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Case Study

Four Cases of Cholangiopathy Post-COVID

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Abstract

The article explores the emergence of cholangiopathy as a post-COVID-19 complication, presenting a detailed analysis of four cases observed in tertiary hospitals in Brazil. The study focuses on patients who developed cholestatic disorders following severe COVID-19, revealing clinical, laboratory, and radiological manifestations. The patients, predominantly male, experienced prolonged hospitalization, mechanical ventilation, and hemodynamic support during their initial COVID-19 diagnosis. The cholangiopathy cases exhibited alterations in canalicular enzymes, liver transaminases, and bilirubins, with a radiological pattern resembling Primary Sclerosing Cholangitis. The findings contribute to the growing body of literature on this novel complication, emphasizing the importance of further research and understanding in the medical community.

Keywords: COVID-19; Brazil; SARS-CoV-2

Introduction

The emergence of a viral pandemic in 2019, caused by SARS-CoV-2, brought forth new social and economic challenges, but, above all, clinical and scientific challenges to the world [1]. The coronavirus-related disease (COVID-19) primarily manifests its symptoms in the upper airways, resembling a flu-like syndrome, progressing in severe forms to acute respiratory distress syndrome (ARDS) with high morbidity and mortality [2].

In addition to the respiratory manifestation, gastrointestinal symptoms stand out, such as diarrhea, nausea, and vomiting, along with the presence of changes in liver transaminases and canalicular enzymes in follow-up laboratory tests of COVID-19 patients [3].

Some patients have developed hepatic sequelae from COVID-19, and several case reports describe clinical, laboratory, and radiological changes related to the bile ducts in patients with a recent history of severe COVID-19 infection. Therefore, this article describes four cases of cholangiopathy secondary to COVID-19 in Brazil with the aim of contributing insights developed in four patients under observation.

Methods

Adult patients followed in the hepatology outpatient clinic of a tertiary hospital in Brasília, with their first consultation in 2021, were included. These patients had a recent history of severe COVID-19. The diagnosis of COVID-19 was confirmed using the rt-PCR technique, polymerase chain reaction, in all patients. Cholestatic alterations included elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) and/or changes in the intrahepatic bile duct identified by magnetic resonance imaging.

The project was approved by the Research Ethics Committee under CAAE number: 34845220.8.2052.8153.

Demographic and clinical data related to hospitalization and outpatient follow-up of these patients were analyzed, including laboratory, radiological, and histopathological results when available. Demographic information included age, gender, and pathological history before hospitalization due to COVID-19. From this point, information was obtained regarding the length of hospitalization, intensive care unit (ICU) admission, and the use of ICU-specific measures such as mechanical ventilation parameters, vasoactive drugs, sedoanalgesia, antimicrobials, and complications during hospitalization. Additionally, laboratory results were collected from the first recorded alteration after the onset of the disease, its peak serum level, and the last follow-up, including values for AST, ALT, ALP, GGT, and bilirubins.

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Four patients were identified who, despite complete recovery from severe COVID-19, showed sequelae of a cholestatic disorder

during their outpatient follow-up. All patients were unaware of any liver disease prior to hospitalization, except for patient 2, who was being followed for hepatic steatosis in outpatient care. Three patients were male and one female, with an average age of 58 years, and the most significant medical history was dyslipidemia (66.6%) (see Table 1).

	Patient 1	Patient 2	Patient 3	Patient 4
Age (in years)	66	54	78	36
Gender	Male	Male	Female	Male
Hypertersion	No	Yes	Yes	Não
Diabetes Mellitus	No	Yes	No	Não
Dyslipidemia	No	Yes	Yes	Não
Obesity	No	Yes	No	Não
Others	No	Yes	No	Gout

Table 1: Demographic and Clinical Aspects.

	Internment			
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Date of COVID diagnosis (rtPCR)	February 2021	July 2021	January 2021	January 2021
Date of first consultation in Hepatology	May 2021	December 2021	July 2021	July 2021
Hospitalization Days	32 days	134 days	80 days	38 days
ICU days	22 days	114 days	50 days	26 days
Mechanical Ventilation ?	Yes	Yes	Yes	Yes
FiO^2 > 80%	Yes	Yes	Yes	Yes
PEEP > 10	Yes	Yes	Yes	Yes
PaO^2/FiO < 150	Yes	Yes	Yes	Yes
Pronation	No	Yes	Yes	Yes
ECMO ?	No	No	No	Yes
Tracheostomy?	No	Yes	Yes	Yes
Vasoactive drugs ?	Noradrenaline + Vasopressin	Noradrenaline + Vasopressin	Noradrenaline + Vasopressin	Noradrenaline + Vasopressin
Parenteral Sedoanalgesia?	Midazolam + Fentanyl	Ketamine + Propofol + Midazolam + Fentanyl +Dexmedetomidine	Midazolam + Fentanyl	Ketamina + Propofol + Fentanyl + Dexmedetomidine
Broad spectrum antibiotic?	Yes	Yes	Yes	Yes
Acute Kidney Injury?	Yes	Yes	Yes	Yes
Corticosteroid therapy?	Dexamethasone + Prednisone	Methylprednisolone + Prednisone	Methylprednisolone + Dexamethasone + Prednisone	Dexamethasone + Prednisone

Table 2: Characteristics of Initial Hospitalization for Severe COVID-19.

