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Viral Hepatitis in COVID-Era

Lovepreet Singh
Henry Ford Health, lsingh1@hfhs.org

Jordan Siu
Henry Ford Health, JSiu3@hfhs.org

Arsalan Abbasi
Henry Ford Health, aabbasi1@hfhs.org

Ramanpreet Bajwa
Henry Ford Health

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HENRY FORD MACOMB HOSPITAL

L. Singh MD, J. Siu DO, A. Abbasi MD, R.Bajwa OMS3
Rene Peleman MD

Introduction

SARS-CoV-2, is a novel coronavirus responsible for causing the disease COVID-19, which has been classified as a pandemic by the World Health Organization. The virus, which originated from Wuhan, China, is the most recently identified coronavirus. Two other recent coronaviruses, SARS-CoV (severe acute respiratory syndrome) and MERS-CoV (middle eastern respiratory syndrome) each resulted in epidemics. These three viruses share more than 50% genome sequences. Disease severity of COVID-19 has varied from mild to severe with patients experiencing respiratory and/or multisystem organ dysfunction. Most commonly patients present with fever, cough, fatigue, shortness of breath, muscle ache and headache with associated radiographic findings of a bilateral multifocal pneumonia. Several studies have documented the presence of elevated liver enzymes at time of presentation or during the course of hospitalization for COVID-19. Additionally, there is 1 case report of a patient presenting with acute hepatitis, who then later during admission tested positive for SARS-CoV-2.We present the case of a 44 year old female with acute hepatitis secondary to SARS-CoV-2 infection.

Case Description

The patient is a 44 year old female with a significant medical history of Hashimoto's thyroiditis, hypertension, GERD and neuropathy, who presented to the hospital with the chief complaint of worsening shortness of breath. She initially presented to an urgent care 5 days prior with symptoms of cough, body aches, fever, chills, nausea and vomiting, and was found to test positive for SARS-CoV-2. Vitals documented show pulse ox saturations of 92% at rest and 80% with ambulation on room air; other vital signs stable. Her initial chest x-ray displayed patchy bilateral interstitial and alveolar airspace opacities. Significant labs at time of admission included ALT/AST 588/321 IU/L (n<52/32 respectively), normal TBili and Alk Phos, Ferritin 712 ng/mL, CRP 6.3 mg/dL, LDH 284 IU/L, WBC 3.4 K/uL, absolute lymphocytes 0.60, and D-dimer 1.27 ug/mL. The patient had no prior history of hepatitis, blood transfusions, recent travel, diarrhea, alcohol abuse, IV drug use or family history of liver disease. She also had no recent medication changes or use of over the counter supplements. Her ALT/AST peaked at 1,404/360 on day 5 of hospitalization. Work-up for the elevated transaminases included a viral hepatitis panel, abdominal ultrasound with and without Doppler, ANA, autoimmune liver panel, all of which resulted as negative. Given her rising transaminases, and that a small percentage of cases of autoimmune hepatitis will be seronegative, a liver biopsy was obtained for definitive diagnosis. During hospitalization, she was placed on high dose steroids for her acute respiratory failure, thus covering for possible etiology of autoimmune hepatitis. She remained hemodynamically stable during hospitalization with weaning oxygen requirements. On day 6 a preliminary pathology report was negative for autoimmune hepatitis, steroids were discontinued at that time and she was discharged in medically stable condition. Final pathology report is notable for, "morphologic findings demonstrating mild lobular inflammation," with a negative CMV immunostaining. Most recent ALT/AST were 302/49, obtained 1 week after discharge.

Lab values

	INR	ALT (IU/L)	AST (IU/L)	Alkaline phosphate (IU/L)	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)
Admission	0.89	588	321	48	0.9	0.2
Day 1	0.93	623	323	46	0.9	0.2
Day 2	0.92	790	332	46	0.6	0.3
Day 3	0.93	999	374	45	0.6	0.3
Day 4	0.92	1206	354	46	0.7	-
Day 5	0.93	1404	360	43	0.6	-
Discharge	0.92	1313	277	43	0.6	-
Post D/C	-	302	49	-	-	-

Table 1: On admission pt had elevated ALT/AST, initially ruled out acute hepatitis, portal/hepatic vein thrombosis, ANA negative. Pt was already getting steroids for COVID-19. LFTs peaked on day 5 of admission and trended downwards and pt was discharged home. As we can see above 7 days after discharge her LFTs trended downwards.

