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Case Report

COVID-19 Infection Causing Liver Infarction, Severe Cholangiopathy, and Biliary Cast Syndrome

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ABSTRACT

We present a patient with COVID-19 pneumonia with severe multi-organ failure who developed a liver infarction in the setting of acute illness and following recovery, had persistent cholestatic liver injury. On further evaluation, he was found to have a severe destruction of the intrahepatic bile ducts and biliary cast syndrome and ultimately, was felt to have severe ischemic cholangiopathy in the setting of recent COVID-19 infection. Because of the extent of destruction and persistent cholestasis, he is at risk of secondary biliary cirrhosis and is therefore undergoing a liver transplant evaluation. This case highlights a rare entity of liver infarction and severe cholangiopathy with biliary cast syndrome in the setting of COVID-19 infection. It is the first case of this reported to date, and its recognition in the presence of the COVID-19 pandemic is important.

Keywords: *Biliary cast, Cirrhosis, Cholangiopathy , COVID-19, Liver infarction.*

INTRODUCTION

A 54-year-old man with a past medical history of hypertension, prediabetes, and obesity with a body mass index of 35 kg/m2 presented to an outside hospital with dyspnea on exertion, found to have COVID-19 pneumonia. He rapidly developed progressive hypoxemic respiratory failure requiring prolonged intubation and mechanical ventilation for four weeks, cardiac arrest with return of spontaneous circulation after cardio-pulmonary resuscitation, and shock requiring vasopressor support. His course was complicated by thrombotic and inflammatory complications related to COVID-19 including ischemic colitis requiring right hemicolectomy and end ileostomy, acute renal failure, and digit necrosis requiring amputation. As a result, he was placed on a heparin infusion which was then complicated by spontaneous retroperitoneal and intraperitoneal hematomas requiring discontinuation of anticoagulation. In the setting of multi-organ failure, he developed profoundly elevated transaminases with peak aspartate aminotransferase (AST) of 8491 U/L and alanine aminotransferase (ALT) of 6899 U/L attributed to ischemic liver injury. This was managed conservatively with gradual decrease of his transaminase levels. However, he then developed progressive cholestatic liver injury with an alkaline phosphatase (AP) of 790 U/L and total bilirubin of 13.9 mg/dL (AST 119 U/L, ALT 159 U/L). He was transferred to our tertiary care center for consideration of orthotopic liver transplantation.

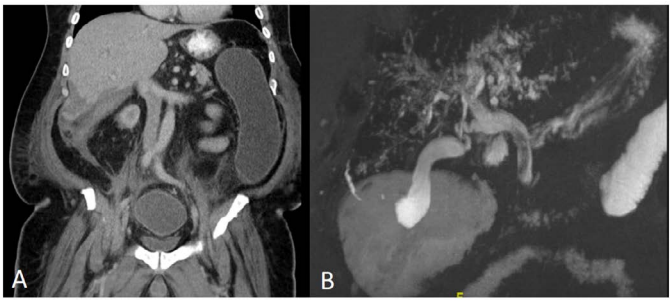
The patient had no known pre-existing liver disease. He denied any prior history of jaundice, hepatic encephalopathy, gastrointestinal bleeding, ascites, or lower extremity edema. He had no prior surgeries, no known allergies, and his only previous medication was losartan. He did not use any over the counter supplements. He lives with his wife and children and was previously in the Marine Corps and now works in sales. He drinks about 3-4 alcoholic beverages per week and uses occasional recreational marijuana but denied any previous or current tobacco use or intravenous drug use.

On presentation, physical examination revealed normal vital signs. The patient was jaundiced with icteric sclera. The abdomen was obese, soft and non-tender with healthy-appearing left lower quadrant ileostomy and no hepatosplenomegaly, and there were no stigmata of chronic liver disease. On laboratory evaluation, the patient had a white blood cell count of 7,160/uL, hemoglobin level of 8.3 g/dL, and platelet count of 503,000/uL. The renal function was normal. His liver tests were as follows: AST 115 U/L, ALT 156 U/L, AP 806 U/L, and the total bilirubin was 13.1(direct bilirubin was 11.0, gamma-glutamyl transferase (GGT) 920 U/L). The international normalized ratio (INR) was 1.2. Viral hepatitis serologies including hepatitis A IgM, hepatitis A IgG, anti-hepatitis B surface antibody, anti-hepatitis B core antibody, hepatitis B surface antigen, anti-hepatitis C virus antibody, hepatitis E IgM, hepatitis E IgG were all negative. Blood cultures were negative. Anti-nuclear