FiO^2: Inspired Oxygen Fraction; PEEP: Positive End-Expiratory Pressure; PaO^2/FiO^2: Arterial Pressure of Oxygen/ Inspired Oxygen Fraction; ECMO: Extracorporeal Membrane Oxygenation.

	Patient 1	Patient 2	Patient 3	Patient 4
First laboratory change, the maximum and the most recent, in that order				
ALT/ALP	596/680/118	729/837/837	1049/1049/642	797/1017/139
GGT	986/1158/80	924/924/500	523/956/796	898/1108/71
AST	152/227/28	118/118/45	76/219/219	179/179/24
ALT	126/497/21	210/210/53	126/497/21	468/468/15
Bilirubins	1,7/1,7/0,82	1,34/1,66/1,66	10,15/22,6/20,19	0,36/0,7/0,5

Table 3: Initial Alteration, Peak, and Most Recent Values of Canalicular Enzymes, Transaminases, and Bilirubins After COVID-19 Infection.

Alanine Transaminase (U/L) (AST: Aspartate Transaminase (U/L), ALP: Alkaline Phosphatase (U/L), GGT: Gamma-Glutamyl Transferase (U/L), Bilirubins (mg/dL).

In detail, regarding patient 1, alterations in liver enzymes were identified even during hospitalization, with a predominance of canalicular enzyme elevation. They initiated outpatient follow-up with a hepatologist two months after the COVID-19 diagnosis when they began using Ursodeoxycholic Acid (UDCA) at a dose of 15 mg/kg/day.

In June 2021, three months after the disease diagnosis, the patient underwent magnetic resonance cholangiopancreatography (MRCP), revealing evidence of areas of dilation and stenosis in intrahepatic bile ducts with irregular contours similar to Primary Sclerosing Cholangitis. At the 12-month follow-up, endoscopic ultrasound was performed due to elevated CA 19.9 and persistent liver enzyme levels, revealing biliary casts, which were removed by Endoscopic Retrograde Cholangiopancreatography (ERCP), subsequently leading to a reduction in enzyme levels and CA 19.9. The patient did not present pruritus or jaundice.

In the follow-up, 18 months after COVID-19 infection, the patient developed significant portal hypertension, esophageal varices in endoscopy on August 23, 2022, and signs of chronic liver disease in a total abdominal MRI on August 27, 2022. The patient underwent elastic band ligation of varices after an episode of melena. The patient continues outpatient follow-up for chronic liver disease with the use of carvedilol and an elastic band ligation protocol for esophageal varices, maintaining good control of portal hypertension. The patient remains in outpatient follow-up, with the last consultation in July 2023.

For patient 2, Magnetic Resonance Cholangiography on September 26, 2021, while still hospitalized for COVID-19, revealed disseminated cystic lesions in both hepatic lobes, suggesting microabscesses, along with thrombosis of the posterior branch of the portal vein, documented in the outpatient follow-up in April 2022 by contrast-enhanced abdominal CT. Therefore, the patient underwent a 60-day course of antibiotic therapy with ciprofloxacin and clindamycin, as well as full anticoagulation from November 2021 to May 2022, suspended after portal vein recanalization in a follow-up image. In November 2022, 16 months after COVID-19 infection, the patient presented with clinical cholestasis, pruritus, jaundice, and the appearance of an obstructive image in the right bile duct, managed with dilation and removal of biliary casts through spyglass on four occasions. The patient did not develop portal hypertension, and repeated episodes of cholangitis led to the indication for liver transplantation.

The patient has been using UDCA since the first hepatology consultation. A liver biopsy performed 20 months after the initial hospitalization for systemic viral infection showed portal fibrosis with onion-skin pattern, portal-portal bridges, and marked marginal ductular reaction with a discrete mixed inflammatory pattern. The remaining original bile ducts exhibited marked degenerative changes. The patient remains in outpatient follow-up, with the last consultation in July 2023.

For patient 3, clinical cholestasis began two months after COVID-19, with pruritus, jaundice, acholic stools, leading to the use of UDCA at a dose of 15 mg/kg. Although there was symptomatic improvement, there was no laboratory response. A contrast-enhanced total abdominal MRI revealed alternating points between dilation and stenosis of the intrahepatic bile duct, without common bile duct involvement.

After 9 months of hospitalization for COVID-19, obstructive cholestasis with proximal common bile duct stenosis was evident, hindering the contrast of intrahepatic bile ducts. The hypothesis of Cholangiocarcinoma was suggested. Attempts at deblocking and placing a biliary stent were unsuccessful. The patient experienced progressive liver function loss, with a progressive increase in INR and bilirubin levels. In September 2021, the patient succumbed to

sepsis secondary to cholangitis, 12 months after the COVID-19 diagnosis.