Interestingly this patient presented to the hospital with elevated ALT/AST without any recent medication changes or taking over the counter supplements. She was tested for SARS-CoV-2 on 4/9/20 with results coming back on 4/14 the day of hospitalization. Liver biopsy was obtained on day 3 of hospitalization as liver enzymes were climbing without a clear explanation.

While in the hospital she was placed on Azithromycin (4/15-4/16) and plaquanil (4/14-4/17) these medications were discontinued given the rising LFTs without a particular source. Lab work was obtained at 10am and azithromycin and plaquanil were not administered until late in the evening, therefore DILI was less likely on the differential.

Home medications included the following: ASA 81mg, Symbicort inhaler, Vit D2, Zyrtec, Cardizem, Flonase, Levothyroxine, Amitriptyline and Lyrica.

Additional Workup/Labs & Liver biopsy

ANA, ALKM, ASMA and AMA negative
Hep A/B/C Negative
CMV Immunostain Negative

US Doppler liver: IVC, hepatic, portal and splenic veins patent.

Liver Biopsy: The portal tracts are unremarkable and do not demonstrates significant inflammation. Bile ducts are identified and are normal. The lobular parenchyma demonstrates mild lobular inflammation with occasional hepatocyte drop-out and mild sinusoidal congestion; without steatosis, granuloma or necrosis. Central veins are unremarkable, trichrome stain reveals mild focal portal fibrosis. No stainable iron is seen.

In summary, morphologic findings demonstrate mild lobular inflammation. These findings may be due to the patient's SARS-CoV-2 infection.

A special thanks to Dr. Kucy and Dr. Zakhia

Pathology Photos

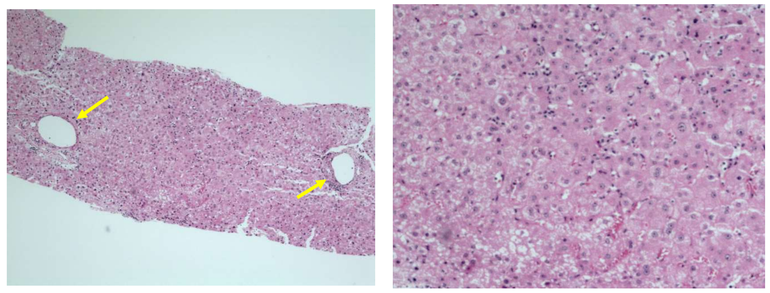

Figure 1. Liver biopsy demonstrating normal portal tracts (yellow arrows) and mild lobular inflammation of the without steatosis, granuloma or necrosis.

Discussion & Conclusion

The goal of management in cases of COVID-19 has primarily been focused on respiratory support and specifically finding treatment options to help reduce the "cytokine storm" that leads to the catastrophic cardiopulmonary failure. As we look beyond into the extra-pulmonary manifestations of this illness we see the magnitude of the fallout. Laboratory monitoring of inflammatory markers such as ferritin, CRP, and LDH are assisting clinicians in assessing the severity of disease and to gauge efficacy of treatment. It is imperative to note that in these elevated inflammatory states, laboratory monitoring of other organ systems is not over looked. A study recently submitted to the Journal of Hepatology evaluated the clinical characteristics of COVID-19 in 417 patients. Of these patients, 318 exhibited elevations in liver functions test, 90 of whom had liver injury during the hospitalization. It was noted that utilization of certain antiviral medications contributed significantly to the detrimental effects.

As is the circumstances in our presented case, the patient was being treated with a combination of azithromycin, Plaquenil, and a short course of corticosteroids. LFT elevations were noted to progressively increase throughout the hospital stay, despite a full workup including hepatitis panels, autoimmune serology, etc. Ultimately leading to a liver biopsy to find inflammation induced injury. Throughout the case close monitoring of LFTs was essential in making treatment decisions such as pre-emptively discontinuing azithromycin given its effects against the liver.

In the short span of a few months, several cases of COVID-19 induced liver injuries have been seen across the world. This is has shed light on identifying at risk populations. As we navigate through the "new normal" of COVID-19 world populations with pre-existing conditions, most notably anyone with underlying liver disease should be closely monitored for hepatocellular failure. Further research is needed in determining the causes of liver injury in COVID 19 patients.

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