Presentation of Severe Acute Respiratory Syndrome-Coronavirus 2 Infection as Cholestatic Jaundice in Two Healthy Adolescents

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Liver abnormalities in severe acute respiratory syndrome-coronavirus 2 infection, including hepatitis and cholestasis, have been observed in adults and are associated with worse outcomes. We describe 2 adolescents with cholestasis and hepatitis with mild presentation of severe acute respiratory syndrome-coronavirus 2 lacking typical symptoms. Our intention is to raise index of suspicion for testing and protective equipment use.

Methods

Institutional review board approval was obtained at Albert Einstein College of Medicine. These case reports were exempt from institutional review board oversight at Feinstein Institutes for Medical Research of Northwell Health. Patients described here are unique to this report and are excluded from our registry of COVID-19 patients. Demographic information and clinical, laboratory, and imaging results were examined.

Case 1

A 16-year-old boy presented to the emergency department (ED) of the Children’s Hospital at Montefiore in the Bronx, New York, with 1 day of scleral icterus, epigastric abdominal pain, nausea, 2 episodes of nonbloody, nonbilious emesis, decreased oral intake, and dark urine. No respiratory symptoms or diarrhea were present. The patient and family reported staying at home in the preceding 3 weeks without any exposure to sick contacts, a known COVID-19 case, essential workers, or travel. Patient denied any drug or alcohol use.

His medical history was significant for elevated serum hepatic enzymes with acute cholestasis 3 years previously, secondary to cholelithiasis for which he underwent cholecystectomy. His hepatic enzymes and bilirubin level had normalized. He was found to carry reduced activity in uridine diphosphate-glucuronosyltransferase A1 gene associated with Gilbert syndrome.11
Upon arrival to the ED, he was noted to have tachycardia to 128 bpm and was afebrile. Physical examination was notable for scleral icterus, dry mucous membranes, and epigastric tenderness. He was found to have significantly elevated serum AST and ALT at 655 U/L and 767 U/L, respectively. Conjugated hyperbilirubinemia was also detected with total bilirubin/direct bilirubin at 3.6/2.2 mg/dL. Gamma-glutamyl transferase was 147 U/L. Liver synthetic function, international normalized ratio, albumin, and platelets were normal (11 and 15 U/L, respectively). Total and direct bilirubin levels were 3.4/1 mg/dL and gamma-glutamyl transferase was 147 U/L. Liver synthetic function, international normalized ratio, albumin, and platelets were normal (Table). Ultrasound examination of the liver and biliary tree was normal.

Given his prior history of cholelithiasis with cholecystectomy and concern for an obstructive process, magnetic resonance cholangiopancreatography was obtained to further assess for any anatomic abnormalities and revealed no evidence of intrahepatic or extrahepatic ductal dilatation or biliary stricture. Although he had no fever or respiratory symptoms, COVID-19 hepatitis was considered in the differential diagnosis, and his SARS-CoV-2 polymerase chain reaction test results were positive.

The patient was admitted for monitoring. No treatment targeting COVID-19 was initiated owing to a lack of supporting evidence and otherwise well-being. Airborne/special contact precautions were maintained during his hospitalization. The patient never developed respiratory or other systemic inflammatory symptoms. After 24 hours, his direct bilirubin level decreased to 0.4 mg/dL. Three weeks later, AST/ALT decreased to 47/76 U/L and total bilirubin remained elevated at 1.7 mg/dL with normal direct fraction of <0.5 mg/dL (consistent with prior diagnosis of Gilbert).

### Table. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>59.7</td>
<td>56.9</td>
</tr>
<tr>
<td>Body mass index, kg/m² (percentile)</td>
<td>23.6 (79)</td>
<td>21.2 (55)</td>
</tr>
</tbody>
</table>

Upon admission, his total bilirubin was 3.6 mg/dL, direct bilirubin was 2.2 mg/dL, gamma-glutamyl transferase was 319 U/L, AST was 655 U/L, ALT was 767 U/L, alkaline phosphatase was 259 U/L, albumin was 4.8 g/dL, platelet count was 244 k/μL, international normalized ratio was 1.1, white blood cell count was 4.0 k/μL, absolute lymphocyte count was 1240 cells/μL, C-reactive protein was <0.5 mg/dL, and lipase was 43 U/L.

