood flow to bile duct cells (cholangiocytes), with the development of bile duct ischemia, scars and strictures [16]. Biliary ischemia seems to play a major role in the development of PCC, especially as cholangiocytes are susceptible to ischemic changes more than hepatocytes, due to blood supply. 2) The direct injury hypothesis. Cholangiocytes are characterized by a high concentration level of ACE2 receptors. This facilitates the direct entry of the virus into the cells, causing direct cholangiocytes damage [17, 18]. 3) The toxic injury hypothesis. Toxic viral particles, as well as hepatotoxic medications used in the management of critically ill patients at ICUs can lead to direct toxic metabolic injury to intra and extra-hepatic cholangiocytes [11, 19]. 4) The immune-mediated hypothesis. This hypothesis is explained by the severe inflammatory response with proinflammatory cytokines release and

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[a]Department of General Surgery, Rambam Medical Center, Haifa, Israel
[b]HPB and Surgical Oncology Unit, Rambam Medical Center, Haifa, Israel
[c]Colorectal Surgery Unit, Rambam Medical Center, Haifa, Israel
[d]Corresponding Author: Safi Khuri, Department of General Surgery, Rambam Medical Center, Haifa, Israel. Email: s_khuri@rambam.health.gov.il

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immune cell storm aid to the development of toxic bile and contribute to necrosis of the cholangiocytes [20].

In spite of several proposed mechanisms of injury, it is believed that the precise pathogenesis for PCC is multifactorial, with combination of all/some of the previously mentioned hypothesis. The combination of ischemic changes of the biliary tree, biliary infection due to stasis, direct intracellular viral entry and profound systemic inflammatory response seems more logical for PCC.

Diagnosis of PCC

In spite of being a known medical entity and highly reported recently, a precise definition of PCC is lacking. Diagnosis usually involves a constellation of laboratory, endoscopic, radiological and/or histopathological findings characteristics for cholangiopathy following severe COVID-19 infection [21].

Laboratory abnormalities used for the suspicion of PCC were reported in a minority of patients [12-15]. The used criteria differed from article to another and included the following parameters: 1) High levels of alkaline phosphatase (ALP) (1.5 times or more than the upper normal levels (UNLs)); 2) High bilirubin levels (≥ 2 UNL); 3) Abnormal levels of gamma-glutamyl transferase (GGT) (≥ 3 UNL); 4) Absence of active systemic infectious disease; and 5) Absence of underlying chronic liver disease.

Elevated levels of ALP were the most common abnormal laboratory result [14, 15, 22], and two patients had normal LFT at the time of PCC diagnosis [19]. Worth mentioning, according to the English literature, there is no difference in laboratory parameters used for diagnosis of PCC or non-COVID-19 cholangiopathy.

Endoscopic retrograde cholangiography (ERCP) was used in almost 40% of patients during the workup of PCC. The most common cholangiographic abnormality was multiple strictures involving the intrahepatic bile duct, in addition to the presence of bile duct stones/sludge, necessitating extraction [12, 14, 15, 19]. Half of the patients who underwent ERCP required more than one endoscopic intervention, especially for stent retrieval (when stent was inserted during the first procedure) [14, 15, 19]. Worth mentioning, although endoscopic interventions, by either balloon dilation and stent insertion or spincterotomy, did improve bile duct obstructions and LFTs, it did not affect prognosis of patients that were evaluated for liver transplantation [12, 15, 19].

Magnetic resonance cholangiopancreatography (MRCP) was the most commonly used diagnostic modality, reported in 23 patients (77%) [11-15, 19, 22, 23]. Mild intrahepatic bile duct dilation due to multifocal strictures and beading were the most common findings [11, 12, 15, 19, 22, 24-27]. Other less reported MRCP findings include cystic lesion in segment VII of the liver [13], bile duct thickening and hyper enhancement, peribiliary diffusion high signal [15] and common bile duct (CBD) dilation [14].

Histopathological characteristics were available in almost half patients diagnosed with PCC as only 14 patients underwent liver biopsy during the diagnostic workup. Histological findings include periportal fibrosis, degenerative cholangiocytes injury, small bile duct obstruction, large bile duct obstruction and absence of bile ducts, reported in eight, six, one, three and four patients, respectively [11-13, 15, 22, 23]. A combination of the aforementioned histological characteristics was by far more common than a single finding.

PCC and liver transplantation

Being a relatively new disease, which was recently introduced by physicians worldwide, the gold standard therapeutic management of PCC is still regarded as a controversial issue. The fact that a few cases of PCC are reported in the English literature makes for a difficult therapeutic decision, usually based on personal experience of the treating group of physicians. Thus, up to date, therapeutic consensus is absent.

Reported therapeutic options include the broad-spectrum antiviral medication "remdesivir", the anti-malarial drug "hydroxychloroquine" and ursodeoxycholic acid (ursodiol), with the latter proved to be of low benefit in treating PCC [13-15]. These medications proved to have no prognostic effect for patients with PCC who eventually needed liver transplantation.

