CASE REPORT

Fulminant Hepatic Failure in a SARS-CoV-2 Positive Pediatric Patient: A Case Report

Jerrymae R. Blasurca, M.D.
Jaime A. Santos, M.D.
Maria Anna P. Bañez, M.D
Fatima I. Gimenez, M.D.
Mary Antonette C. Madrid, M.D.

Philippine Children's Medical Center

Correspondence:
Dr. Jerrymae R. Blasurca
Email: ipcc.pcmc@yahoo.com

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ABSTRACT

Respiratory symptoms are the most common manifestation of COVID-19 across all age groups and it is most often associated with radiographical findings consistent with pneumonia.[2] A recent systematic review estimated that 16% of children with SARS-CoV-2 infection are asymptomatic,[3] or others may present with seizures, gastrointestinal bleeding or jaundice. This reports a 2-year old boy with no known co-morbidity who had a 2-week history of abdominal pain and jaundice then had a rapidly progressive course of neurological deterioration and eventual demise. He had markedly elevated liver enzymes and deranged bleeding parameters with elevated ammonia and ferritin levels. Hepatitis B and hepatitis A titers were non-reactive. He was managed as a case of hepatic encephalopathy secondary to cholestatic jaundice. His chest x-ray was normal but his SARS-CoV-2 RT PCR result was positive with a low cycle threshold. Locally, this is the first reported case of SARS-CoV-2 RT-PCR positive pediatric patient presenting as fulminant hepatic failure with no associated respiratory manifestations. Clinicians should be mindful that such presentation, however uncommon, is possible and a high index of suspicion should be maintained.

KEYWORDS: *COVID-19, SARS-CoV-2, hepatic failure, fulminant hepatitis, case report*

INTRODUCTION

According to the Philippines' Department of Health (DOH) data as of February 11, 2021, around 9.7% of COVID-19 cases are of the pediatric population.[1] Respiratory symptoms are the most common manifestation of COVID-19 across all age groups and it is most often associated with radiographical findings consistent with pneumonia.[2] A recent systematic review estimated that 16% of children with SARS-CoV-2 infection are asymptomatic,[3] or some may present with seizures, gastrointestinal bleeding or jaundice. Other typical manifestations since this disease emerged last December 2019 include fever, diarrhea, weakness and fatigue.[4] However, in our institution's experience, a tertiary pediatric referral center, the manifestations in children are varied. One rare manifestation we encountered is jaundice with a rapidly progressive course causing fulminant hepatic failure. Infected children are reported to have a milder disease course and a better prognosis than adults[5]. The incidence ranges from 5%-22% of pediatric patients with laboratory-confirmed COVID-19 exhibiting only mildly elevated liver enzymes[6,7] In this case though, we report a child with fulminant hepatic failure who tested positive for SARS-CoV-2.

CASE REPORT

This is a case of a 2-year-old boy presenting with irritability, abdominal pain, and jaundice of 2 weeks duration.

14 days prior to admission, he had intermittent generalized abdominal pain accompanied by development of icteric sclerae. He had no fever, changes in bowel habits, abdominal distention nor vomiting. His abdominal pain would be relieved spontaneously hence no medications were given.

12 days prior to admission, he was brought to a pediatrician due to the persistence of symptoms. He was assessed to have hepatitis A. Laboratories were requested which were not complied with. No medications were given.

7 days prior to admission, he still had persistence of abdominal pain and jaundice. Work-up was done revealing: elevated liver transaminases [ALT (3,378U/L), AST (4,010.05U/L)], and bilirubin levels: total bilirubin 11.62mg/dL, direct bilirubin 10.87mg/dL, indirect bilirubin 0.76mg/dL. Abdominal ultrasound showed minimal ascites, hepatosplenomegaly, and a thickened gallbladder wall. Telemedicine consult was done with the pediatrician and he was given unrecalled medications. In the interim, there was progression of jaundice and note of acholic stools and tea-colored urine. He remained afebrile and active with good appetite.

4 days prior to admission, with the progression of symptoms, he was brought to a hospital. The patient and his mother adhered to minimum infection control measures and wore masks and face shields during the entire time. HBsAg, anti-HBe, HBeAg, total anti-HBc, anti-HAV IgM results were nonreactive and anti-HBs was reactive. Protime was 23.9 sec, INR 1.68, percent activity 52%. Further work-up including serum ceruloplasmin, serum copper levels, ANA, anti-smooth muscle antibody, anti-LKMI, and liver biopsy were requested. The patient was assessed by a gastroenterologist to have viral hepatitis versus Wilson's disease. Ursodeoxycholate was started and they were advised admission but because of financial constraints, the patient was lost to follow-up. 3 days after, there was further progression of jaundice, persistence of abdominal pain and the patient became irritable, hence he was brought to our medical center and subsequently admitted.