antibody (ANA) was negative, anti-smooth muscle antibody (ASMA) was weakly positive at 1:20, anti-mitochondrial antibody (AMA) was negative, and total immunoglobulin level was mildly elevated at 1,690 mg/dL. Iron studies were normal and percent saturation was 46%.

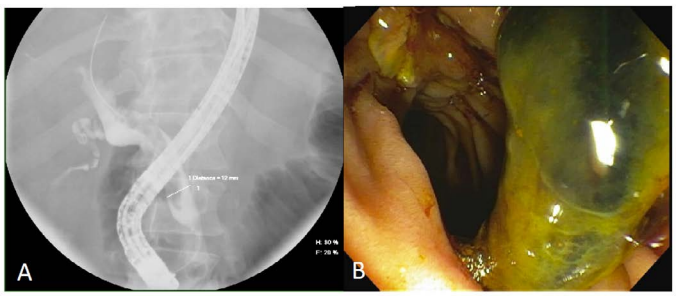
Computed tomography (CT) of abdomen and pelvis with intravenous contrast demonstrated geographic wedge-shaped non-enhancing hypodensities in the right inferior liver which were decreased in size compared to imaging four weeks prior at the outside hospital (Figure 1A). This was suspected to represent evolving liver injury or infarction. An ultrasound of the abdomen was obtained to further characterize the intrahepatic hypodensity which demonstrated an ill-defined wedge-shaped area of increased echogenicity in the right lobe. In addition, there was mild intrahepatic and extra hepatic biliary ductal dilatation with echogenic non-shadowing material in the common bile duct (CBD). The biliary duct dilation was further evaluated with magnetic resonance cholangiopancreatography (MRCP) which revealed complete destruction of the intrahepatic biliary tree; in the expected location of intrahepatic biliary ducts, there were innumerable tiny cystic foci and remnant ductal elements (Figure 1B). The CBD contained a linear long-segment filling defect, about 4.6 cm in length (Figure 1b). The geographic wedge-shaped areas of T1 signal hypo-intensity and non-enhancement were re-demonstrated in the right inferior liver.

Figure 1A: CT abdomen and pelvis with IV contrast. Hepatic infarction in right lower lobe (yellow arrow).
Figure 1B: MRCP image. T2-weighted coronal MRI image showing a dilated common bile duct with hypoechoic filling defect spanning from the hilum to the distal duct and complete destruction of the bilateral intrahepatic biliary tree, with innumerable tiny cystic foci and remnant ductal elements.



An endoscopic retrograde cholangiopancreatography (ERCP) was then performed. Cholangiogram demonstrated severe CBD dilation measuring 11 to 21 mm in diameter with multiple hypoechoic oblong filling defects occupying the entire common duct up into both the right and left hepatic ducts, which contained similar irregular filling defects into the intrahepatic ducts (Figure 2A). A biliary sphincterotomy was made and multiple balloon sweeps of the CBD and left and right main hepatic ducts were performed with removal of large black oblong debris consistent with large necrotic biliary casts (Figure 2B). On final occlusion cholangiogram, there was a relative paucity of intrahepatic bile ducts with significant filling defects consistent with retained casts that were not accessible for endoscopic removal. After ERCP, the alkaline phosphatase level was only mildly improved to 570 U/L and the total bilirubin improved to 11.5 mg/dL but subsequently stabilized at these levels. The patient was discharged in stable condition with plans for outpatient follow up with Hepatology. At his one-month post-discharge follow-up, he remains asymptomatic but has persistently elevated total bilirubin at 11.9 mg/dL, AP 987 U/L, AST 166 U/L, and ALT 154 U/L though his INR and renal function have normalized. Due to concerns for development of secondary biliary cirrhosis, he is undergoing evaluation for orthotopic liver transplantation as an outpatient.

