A Case of COVID Cholangiopathy and Literature Review

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ABSTRACT

Introduction: With cholangiopathy, the bile ducts become inflamed and have a "beads on string appearance" with elevated bilirubin. It is typically associated with primary sclerosing cholangitis but is now being reported as a post-COVID complication.

Case Presentation: A 65-year-old White male presented with resolved respiratory failure from COVID-19 pneumonia, jaundice, and likely subacute kidney injury. He was diagnosed with COVID-19 cholangiopathy due to clinical picture and magnetic resonance cholangiopancreatography imaging. Unfortunately, due to a massive refractory gastrointestinal bleed, he was transitioned to hospice care.

Discussion: COVID-19 has been shown to have both short- and long-term effects on multiple organ systems. Cholangiopathy is a rare complication of COVID-19. Most of these cases result in severe liver failure and require liver transplant, similar to primary sclerosing cholangitis.

Conclusions: We report this case to increase awareness among clinicians to consider COVID-19 cholangiopathy in patients with unexplained jaundice and a history of severe COVID-19 infection.

INTRODUCTION

COVID-19 is a disease that has short- and long-term effects on multiple organ systems, ranging from classic symptoms of runny nose, cough, and fever to more severe cases that can include acute respiratory distress syndrome and cardiomyopathy secondary to an inflammatory response.[1] Interestingly, hepatic and bile duct involvement after severe COVID-19 infection also have been reported.[2] The 2 leading theories for this cholangiopathy are that a prolonged inflammatory state causes chronic cholangitis resulting in cholangiopathy and ischemic injury of the biliary epithelium causing cholangiopathy.[3] In literature, this has been classified as cholangiopathy secondary to COVID-19—different from primary sclerosing cholangitis (PSC). However, both have the same treatment options with supportive management of hyperbilirubinemia and ultimately require liver transplantation for a cure. Here we report a case of a patient who had a severe COVID-19 infection and developed COVID-19 cholangiopathy, with comparisons to other cases reported in the literature.

CASE PRESENTATION

A previously healthy 65-year-old unvaccinated White male with no significant past medical history presented from an outside hospital after transfer from Brazil. He had contracted COVID-19 in May 2021 and was immediately admitted to an intensive care unit (ICU) in Brazil until mid-June. He had received dexamethasone and mavrilimumab for acute respiratory distress syndrome, was intubated for 10 days, and placed on extracorporeal membrane oxygenation (ECMO) for a week. Records from Brazil were not provided, and the timeline is based on his wife's recollection/in-flight physician handoff. He was then extubated and transferred to the floor until mid-July.

While still in Brazil, the patient developed acute hepatitis with bilirubin to 16mg/dL, elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) to 200s IU/L. According to his wife, jaundice and acute hepatitis developed 4 days prior to transfer. On arrival to the initial admitting hospital in Wisconsin, he was febrile, blood culture was positive for *Stenotrophomonas maltophilia*, and x-ray revealed stage 4 sacral

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ulcer with sacral osteomyelitis. His labs included the following: white blood cell count 26K/uL, hemoglobin 9.8g/dL, AST 219 IU/L, ALT 241 IU/L, bilirubin 14.1mg/dL (direct 12.8mg/dL), alkaline phosphatase 1622 U/L, and creatinine 3.02mg/dL. He was started on cefepime, metronidazole, and vancomycin. He also had not had a bowel movement for 4 days. Given the need for higher level of care, he was transferred to Froedtert Hospital in Milwaukee, Wisconsin.

On arrival, the patient's vitals were as follows: temperature 97.6 °F, pulse 97 beats per minute, blood pressure 118/63 mmHg, 99% oxygen saturation on room air, and fraction of inspired oxygen (FiO2) 21%. Labs were bicarbonate 19 mEq/L, international normalized ratio 1.1, total bilirubin 15 mg/dL, AST 181 IU/L, ALT 200 IU/L, and alkaline phosphatase of 1391 U/L. He initially was evaluated for cholestasis of sepsis, drug-induced liver injury, and acute cholangitis. However, right upper quadrant ultrasound was negative for obstruction/dilation of the common bile duct, and no altered mental status was present. He was started on N-acetyl cysteine and ursodiol due to jaundice, alongside piperacillin and tazobactam given concerns of acute cholangitis. Anti-smooth muscle antibody (ASMA), antinuclear antibody (ANA), perinuclear antineutrophil cytoplasmic antibodies (pANCA), and IgG4 labs were drawn to isolate causes of acute hepatitis and cholangiopathy. The following day, magnetic resonance cholangiopancreatography (MRCP) was significantly motion degraded but showed no evidence of hepatic contour nodularity, with mild multifocal intrahepatic biliary dilation and normally patent hepatic vasculature and mild periportal edema. There was no evidence of portal hypertension. Furthermore, the patient's clinical picture included no history of inflammatory bowel disease and no prior abnormal liver chemistries. Due to the MRCP results, with negative pANCA, IgG4, ASMA, and ANA, he was diagnosed with COVID-19 cholangiopathy (Figures 1 and 2).

