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A Case of Significant Transaminitis with Liver Biopsy in a Pregnant Patient with COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, has led to a global health crisis. The virus can cause varying severity of liver injury, but the mechanism has not yet been elucidated, especially in pregnancy. We present a morbidly obese 30-year-old woman with COVID-19 at 28 weeks' gestation complicated by significant transaminitis with peak liver enzymes levels of 501/1,313 (aspartate aminotransferase/alanine aminotransferase). Liver biopsy showed reactive changes consistent with medication effect and mild steatosis.

Significant transaminitis has been found in both pregnant and nonpregnant patients with COVID-19. Our case demonstrates the multifactorial nature of liver injury in COVID-19 patients including mild underlying liver steatosis combined with possible viral potentiation of medication effect.

Keywords

- COVID-19
- pregnancy
- hepatic manifestations
- liver
- transaminitis
- viral injury
- hepatocellular damage

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in December 2019 in Wuhan, China and spread rapidly around the world, becoming a substantial threat to public health globally. Certain vulnerable populations such as the elderly[1] and those with medical comorbidities[2–4] have been found to be at greater risk of severe disease, and there is speculation that pregnancy may be another vulnerable population.[5,6] COVID-19 primarily impacts the lungs, causing acute respiratory distress syndrome; however, other organs have been found to be affected as well, including the kidneys,[3] heart,[7] gastrointestinal tract, bile ducts, and liver.[8,9] The virus has been found to cause liver function abnormalities of varying degrees from mild transaminitis to severe liver injury,[9,10] but the exact mechanism of liver injury in these cases is unknown. Here, we describe a case of a pregnant woman with COVID-19 who developed significant transaminitis and had a liver biopsy performed.

Case

A 30-year-old gravida 3 para 1101 with diet-controlled gestational diabetes, obesity with body mass index (BMI) 45, fatty liver found on ultrasound 7 years prior, history of laparoscopic cholecystectomy, and a history of preterm delivery had sore throat, cough, and fever and was found

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to have a positive COVID-19 test 2 days later. Six days after her positive COVID-19 test ($28^{5/7}$ weeks), she presented with worsening cough, new shortness of breath, and persistent fever up to 101.7. She had taken a limited amount of acetaminophen (less than 3 g/24 hours) at home prior to admission. She was admitted to the hospital for observation and supportive care.

On the day of admission, her temperature was 100.2, heart rate 114, and peripheral capillary oxygen saturation (SpO2) 91 to 94% on room air. She was started on supplemental oxygen by nasal cannula (1–3 L per minute throughout her hospitalization). Medications included dexamethasone 6 mg by mouth daily, a therapeutic heparin drip, and a vitamin regimen (melatonin, thiamine, zinc, ascorbic acid) per hospital COVID-19 protocol. Additional medications included prenatal vitamin, famotidine, calcium carbonate, and acetaminophen pro re nata.

Her acetaminophen quantity throughout the hospitalization was 1,000 mg on hospital day (HD) 1, 1,650 mg on HD 2, and 650 mg on two other occasions (HD 6, HD 10). She received her weekly 17-hydroxyprogesterone injection (for history of preterm delivery) on HD 5; however, this was subsequently discontinued.

Throughout her hospitalization she continued to symptomatically improve. While her cough was persistent, hypoxia was mostly isolated to nighttime during sleeping, requiring between 1 and 3 L per minute supplemental oxygen by nasal cannula at night. Fetal monitoring was reassuring.

On HD 5, despite symptom improvement, her liver function tests were noted to have increased, with aspartate aminotransferase (AST) of 172 and alanine aminotransferase (ALT) of 209 (►**Table 1**). Notably, baseline liver function tests prior to and at the beginning of pregnancy were within normal limits. She felt well subjectively and denied any symptoms suggestive of preeclampsia. Blood pressure remained normal. She appeared well on physical exam without hyperreflexia or abdominal discomfort.

Other notable negative laboratories included hepatitis A, B, C, and E serologies, Epstein–Barr virus, cytomegalovirus immunoglobulin M (IgM), herpes simplex virus IgM, antimitochondrial and anti-smooth muscle antibodies, antinuclear antibody, and antineutrophil cytoplasmic antibody. She had a negative immunoglobulin panel and ammonia levels within normal limits.

Her urine protein to creatinine ratio was 0.22 with a 24-hour urine protein of 319. Her creatinine, platelets, international normalized ratio, and haptoglobin remained normal.