Figure 2A: Fluoroscopy image on ERCP showing dilated extrahepatic duct to 12 mm with longitudinal filling defect.
Figure 2B: Endoscopic image from duodenoscope demonstrating debris removed from bile ducts consistent with biliary cast.



DISCUSSION

To date, this is the first reported case of a hepatic infarction, severe cholangiopathy, and biliary cast syndrome in a patient with COVID-19 pneumonia. Liver infarction is a rare occurrence because of the dual hepatic arterial and portal blood supply which provides redundancy in blood flow to the hepatic parenchyma.[1] When infarction does occur, it is thought to result from interruption in flow of the hepatic artery rather than the portal vein. At present, the literature on liver infarcts includes only case reports and small case series. Hepatic infarcts have been reported in polyarteritis nodosa1; in either bland embolism or septic embolism to the hepatic artery;[2] in hepatic artery thrombosis (ie, in the setting of metastatic carcinoma or mycotic aneurysms);[2] and in HELLP syndrome, which is on the spectrum of thrombotic microangiopathy, either in association with or without catastrophic anti-phospholipid syndrome;[3,4] and in the setting of compression of hepatic arterial vessels by primary liver cancer.[5] COVID-19 pneumonia is recognized as a uniquely hypercoagulable clinical syndrome. A coagulopathy has been reported in up to 50% of patients with severe COVID-19 manifestations, and limited data suggest a high incidence of venous thromboembolism, in up to 40% of patients, despite the use of prophylactic anticoagulation.[6] In contrast to sepsis-associated disseminated intravascular coagulation syndrome, venous thromboembolism and arterial thrombosis are more frequent in COVID-19 associated coagulopathy (CAC).[7] Our patient had multiple thrombotic complications of COVID-19 infection as previously discussed including ischemic colitis and digit necrosis. We speculate that a large branch of the hepatic artery could similarly have been compromised with thrombosis and inflammatory vasculopathy causing the hepatic infarction.

In addition, the severe destructive cholangiopathy with rarefication of intrahepatic bile ducts and extensive biliary cast syndrome seen in this case is striking. Cholangiopathy occurring after septic shock or systemic disease with microvascular involvement has been described, and an entity called secondary sclerosing cholangitis in critically ill patients (SSC-CIP) is increasingly recognized as a distinct entity. The defining features include evidence of biliary casts, progressive destruc-

tion of intrahepatic bile ducts, and a pruned biliary tree,[8] as was seen in our patient. Patients diagnosed with SSC-CIP have no pre-existing liver disease. The pathogenesis is thought to involve ischemic injury to the intrahepatic bile ducts caused by prolonged shock and/or mechanical ventilation in patients treated in the intensive care unit.[9] In contrast to the hepatic parenchyma, the biliary tree is supplied exclusively by the hepatic artery and is therefore more susceptible to ischemic injury. The intra-hepatic arteries run in close proximity to the bile ducts and resolve into a rich microvascular network called the peribiliary plexus.[10] While obstruction of large arteries can be compensated for by collateral flow from intra-hepatic or trans-capsular arteries, occlusion of or injury to the small hepatic arteries or the peribiliary vascular plexus can cause ischemic cholangiopathy.[11] There are well-known iatrogenic causes of ischemic cholangiopathy including hepatic arterial infusion of chemotherapeutic agents, radiotherapy of the liver, post-cholecystectomy biliary strictures, and complications of liver transplantation.[11] However, there are also several small- and medium-vessel vasculopathies that are implicated in ischemic cholangiopathy but are much rarer in the literature: HSP, SLE, anti-phospholipid syndrome, PAN, Kawasaki disease.[11] This notion of a microangiopathy causing severe cholangiopathy is of interest in the context of our patient with COVID-19 pneumonia because microvascular thrombosis and endothelial dysfunction has been demonstrated in patients with COVID-19.[12,13] Recent evidence suggests that the coagulopathy in COVID-19 resembles a complement-mediated thrombotic microangiopathy (TMA) syndrome which are well known in rheumatologic conditions.[14] This TMA syndrome is thought to mediate organ injury, including progressive respiratory failure in COVID-19.[6,13] Our patient appears to have an SSC-CIP-type of cholangiopathy, and we speculate this may be due to a TMA syndrome occurring in the setting of COVID-19 infection.