He was born full term in a lying-in clinic with no feto-maternal complications and was discharged well after 24 hours of life. He was breastfed and given milk formula since birth and currently consumes table food prepared by his mother. His neurodevelopmental milestones were at par with age. He has completed his primary childhood immunizations from a health center that included BCG, 3 doses of hepatitis B vaccine, DPT, polio and Hib vaccines and a dose of measles vaccine. He had no known past illnesses, no previous hospitalizations and no heredo-familial diseases including liver diseases nor jaundice. There was no intake of paracetamol or other hepatotoxic drugs. He is the only child and his parents denies having any flu-like illness nor exposure to any COVID-confirmed case for the past 2 weeks. His father works as a private driver and his mother is a production operator. They use purified water for drinking and, due to the pandemic, buys food from a local supermarket while observing strict social distancing and wearing of masks.

At the Emergency Department, the patient was alert, irritable but consolable. He was afebrile, normotensive, with stable vital signs, no desaturations at

room air. There was generalized jaundice. No rashes, pruritus nor bleeding were noted. Cardio-pulmonary examination was essentially normal. The abdomen was flat, soft, with a palpable, non-tender liver at 4cm below right subcostal margin midclavicular line and a palpable non-tender spleen at 2-3cm on the left upper quadrant. The abdomen was negative for fluid wave. There were no palpable lymph nodes. He was managed as a case of hepatic encephalopathy secondary to cholestatic jaundice, to rule out Wilson's disease. Intravenous fluid was started. He was given vitamins A, D, E, K, zinc and ursodeoxycholate. Other laboratory tests including serum ceruloplasmin, alpha-1 anti-trypsin, urine toxicology screening were requested however were not done immediately due to financial constraints. A schedule for liver biopsy was requested. 2 units of fresh frozen plasma were secured. Twelve hours into admission, he was observed to be more irritable and agitated.

Other laboratory test results were: chest radiograph was normal, complete blood count: white blood cell 6.9 x 10^9/l, segmenters 0.55, lymphocyte 0.37, platelet count 216; ALT 4,320 (86x elevated), AST 7,282 (123x elevated), alkaline phosphatase 433 (3.4x elevated), total bilirubin 41.2 mg/dL, direct bilirubin 33.7 mg/dL, indirect bilirubin 7.6 mg/dL (3x elevated), protime 54.7 sec, INR 4.42, APTT 53.0 sec. Direct Coomb's test was negative and reticulocyte count was 13.1 (8x elevated). CRP <5mg/dl and procalcitonin was 0.463 ug/l. Blood culture was negative.

On the 36th hour after admission, he had decreased sensorium with a Glasgow Coma Scale (GCS) of 11 (E4V2M5) and developed fever (38.6-39°C). His ammonia level was at 105 umol/L (3.2x elevated) on admission and further elevated to 323 umol/L (10x elevated) hence metronidazole and cefotaxime were started.

On the 40th hour of admission, a repeat chest x-ray was done that still showed normal results. Due to persistent fever with changes in sensorium, SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (RT-PCR) nasopharyngeal and oropharyngeal swab samples were obtained. Serum ferritin was elevated at 3,957 ng/ml (9.8x) and LDH 1,583 U/L (6.4x elevated). IVIG was given at 1g/kg/dose x 1 dose. Despite medical and supportive measures, the patient's sensorium further decreased with development of bradycardia. He was transferred to the COVID-19 ward and required intubation but the patient eventually expired on the 48th hour of admission with a final diagnosis of indeterminate fulminant hepatic failure.

The RT-PCR for SARS-CoV-2 results came in 3 days after the patient's demise revealing a positive result for SARS-CoV-2 with a cycle threshold value of 15.59. Patients in the same room who were exposed to him were swabbed 5 days after exposure and all revealed negative results. His parents were referred to their regional epidemiologic surveillance unit and the mother also tested positive for SARS-CoV-2 on RT-PCR, but remained asymptomatic.

Parents did not consent to an autopsy. Consent to submit this case for publication was obtained from the parents.