An abdominal ultrasound suggested hepatomegaly (craniocaudal diameter 21.27 cm). Liver echogenicity was slightly increased, and liver echotexture was coarse. The gallbladder was surgically absent, and the abdominal vasculature was normal.

While her 24-hour urine protein was suggestive of mild proteinuria, the absence of elevate blood pressures or symptoms of preeclampsia made both preeclampsia and acute fatty liver disease of pregnancy unlikely.

On HD 10, a liver biopsy was performed given concern for persistently increasing transaminases, with AST max of 501 and ALT max of 1,313.

The liver biopsy showed reactive changes consistent with medication effect—prescription or over-the-counter supplement—as well as mild steatosis (►**Figs. 1** and **2**). Trichrome and reticulin stains were performed. There was no significant

Table 1 Pertinent laboratory values throughout hospital admission

	HD 1	HD 5	HD 6	HD 7	HD 8	HD 9	HD 10	HD 11	HD 12	HD 13	11 days discharge
Total bilirubin, mg/dL	1.6	1.3	1.0	1.1	1.0	1.3	1.2	1.2	0.5	0.9	0.4
Aspartate aminotransferase (AST), U/L	30	172	212	284	441	501	500	415	321	269	47
Alanine aminotransferase (ALT), U/L	30	209	337	524	846	1,115	1,313	1,336	1,093	981	105
Alkaline phosphatase, U/L	100	118	120	117	121	121	124	114	102	100	71
International normalized ratio (INR)	0.9			1.2	1.0	1.1	1.0	1.0	1.0	1.0	
Platelets	197	385	396	470	495	529	550	489	365	362	190
Fibrinogen, mg/dL	750	1,043	886	934	912	966	980	8,766	817	821	
Ferritin, ng/mL	178	623	683	568	1,036	1,159	979	757	463	366	
Lactate dehydrogenase (LDH), IU/L	198	400	342	346	380	433	406	295	257	323	

Abbreviation: HD, hospital day.

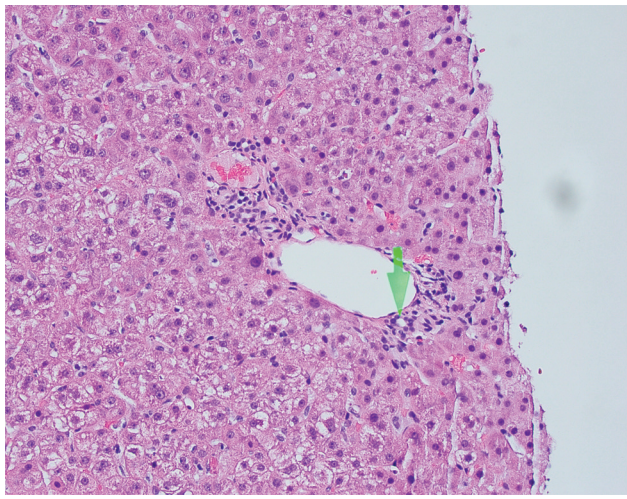

Fig. 1 Hematoxylin-eosin-stained liver biopsy showing portal tract with normal bile duct (*arrow*) (magnification ×100).

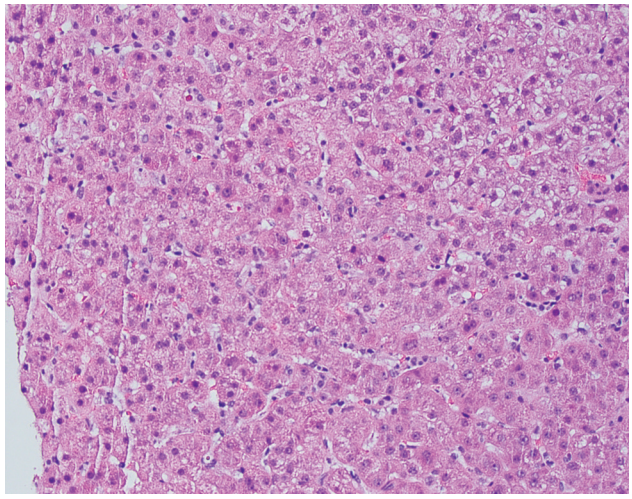

Fig. 2 Hematoxylin-eosin-stained liver biopsy showing reactive changes (magnification ×80).

fibrosis. Iron stains were negative as was the periodic acid-Schiff with and without diastase stain for α-1 antitrypsin granules.