Labs showed no changes from the previous day. Due to the patient's relative stability and request, his nasogastric tube was removed. He also underwent an abdominal x-ray due to constipation. It showed large stool caliber in bowels with no obstruction. As such, he was given polyethylene glycol and an enema.

The following morning, the patient passed a large melanotic stool and proceeded to become hypotensive and hypoxic. He was given 1 L of lactated ringer and blood pressure up to 138/73 mmHg. Hemoglobin and hematocrit levels also showed a hemoglobin of 5.7 g/dL – down from 9.0 g/dL on admission – and he was given 2 units of packed red blood cells (pRBC). At this point, due to hemodynamic/respiratory instability and the need for massive transfusion protocol, he was transferred to the ICU.

The patient underwent an esophagogastroduodenoscopy (EGD) and was found to have a large 2-cm ulcer in the distal duodenum bulb, oozing with no portal hypertension. Despite multiple hemoclips and multiple epinephrine injections, the ulcer did not stop bleeding. Interventional radiology was consulted and embolized the duodenal ulcer artery. Computed tomography angiography (CTA) performed the day after the procedure did not demonstrate a place for intervention radiology to intervene. However, given continued bleeding, the day after CTA imaging, an additional EGD was performed and 3 hemoclips were placed.

Figure 1. Magnetic Resonance Cholangiopancreatography Image of Patient's Dilated Intrahepatic Bile Ducts

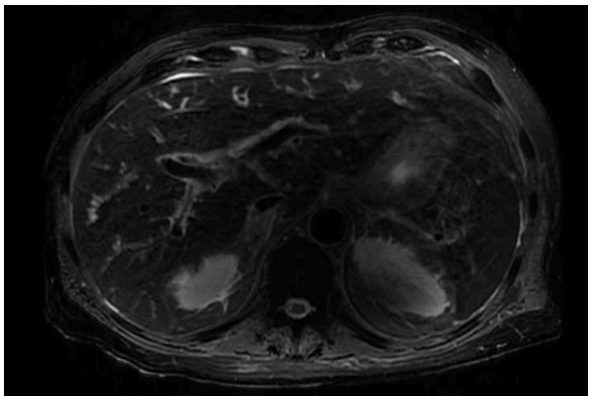
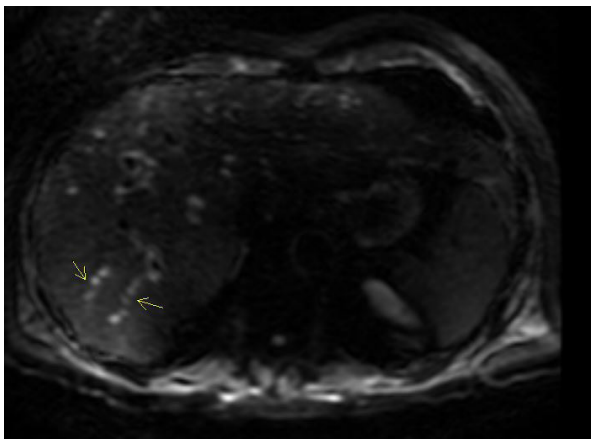


Figure 2. "Beaded" Appearance of Distal Ducts



After the second EGD, the patient was given additional pRBC units due to low hemoglobin and started to develop delirium. He also continued to have melanotic stools and required additional transfusions to keep hemoglobin greater than 7.0 g/dL. Unfortunately, he continued to bleed from the ulcer site and hemoglobin continued to decline.

Despite 2 EGDs and embolization of the gastric duodenal artery, the patient continued to have bleeding and a third EGD was performed in late July. The same duodenal bulb ulcer was treated with epinephrine, gold probe, and hemoclip. After the third EGD, his hemoglobin stabilized, and acute care surgery was

consulted a few days later given the potential need for surgical intervention due to exhaustion of nonsurgical options. However, because of the patient's comorbidities and likely need for long-term hemodialysis or potential organ transplant, acute care surgery did not offer surgical options. As both options were against the patient's wishes, the following day he decided to discontinue treatment and be placed on comfort care.