Ultimately, of concern is the development of progressive biliary cirrhosis given the severe destruction of the intrahepatic biliary tree. In the available literature, SSC-CIP is associated with a mean transplant-free survival of 40 months[8] and a 55% transplant-free survival after 1 year.[15] The reported 1-, 3-, and 5-year post-transplant survival rates of patients with SSC-CIP were comparable to transplantation for other indications, and quality of life indices improved significantly after LT in SSC-CIP.[14] Because of these data, transplantation is a valid option. The plan is for completion of liver transplant evaluation and monitoring closely for potential recovery.

REFERENCES

1. Kanter DM. Hepatic Infarction. *Arch Intern Med*. 1965; 115: 479-481. doi: 10.1001/archinte.1965.03860160105019

2. Seeley TT, Blumenfeld CM, Ikeda R, Knapp W, Ruebner BH. *Hum Pathol*. 1972; 3(2): 265-276. doi: 10.1016/s0046-8177(72)80080-7

3. Sakhel K, Usta IM, Hannoun A, Arayssi T, Nassar AH. Liver infarction in a woman with systemic lupus erythematosus and secondary antiphospholipid and HELLP syndrome. *Scand J Rheumatol*. 2006; 35(5): 405-408. doi: 10.1080/03009740600588343

4. Guo Q, Yang Z, Guo J, et al. Hepatic infarction induced by HELLP syndrome: A case report and review of the literature. *BMC Pregnancy Childbirth*. 2018; 18(1): 191. doi: 10.1186/s12884-018-1799-9

5. Wang FH, Yang NN, Liu F, Tian H. Unexplained huge liver infarction presenting as a tumor with bleeding: A case report. *World J Clin Cases*. 2020; 8(10): 2016-2022. doi: 10.12998/wjcc.v8.i10.2016

6. Miesbach W, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. Clin Appl Thromb Hemost. 2020; 26: 1076029620938149. doi: 10.1177/1076029620938149

7. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopath. *Crit Care*. 2020; 24(1): 360. doi: 10.1186/s13054-020-03077-0

8. Leonhardt S, Veltzke-Schlieker W, Adler A, et al. Secondary Sclerosing Cholangitis in Critically Ill Patients: Clinical Presentation, Cholangiographic Features, Natural History, and Outcome: A Series of 16 Cases. *Medicine (Baltimore)*. 2015; 94(49): e2188. doi: 10.1097/MD.0000000000002188

9. Gudnason HO, Björnsson ES. Secondary sclerosing cholangitis in critically ill patients: Current perspectives. *Clin Exp Gastroenterol*. 2017; 10: 105-111. doi: 10.2147/CEG.S115518

10. Deltenre P, Valla D-C. Ischemic cholangiopathy. *J Hepatol*. 2006; 44(4): 806-817. doi: 10.1016/j.jhep.2006.01.009

11. Deltenre P, Valla DC. Ischemic cholangiopathy. *Semin Liver Dis*. 2008; 28(3): 235-246. doi: 10.1055/s-0028-1085092

12. Bray MA, Sartain SE, Gollamudi J, Rumbaut RE. Microvascular thrombosis: Experimental and clinical implications. *Transl Res*. 2020; 225: 105-130. doi: 10.1016/j.trsl.2020.05.006

13. Gavriilaki E, Brodsky RA. Severe COVID-19 infection and thrombotic microangiopathy: Success does not come easily. *Br J Haematol*. 2020; 189(6): e227-e230. doi: 10.1111/bjh.16783

14. Voigtländer T, Jaeckel E, Lehner F, Manns MP, Lankisch TO. Liver transplantation for critically Ill patients with secondary sclerosing cholangitis: Outcome and complications. *Liver Transpl*. 2015; 21(10): 1295-1299. doi: 10.1002/lt.24192

15. Kulaksiz H, Heuberger D, Engler S, Stiehl A. Poor outcome in progressive sclerosing cholangitis after septic shock. Endoscopy. 2008; 40(3): 214-218. doi: 10.1055/s-2007-967024