Following the biopsy, her transaminases stabilized and as she had appeared well for several days therefore was discharged home with follow-up. Eleven days following her hospitalization her transaminases had declined and she continued to feel well.

Discussion

COVID-19 has become a global health crisis and there remain many unknowns regarding which populations are the most vulnerable and how the virus impacts different organ systems of the body.

Prior pandemics such as that from H1N1 influenza suggest higher morbidity and mortality among affected pregnant women[11]; however, current evidence is mixed regarding the relationship between pregnancy and the severity of COVID-19. Reports from early in the pandemic from China, the epicenter of the outbreak, suggested that pregnant women are not more severely affected by COVID-19.[12,13] And a study from March to April 2020 in New York City did not find higher rates of intensive care unit admission in pregnant compared with nonpregnant women.[6] However, more recently there have been several case reports demonstrating severe maternal morbidity secondary to COVID-19 in pregnancy,[5,14–18] and subsequent studies have suggested that pregnant women may be a more vulnerable population.[19]

While the lung is the primary organ affected by the virus in both pregnant and nonpregnant individuals, other organs including the liver have been found to be impacted as well, especially in more severe cases. Guan et al report incidence of elevated AST levels to be 18.2 and 39.4% of patients with nonsevere and severe disease, respectively, and incidence of elevated ALT levels to be 19.8 and 28.1% of patients with nonsevere and severe disease, respectively.[20] Data from large U.S. studies show elevated ALT is observed in approximately 39% of patients with COVID-19 infection, mostly below 80 U/L.[21,22] It is not currently known if SARS-CoV-2 causes direct liver injury or if liver injury in the setting of COVID-19 is secondary to other factors. Other proposed mechanisms of secondary liver injury as a result of COVID-19 include simultaneous use of hepatotoxic drugs, systemic inflammatory response, respiratory distress syndrome-induced hypoxia, and multiple organ failure.[8] Hepatotoxic drugs that may be administered in the setting of COVID-19 include antiviral medications, investigational drugs, or more commonly used medications such as acetaminophen. In our case, the patient had taken limited amount of acetaminophen prior to hospital admission (< 3 g/24 h) and then 1,000 mg on HD 1, 1,650 mg on HD 2, and 650 mg on two other occasions. In addition, she had received her scheduled dose of 17-hydroxyprogesterone.

There have been some reports of liver biopsies among patients with liver injury in the setting of COVID-19. One case report from a patient with severe acute respiratory distress who died from COVID-19 in China reported a liver biopsy showing moderate microvesicular steatosis and mild lobular and portal activity, consistent with either viral injury or drug-induced liver injury.[23] Other cases report liver pathologic findings of mild sinusoidal lymphocytic infiltration and sinusoidal dilatation, with some reports of multifocal hepatic necrosis as well.[10] Our case reports a liver biopsy with reactive changes consistent with medication effect as well as mild steatosis.

Some have suggested that obesity and nonalcoholic fatty liver disease (NAFLD) may be a risk factor in the development of drug-induced hepatotoxicity,[24] including acetaminophen-induced liver injury.[25] The patient presenting in our case had morbid obesity with a BMI of 45 with known radiologic evidence suggesting fatty liver on ultrasound, therefore it is possible that underlying obesity and mild NAFLD may have contributed to the acute liver injury during her COVID-19 course.

There has also been data to suggest that certain viruses such as human immunodeficiency virus and hepatitis C may

increase susceptibility for drug-induced liver disease such as secondary to acetaminophen toxicity.[26–28] It is possible that SARS-CoV-2 has a similar effect of potentiating hepatotoxic drug effects on the liver.

There remain many unknowns both about the effect of COVID-19 on pregnancy and on acute liver injury. In our case, it is likely that the liver injury with an unusual elevation of ALT above 1,000 U/L in the setting of COVID-19 is multifactorial with contribution from the virus itself, and medications with liver metabolism (acetaminophen and 17-hydroxyprogesterone) on a liver potentially already affected by preexisting fatty liver disease. This case also demonstrates the significant transaminitis that can occur in such cases. Further investigation regarding the impact of COVID-19 on the liver as well as the mechanism of action of these effects is warranted.

Conflict of Interest
None declared.

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