DISCUSSION

Since COVID-19 was first recognized by the World Health Organization in December 2019, it has infected 219 million people and killed 4.55 million people around the world.[4] At the time of this report, in the state of Wisconsin, there had been over 700 000 cases and over 8000 deaths due to COVID-19.[5] COVID-19 also has developed a multitude of variants and presentations, including the Omicron BA.4 and BA.5 subvariants, which are proving incredibly virulent and responsible for a majority of infections.[6]

While most commonly known for its effect on the lungs, COVID-19 is a disease that affects multiple organ systems and can cause long-term effects, some of which are still unknown. There have been many reports of damage to the vascular endothelial cells, brain, kidneys, intestines, and increased risk of clotting.[7] Many of these are believed secondary to the immense inflammatory response caused by COVID-19, which involves an increase in cytokines and interleukin (IL)-1, IL-2, IL-6, IL-8, IL-17, IL-19, and interferon gamma.[8,9]

We present this case of hepatobiliary involvement as a relatively new and rare discovery. Although there is no current agreement on the exact pathophysiology of COVID-19 cholangiopathy, we agree with Faruqui et al, who suggest that given the similarities of COVID cholangiopathy and secondary sclerosing cholangitis in critically ill patients, the pathophysiology of the diseases are similar.[3,10,11] The main component of this pathophysiology is that the biliary epithelium is vulnerable to ischemic injury due to its singular blood supply from the peribiliary vascular plexus, supplied by hepatic arterial branches. The hepatic parenchyma, on the other hand, has dual blood supply from both the portal vein and hepatic arteries.[3] Should the pathophysiology of COVID-19 cholangiopathy be proven similar to secondary sclerosing cholangitis in critical illness, it could be speculated that it is worsened by SARS-CoV-2 epithelial infection, microthrombi, and/or the magnitude of cytokine release syndrome particular to COVID-19. With these theories, the end result is that there is damage to the biliary epithelium that presents with an elevation in the total bilirubin, elevation in liver enzymes, and inflammation of the bile ducts, diagnosed as cholangiopathy.

Our patient likely had COVID-19 cholangiopathy, supported by his recent severe COVID infection, elevated total bilirubin, elevated liver enzymes, elevated alkaline phosphatase, and elevated inflammatory markers like C-reactive protein. All these pointed towards hepatobiliary involvement. In addition, the right upper quadrant ultrasound was negative for cystic duct dilation or stones, no fever was present during Froedtert Hospital admission, and pANCA, ASMA, IgG4 labs were all negative; this led to COVID-19 cholangiopathy as the most likely diagnosis. MRCP further supported the diagnosis with the classic "beading" patterning of the intra and extra hepatic bile ducts. Due to this presentation 3 months after COVID-19 infection, the lack of major medical histories, and the lack of markers for PSC, the diagnosis of exclusion of COVID-19 cholangiopathy was made. Our case is unique due to the lack of documented cases of COVID-19 cholangiopathy; the Table represents a brief overview of cases presented in literature, including two from our own institution.

In the literature, COVID-19 cholangiopathy has very bleak outcomes, with supportive care being the only management option before definitive treatement.[3,12] As stated by Faruqui et al, because the pathophysiology of COVID-19 cholangiopathy and PSC is so similar, the definitive treatment is also similar: liver transplant and urdoxylic acid used for symptomatic management.[3] However, due to this patient's multisystem organ failure, refractory gastrointestinal (GI) bleed, and recurrence of respiratory failure, liver transplant was not discussed and the patient was managed with urdoxylic acid and hospice care.

Furthermore, due to the patient's severe presentation and rapid deterioration after admission secondary to GI bleed, we believe our case is an excellent teaching case that shows the workup process for COVID-19 cholangiopathy and the potentially fatal outcomes that can result. Additionally, given that refractory bleeding appears to be the cause of death in a number of these patients, if this pattern becomes recognizable, it would be reason for a more emergent referral to liver transplantation. While we were able to identify what was causing this patient's hepatic dysfunction, due to his multisystem organ failure and massive refractory GI bleed, little could be done other than supportive care.

Management of cholangiopathy is supportive only as a bridge to transplant.[12] While hospitalized, it is important to monitor daily labs, including coagulation parameters and hemoglobin. It is also important to monitor for melena or hematochezia. If the patient is otherwise stable, then liver transplantation is the only viable cure in these cases, but the patient can receive supportive treatment with urdoxylic acid treatment to decrease total bilirubin.