Orthotropic liver transplantation was indicated in four patients with PCC [12, 19, 23, 26]. PCC has been classified as a variant of secondary sclerosing cholangitis in critically ill patients. Although the role of liver transplantation as a therapeutic option for PCC is largely unknown, yet prognosis of patients with secondary sclerosing cholangitis in critically ill patients is very poor without liver transplantation, thus, some patients with PCC were treated by liver transplantation.

For the purpose of anticipating preliminary clinical, laboratory, radiological or histopathological findings for patients who will eventually need liver transplantation as a definitive management, patients with PCC were classified into two groups: group A: patients with PCC who underwent liver transplantation and group B: patients who were not treated by liver transplantation.

All patients in group A were males, while male/female (M/F) ratio in group B was 4:1 (Table 1). In both groups, all patients suffered severe COVID-19 pneumonia with prolonged mechanically ventilation. In terms of LFTs, two patients [19, 26] of group A had normal LFTs initially when diagnosed with COVID-19 pneumonia while all patients in group B had an elevated LFTs on presentation. Peak laboratory results, especially ALP, were identical in both groups of patients. Of notice is that total bilirubin levels were within normal limits on admission due to COVID-19 pneumonia and peaked up to levels of 4.4 - 23.9 mg/dL when PCC diagnosis has been made in both groups. Cholangiographic features were diverse and identical for both groups. Histopathological features in patients treated eventually with liver transplantation were more severe than in patients belonging to group B. Diffuse cholangiocytes injury along with severe degenerative changes and marked fibrosis were prominent in group A, while histopathological findings for group B patients reported include mild-moderate degenerative cholangiocyte injury and mild fibrosis.

Clinical and laboratory follow-ups (2 - 8 months) were reported in all patients who underwent liver transplantation: all patients were alive with normal LFTs.

Table 1. Clinical, Laboratory and Histopathological Findings Comparing Patients With PCC Who Underwent Liver Transplantation With Those Who Did not

Parameter	Group A (liver transplantation)	Group B (non-liver transplantation)
Number of patients	4	26
Median age (years)	52	53
Comorbid diseases		
Obesity	2	7
HTN	2	12
HPL	2	6
DM	1	5
Male percentage	100%	80%
Initial LFTs	Normal in 50%	Abnormal in 100%
Initial bilirubin levels	Within normal range	Within normal range
Histopathological findings	Severe and diffuse degenerative changes, marked fibrosis	Mild-moderate degenerative changes, mild fibrosis

DM: diabetes mellitus; LFTs: liver function tests; HPL: hyperlipidemia; HTN: hypertension; PCC: post-COVID-19 cholangiopathy.

Discussion

Since it was labelled as a global pandemic and up to date, we are still discovering the medical consequences of COVID-19. The initial concept of pure respiratory disease has been later transformed into multisystem disease, as SARS-CoV-2 can affect every single organ of the human body. These extra-respiratory consequences have been termed extra-pulmonary complications of COVID-19 [4]. Of these extra-pulmonary complications, the hepatic and biliary tree complications were reported and raise the concern in the medical community. These are known today as PCC. PCC is regarded as a subtype of secondary sclerosing cholangitis in critically ill patients due to severe COVID-19 [11, 12]. The precise pathogenesis by which COVID-19 causes PCC is not fully understood so far, therefore medical facilities lack a sensitive tool that can predict which patients will eventually develop PCC following COVID-19 infection. We rely on the available medical tools, such as laboratory tests, imaging studies and histopathological reports, to anticipate future PCC in selected patients. The strongest risk factor for PCC is severe COVID-19 necessitating prolonged ICU admission, as all reported cases (100%) suffered severe disease [7, 11-16]. The damage caused to the biliary tree is usually irreversible. As such, except for best supportive care with dismal prognosis, there are no effective medical measurements in order to treat this condition which carries a dismal prognosis. Orthotopic liver transplantation (OLT) is the only available tool to try and offer a cure for this gravely ill group of patients. This is an extreme method which has its own high complication rate, including the risk of mortality. There are no considerable series of patients who underwent OLT for this indication but the paucity of published data [12, 19, 23, 26] demonstrated promising results. As mentioned above, the pathogenesis is unclear and probably multifactorial, with low flow state and ischemic sequale playing important role in the critically ill patient population. Thus, it is understandable why only a mechanical solution with a new and health liver cell infrastructure is required. The technical difficulty and expertise required for the procedure with the known lack of available livers worldwide pose additional challenges. More extensive data collection and better understanding of the disease process is mandatory to try and offer less invasive treatments, such as novel anti-viral medications, specific liver regenerative drugs with affinity to the biliary tree and others. Further studies, preferably with a multi-center design are needed before a definitive treatment algorithm can be suggested.

Conclusion

PCC is an important clinical entity in patients with severe COVID-19 infection. OLT is an option that the treating team of physicians has to have in mind when managing with highly challenging complication of COVID-19.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Author Contributions

SM and RM designed the research. RM collected the data and

HG analyzed the data. YK and SK wrote and approved the final paper.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

COVID-19: coronavirus disease 2019; PCC: post-COVID-19 cholangiopathy

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