### Case 2

A 17-year-old previously healthy young woman presented to the ED at Cohen Children’s Medical Center in New York’s Nassau County with 4 days of fever, acute onset of jaundice, and dark urine. She had developed urinary urgency without fever or dysuria 6 days before presentation. She was seen at a clinic, where a urine culture was obtained that was negative. Four days before presentation, her urine turned dark orange/brown and she developed fever with maximum temperature of 103°F. She also complained of chills and night sweats, and had an episode of nonbloody diarrhea. On the day of presentation, she noted that the whites of her eyes seemed to be yellow. No respiratory symptoms (cough, congestion, and/or difficulty breathing) were present. She had no abdominal pain, nausea, or vomiting. She no longer experienced urinary urgency or dysuria. There was no prior history of cholestasis, jaundice, or liver disease. She denied any drug or alcohol use. She confirmed no exposure to a case of COVID-19 or recent travel.

In the ED, she had tachycardia to 111 bpm and was afebrile. Physical examination revealed a nonobese female with scleral icterus without abdominal tenderness. Laboratory test results revealed elevation of serum AST and ALT to 154 and 294 U/L, respectively. One month prior, AST and ALT levels obtained during annual physical examination were normal (11 and 15 U/L, respectively). Total and direct bilirubin levels were 3.4/1 mg/dL and gamma-glutamyl transferase was 147 U/L. Liver synthetic function, international normalized ratio, albumin, and platelets were normal (Table).

An abdominal ultrasound examination revealed hepatomegaly (16.1 cm span) with normal echogenicity and without any gallstones, sludging, or bile duct dilation. SARS-CoV-2 polymerase chain reaction test on nasal specimen was positive. She was discharged home from the ED with close follow-up. Two weeks later, serum AST and ALT levels were 56 and 147 U/L respectively, with total and direct bilirubin levels of 0.6/0.2 mg/dL.

### Discussion

Mild cholestasis in COVID-19 was described in a pediatric patient from Wuhan, China. A 55-day-old infant with pneumonia and acute cardiac injury developed mild hepatitis (AST/ALT of 100/84 IU/L) and conjugated hyperbilirubinemia (total bilirubin/direct bilirubin 2/1.4 mg/dL), which resolved with clinical improvement.

The incidence of liver injury in adult patients with COVID-19 can range from 14.8% to 78.0%. One study of adults with severe COVID-19 admitted to the intensive care unit did not report a significant difference in percentage of patients with liver dysfunction between survivors and nonsurvivors, although biochemical test results of the nonsurvivors showed more abnormalities.

The cause of liver injury can be multifactorial, from drug-induced liver injury (owing to use of antiviral or antibiotic agents, corticosteroids, and natural remedies), hepatic...
congestion associated with high positive end-expiratory pressure, and/or direct liver damage by virus-induced T lymphocytes.\(^9,14\) High levels of proinflammatory cytokine molecules were found in patients with COVID-19 activating T-helper 1 cell response and inducing dysregulation of the innate immune response.\(^9,14\) A postmortem liver biopsy obtained in a patient with COVID-19 from Wuhan, China, demonstrated moderate microvesicular steatosis and mild lobular and portal activity, indicating either virus- or drug-induced liver injury.\(^9,15\)

Recent evidence indicates that angiotensin converting enzyme II is likely the cell receptor of SARS-CoV-2.\(^16,17\) Chai et al were able to identify expression of angiotensin converting enzyme II within bile duct epithelial cells (cholangiocytes), but not hepatocytes in healthy liver tissues.\(^18\) Cholangiocytes are known to play an important role in liver regeneration and immune response, which could be a mechanism underpinning acute cholestasis we observed.\(^19\)

In our 2 cases of acute cholestasis with hepatitis, the patients lacked typical features of COVID-19 such as fever, cough, shortness of breath, myalgia, sore throat, or significant gastrointestinal symptoms, as well as any signs of inflammatory dysregulation seen in multisystem inflammatory syndrome in children.\(^4,20\) Both patients were nonobese adolescents without underlying liver disease or other comorbidities.

Our patients had a mild clinical course. Extensive evaluation for cholestasis may not be necessary in otherwise healthy pediatric patients with SARS-CoV-2 infection. Imaging can be limited to those with symptoms concerning for biliary obstruction. Further studies are needed to ascertain whether a higher rate of cholestasis is associated with SARS-CoV-2 infection in children and adolescents. Recognition and identification of children and adolescents with acute cholestasis secondary to SARS-CoV-2 is important for management, appropriate infection control and proper use of personal protective equipment.

Submitted for publication Jun 29, 2020; last revision received Jul 11, 2020; accepted Jul 17, 2020.

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References


