COVID-19 Induced Liver Injury; A Rare Cause of Acute Cholestasis in a High Risk Patient.

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Introduction

Within the coronavirus pandemic, hepatic dysfunction has been a common finding particularly in the elderly population and those with severe disease. Hepatic injury during coronavirus infection may be related to direct cytopathic effects of the virus, uncontrolled immune reaction, hypoxic changes induced by respiratory failure, vascular changes from coagulopathy, exacerbation of underlying liver disease, sepsis or drug-induced liver injury (DILI) (1-4). Viral entry occurs via the host angiotensin-converting enzyme 2 (ACE2) receptors which are expressed in the gastrointestinal tract, vascular endothelium and cholangiocytes of the liver amongst other organ tissues (3-4). We describe an 82-year-old female presenting with sudden onset jaundice and pruritus with marked elevation in bilirubin and transaminitis secondary to COVID-19 infection.

Case Report

We describe an 82-year-old female with a history of ovarian cancer in remission presenting for jaundice and pruritus. She was admitted one month prior following a mechanical fall complicated by mildly displaced rib fractures; discharged with acetaminophen, tramadol and infusion pump containing 1% lidocaine. She screened positive for COVID-19 despite not having respiratory symptoms and didn't require supplemental oxygen, steroids, or antivirals. Pt denied any new prescribed medications, new OTC medications or antibiotics within the month prior to this admission. She denied any sick exposures or travel. She had a negative history of tobacco, alcoholism, IV drug use, blood product transfusions. Pertinent physical exam findings included marked jaundice with scleral icterus, tender rib palpation, but benign abdominal exam without organomegaly, tenderness or Murphy's sign. She was without any mental status changes. Notable labs included AST 260 IU/L, ALT 260 IU/L and ALP 1015 IU/L, total bilirubin 28 umol/L with direct bilirubin over 15 umol/L. INR was 1.03. Toxicology was negative for acetaminophen, ethanol and illicit drugs. MRI/MRCP demonstrated mild fatty liver with normal liver texture without biliary dilation or signs of obstruction and showed normal gallbladder and pancreatic architecture. ANA was positive at 1:320 with mildly positive anti-smooth muscle antibody level at 22 and with normal total IgG. Viral hepatitis panel, Epstein barr virus, Cytomegalovirus, Tissue transglutaminase antibody, anti-mitochondrial antibodies were not detected. Due to persistent elevation in liver chemistries, a CT-guided liver biopsy was obtained and demonstrated marked hepatocyte cholestasis, rare acidophil body, cholangiocyte injury, portal vein endotheliitis and possible fibrin thrombi (Fig. 1). She was prescribed cholestyramine and Ursodeoxycholic acid with continued monitoring of liver chemistry tests as an outpatient **(Fig. 2).**

Discussion

Hepatic dysfunction ranges from 2.5-76.3% of all COVID-19 cases with liver injury higher in critically ill patients and the elderly population (1-4). Previous coronavirus epidemics including Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) had similar incidences of liver injury at approximately 60%. In vitro studies identified that the coronavirus enters host cells via the ACE2 host receptor (1-3). Immunohistochemical studies from human tissue showed high expression of this receptor protein in the vascular endothelium of the small and large arteries and veins, type 2 alveolar cells within the lungs, within the gastrointestinal tract and abundant levels within cholangiocytes but is rarely expressed within hepatocytes. Additionally, the level of ACE2 expression in cholangiocytes is similar to that in the type 2 alveolar cells of the lungs (1,3).

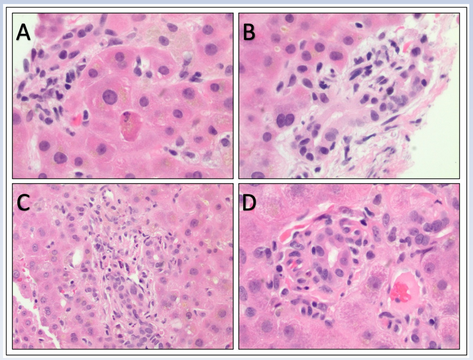

Figure 1: (A) Rare acidophil body present in a background of marked cholestasis. (B) Cholangiopathy evidenced by cholangiocytes demonstrating eosinophilic cytoplasm, nuclear disarray and lymphocyte infiltrate. (C) Endotheliitis in the portal area evidenced by endothelial lifting off by undermining lymphocyte. (D) Fibrin deposition mixed with red blood cells in a small portal vein and a dilated sinusoidal space. A vacuole also present in a cholangiocyte.

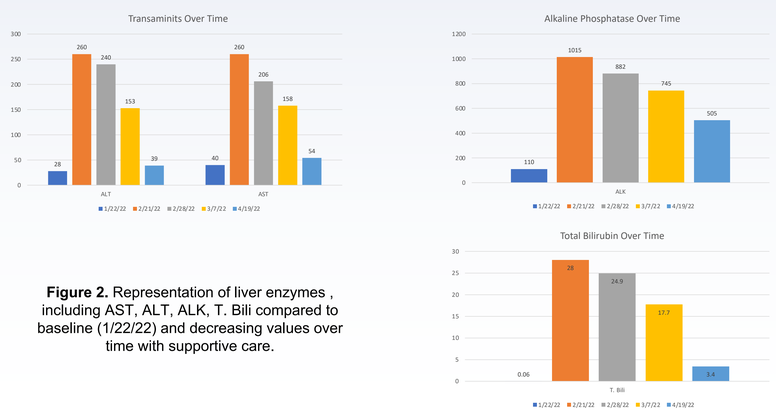

Figure 2. Representation of liver enzymes , including AST, ALT, ALK, T. Bili compared to baseline (1/22/22) and decreasing values over time with supportive care.

Discussion

As to the degree of liver injury, reviews and meta-analysis on transaminitis showed elevated AST in 33.3%, ALT in 24.1% and ALP in 6.1% (2,3). COVID-19 liver injury is likely multifactorial including cytopathic injury directly caused by the virus. As the virus enters through ACE2 receptors in the vascular endothelium, hypercoagulation may also cause liver damage via thrombosis in the porta-hepatic system. Additionally, hypoxemia due to pneumonia may cause liver damage due to hypoxia-reoxygenation with subsequent abundance of reactive oxygen species and proinflammatory factors aggravating microvascular lesions in the liver. Dysregulation of the innate immune response leads to marked activation of inflammatory markers (CRP, lymphocytes, neutrophils and cytokines) which may contribute to pulmonary and extrapulmonary injuries (2,3). Finally, hepatotoxic agents such as nucleoside analogs and protease inhibitors, currently used to treat COVID-19, are known to cause DILI (2,4).

Liver histology from COVID-19 patients includes moderate microvesicular steatosis, mild inflammatory infiltrates in the hepatic lobule and portal tract (1), portal fibrosis, multifactorial acute liver necrosis (4), and degenerative cholangiocyte injury. The potential mechanisms of liver injury includes the fact that biliary epithelia express ACE2, and hence should be susceptible to viral infection (3). However, the pathobiology of this cholangiopathy requires further investigation. It is important to note that the liver injury pattern is not specific for one etiology and can also be seen during sepsis or DILI (3,4), extra- or intra-hepatic biliary obstruction, a vanishing bile duct syndrome, and secondary sclerosing cholangitis of the critically ill patient (SSC-CIP). The portal vein phlebitis and microthrombi in our case is unique comparing to the other biliary injury mentioned above .

Conclusion

We believe the case described herein represents a novel post–COVID-19 cholangiopathy from COVID-19 infection direct hepatic injury.

References

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