Patient 4 underwent MRCP due to cholestasis, which detected alternating dilations and stenoses of bile ducts two months after COVID-19. A liver biopsy performed five months after the COVID-19 diagnosis showed periductal onion-skin fibrosis, portal-portal septa, and a marked marginal ductular reaction with a discrete mixed inflammatory pattern. The patient did not present clinical jaundice or pruritus.

UDCA was initiated at 15 mg/kg/day on July 2, 2021, five months after the COVID-19 diagnosis, with gradual tapering since then. There were no signs of portal hypertension, and 8 months after the infection, MRCP showed no changes, leading to discharge from the hepatology outpatient clinic without new episodes of liver involvement and without laboratory alterations. The patient remains in outpatient follow-up, with the last consultation in July 2023.

Discussion

In this series, we describe four cases of post-COVID cholangiopathy, with only one case (25%) being female and three (75%) male, in accordance with the 83.3% male cases described in the systematic review by Yanny., *et al*. [5]. All cases progressed with the need for Invasive Ventilation, Hemodynamic Support with Vasoactive Drugs, and ICU admission during the initial hospitalization with a diagnosis of SARS-CoV-2, a pattern also evidenced in all cases described in the literature review [5].

Before hospital admission for COVID-19, patients had normal or slightly elevated levels of AST, ALT, GGT, ALP, and Bilirubin. After admission, there is a more pronounced increase in ALP and GGT levels (see Table 3), to the detriment of AST and ALT. This increase in canalicular enzymes was also described in other articles, with a prevalence of 90.3% for ALP and a consistently elevated GGT, above 1000 U/L, in the review by Rasheed., *et al*. [6]. Yanny., *et al*. describe the average serum peaks of ALP and ALT at 2014 U/L and 899 U/L, respectively [5].

In this series, there was a slight increase in bilirubin levels in patients 1 and 2, and more significantly in patient 3. Rasheed., *et al*. [6] also describe hyperbilirubinemia in 63.5% of the patients described, with the majority reaching levels above 5 mg/dL, values not reached by most patients in this series.

The more pronounced elevation of canalicular enzymes and biliary injury, therefore, can be explained by the pathogen's affinity for angiotensin-converting enzyme 2 (ACE2), as it is the cellular receptor for viral invasion and is present in 59% of cholangiocytes, compared to only 2.6% of hepatocytes [7-9]. Additionally, there is also significant expression of this same molecule in vascular endothelial cells, the physiopathological basis for peribiliary thrombotic events, findings described in histopathology in some reports, such as sinusoidal microthrombi [13,14].

Regarding the radiological pattern of post-COVID cholangiopathy, alternating dilations and stenoses in intrahepatic bile ducts are described, unanimous in all patients described in this series, a pattern also demonstrated in 23 out of 30 patients described by Yanny., *et al*. [5]. This radiological pattern mimics Primary Sclerosing Cholangitis.

This radiological pattern is also described in a clinical entity, first described by Scheppach., *et al*. in 2001 [13], called secondary sclerosing cholangitis in critically ill patients. Given this radiological proximity, some authors argue that post-COVID cholangiopathy is a subtype of that, as it shares the context of prolonged intensive care unit admission, mechanical ventilation, and vasoactive drugs [12,13,15]. The pathophysiology described so far suggests direct ischemia, given severe hemodynamic shock in the context of hospitalization, leading to necrosis and shedding of biliary epithelium, with subsequent formation of biliary casts, present in patients 1 and 2 in this series [16].

Regarding histopathology, this series describes the histopathology of patient 4 with 32 portal spaces with moderate fibrosis with portal-portal septa, with bile ducts present in 28 of them, with periductal fibrosis and a marked marginal ductular reaction with a discrete mixed inflammatory pattern. This onion-skin pattern was also found by Lee., *et al*. [17] in the histopathology description of the liver specimen removed in this first description of liver transplantation in the context of post-COVID cholangiopathy. In the other patient with a liver biopsy, a predominant biliary lesion and grade 3 fibrosis of METAVIR were found.

Lee., *et al*. [17], as well as other authors, describe, however, a reduction in bile ducts, always in the description of pieces referring to patients with chronic disease, worsening over time [4,18]. The contrast with our case, where ducts were described in 28 out of 32 portal spaces, is possibly due to the benign evolution of the disease, which progressed to cure in the follow-up.

Finally, post-COVID cholangiopathy is highlighted as an emerging clinical entity, whose first description was published in March 2021 [4]. The first literature reviews were published in 2023, still based on reports and case series. In this context, the importance of this article is emphasized, adding to the number of cases described in the global scientific literature, thus making new reviews more robust.

Conclusion

Post-COVID-19 cholangiopathy was most described in cases of patients affected by COVID-19 in the year 2021. Although some cases presented with a lesser clinical expression of cholestasis, others demonstrated an evolving pattern with progressive worsening of cholestasis and biliary-pattern hepatic fibrosis with consequent hepatic functional losses and manifestations of portal hypertension. Advances in the interpretation of radiological findings of the presence of biliary casts and the possibility of relieving biliary obstructions have led to better outcomes for biliary lesions.

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