In summary, the diagnosis of COVID-19 cholangiopathy should be a diagnosis of exclusion and should only be considered with a prior history of severe COVID-19 infection. It should be worked up with imaging and ruling out PSC and can be confirmed with MRCP that shows "beading" of the intra and extra hepatic bile ducts. Given the continued changes and prevalence of unknown variables from the pandemic, it is imperative for clini-

Table. Additional Cases of COVID-19 Cholangiopathy Reported in Literature

Author	Patient Age	Sex	Medical History	Location	Major Liver Pathology Location	Mode of Diagnosis	Clinical Status
Faruqui, et al[3]	73	M	Diabetes, HTN, HLD, CVA	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive
Faruqui, et al[3]	39	M	HTN, HLD, cocaine use	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive
Faruqui, et al[3]	64	M	Diabetes, HTN, HLD, CVD	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive, had LT
Faruqui, et al[3]	77	M	HTN, HLD, CVD, PD	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive on ursodiol
Faruqui, et al[3]	46	M	HTN	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive
Faruqui, et al[3]	72	M	Obesity	New York, NY	Beading of intrahepatic ducts	MRCP	Deceased from hemiperitoneum, no LT
Faruqui, et al[3]	38	M	None	New York, NY	Beading of intrahepatic ducts	MRCP	Deceased, listed for LT
Faruqui, et al[3]	60	M	Obesity, HTN, HLD	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive on ursodiol, listed for LT
Faruqui, et al[3]	42	M	None	New York, NY	Beading of intrahepatic ducts	MRCP	Deceased from massive GI bleed, no LT
Faruqui, et al[3]	57	M	Obesity, HTN	New York, NY	Unspecified hepatic abnormality	MRCP	Deceased from perforated duodenal ulcer, no LT
Faruqui, et al[3]	68	M	Diabetes, HLD, CVD, HT	New York, NY	Unspecified hepatic abnormality	MRCP	Alive on ursodiol
Faruqui, et al[3]	62	F	Obesity, diabetes, HTN	New York, NY	Beading of intrahepatic ducts, bile duct thickening	MRCP	Alive
Durazo, et al[12]	47	M	Obesity, OSA, HTN, HLD	Milwaukee, WI	Intrahepatic bile ducts	CTAP, ERCP	Alive, had LT
Gourjault, et al[13]	55	M	Obesity	Paris, France	Intrahepatic bile ducts	Hepatic MRI w/ biopsy, ERCP	Alive, listed for LT
Gourjault, et al[13]	45	M	Obesity	Paris, France	Intrahepatic bile ducts	Hepatic MRI	Alive
Gourjault, et al[13]	30	M	None	Paris, France	Intrahepatic bile ducts	Hepatic MRI w/ biopsy	Unknown, had LT
Roth, et al[14]	38	M	None	Manhasset, NY	Intrahepatic bile ducts, terminal hepatic veins, zone 3 region	Hepatic MRI w/ biopsy, ERC	Alive
Roth, et al[14]	25	M	None	Manhasset, NY	Extrahepatic bile ducts, sinusoidal obstruction w/ zone 3 necrosis	Hepatic MRI w/ biopsy, ERC	Alive
Roth, et al[14]	40	F	Diabetes	Manhasset, NY	Severe zone 3 hepatocanalicular cholestasis/focal bile infarcts	Hepatic MRI w/ iopsy, ERC	Alive
Lee, et al[15]	64	M	HTN, HLD, diabetes	St. Louis, MO	Common bile duct, intrahepatic bile ducts	CTAP, ERCP, MRCP	Alive, had LT

Abbreviations: MRCP, magnetic resonance cholangiopancreatography; CTAP, computed tomography of abdomen and pelvis; ERCP, endoscopic retrograde cholangiopancreatography; GI, gastrointestinal; MRI, magnetic resonance imaging; ERC, endoscopic retrograde cholangiography; HTN, hypertension; HLD; hyperlipidemia; CVD, cardiovascular disease; CVA, cerebrovascular disease and/or accident; PD; Parkinson's disease; HT, hypothyroidism; OSA, obstructive sleep apnea; PCR, polymerase chain reaction; LT, lung transplant.

[a]Faruqui, et al report MRCP for all patients; 4 patients underwent hepatic biopsy however unspecified, other tests not specified.

cians to have continued awareness on guidelines of management for cases that may turn severe, such as the COVID-19 cholangiopathy presented here.

CONCLUSIONS

Although COVID-19 cholangiopathy is an uncommon complication of COVID-19 infection, it should be considered in the differential diagnosis of elevated liver enzymes and total bilirubin after severe COVID-19 infection. We report this case and literature review to increase awareness among clinicians treating patients who present with unexplained jaundice and acute hepatitis. Detailed examination and investigation are necessary to make this diagnosis. More reporting of similar cases is essential for attention from clinicians and researchers to develop evidence-based guidelines for the diagnosis and management of this condition.

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