DISCUSSION

We report a pediatric case of fulminant hepatic failure in a SARS-CoV-2 patient. ACE2 receptors are known to be found on type 2 alveolar cells, and up to 59.7% of cholangiocytes, and less commonly, hepatocytes (2.6%).[8] SARS-CoV-2, like SARS-CoV, bind to the angiotensin-converting enzyme 2 (ACE2) receptor to enter target cells,[9] where the virus replicates and subsequently infects other cells in the upper respiratory tract and lung tissue. It is reasonable to consider then that SARS-CoV-2 can bind to the ACE2 receptors of cholangiocytes inducing direct injury to bile ducts, acute liver injury, and even cause acute fulminant hepatitis. A loss of hepatocyte function sets in motion a multiorgan response, characterized by hepatic encephalopathy, a complex coagulopathy, derangements in intrahepatic metabolic pathways, rapid deterioration and hemodynamic disturbances.[9] All of which were reflected in our patient's clinical course. The patient's elevated liver profile may also reflect a direct virus-induced cytopathic effect and/or immune damage from the provoked inflammatory response. Because of the unusual manifestations of COVID-19, and it being a novel virus, it should be ruled out as one of the causes of acute hepatic failure especially in the pediatric age group.

Our patient was a previously well-child with no known co-morbid conditions. The initial presentation was not typical for COVID-19. Viral infections other than SARS-CoV-2, are the most common causes of acute hepatic failure.[10] Work-up for hepatitis A and B were

negative in this case but ideally further work-up to rule out other viruses such as-hepatitis C, E, Epstein-Barr Virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV 1), HSV 2, and human immunodeficiency virus (HIV) should be done. These were not done due to the patient's rapid deterioration. Clinically though, the patient didn't present with abdominal distention, lymphadenopathies, skin nor mucocutaneous lesions that are commonly seen in EBV, CMV, HSV. Considering the patient's age and rapid clinical course, these were also not consistent with the other viral organisms mentioned above.

Wilson's disease, an autosomal recessive disorder of copper metabolism, cannot be excluded in children presenting with hepatic involvement using commonly practiced clinical and laboratory parameters.[11] Due to limited resources and time, serum ceruloplasmin, copper level, slit-lamp exam to check for Kayser-Fleischer ring and liver scan were not performed. The absence of liver disease in both the maternal and paternal side makes the diagnosis of Wilson's disease less likely.

Adult patients with severe COVID-19 have a higher rate of liver dysfunction and infected children were reported to have a milder disease course and a better prognosis.[5] Qiu et al analysed 36 pediatric patients (aged 0-16 years) with laboratory-confirmed COVID-19 in three hospitals in Zhejiang and they recorded only 2 children with elevated liver enzymes.[6] Moreover, in a report involving 31 cases of SARS-CoV-2 infected children, only 22.2% of patients had elevated transaminases levels, being the highest value for ALT and AST were 68 U/L and 67 U/L respectively.[7] In contrast to our case, which revealed ALT at 4,320 U/L (86x elevated) and AST at 7,282 U/L (123x elevated). An autopsy would have helped in the definitive diagnosis; however, the relatives did not consent. Of note, is a study by Bangash et al of liver injury of COVID-19 patients which indicated that post-mortem liver biopsy of COVID-19 patients showed only steatosis, which is common in patients with sepsis.[12]

There have been two case reports on children treated for acute fulminant hepatic failure in the context of COVID-19 but these cases had respiratory symptoms and chest CT scan findings of pneumonia[13,14] in contrast to our patient who didn't present with any respiratory symptoms and had normal chest radiograph results.

Our patient tested positive for SARS-CoV-2 and the ORF1ab cycle threshold (Ct) value was 15.59. Ct values and culture positivity rates were reported to have a significant relationship. It was La Scola et al., who reported that culture positivity rate was shown to be inversely proportional with Ct values. The samples with Ct values of 13 to 17 all led to positive culture; whereas at Ct value of >34, no culture was obtained.[15] The data above may indicate that the lower Ct value of our patient may be associated with his worse course of illness and outcome. Likewise, the mother also testing positive for SARS-CoV-2 RT-PCR makes a false positive result for our patient less likely.

CONCLUSION

This is the first reported pediatric case of fulminant hepatic failure in a SARS-CoV-2 positive patient without respiratory manifestations. Clinicians should be mindful that such presentation, however uncommon, is possible and a high index of suspicion should be maintained. Although literature reports a good prognosis or outcome for children with COVID-19, unusual manifestations with poor prognosis can happen.

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