Received: 12 June 2023 | Accepted: 18 February 2024

DOI: 10.1002/jpr3.12065

JPGN REPORTS

CASE REPORT

Hepatology

Coronavirus HKU1 infection and development of pediatric acute liver failure with immune dysregulation phenotype

Arun Ajmera[1] | **Peter Joseph Pernicone**[2] | **Nishant Patel**[1] | **Stefany Hernandez Benabe**[3]

[1]Center for Digestive Health and Nutrition, Arnold Palmer Hospital for Children, Orlando, Florida, USA

[2]Advent Health at Orlando, Advent Health for Children, Orlando, Florida, USA

[3]Advent Health Medical Group Pediatric Gastroenterology at Orlando, Advent Health for Children, Orlando, Florida, USA

Correspondence

Arun Ajmera, Center for Digestive Health and Nutrition, Arnold Palmer Hospital for Children, 60 W Gore St, Orlando, FL 32806, USA.
Email: Arun.ajmera@orlandohealth.com

Funding information
None

Abstract

Pediatric acute liver failure is a rare but serious complication of Coronavirus infections. Our patient is a previously healthy 8-year-old male who presented with acute liver failure in the setting of human coronavirus HKU1 (HCoV-HKU1) infection while asymptomatic from a respiratory perspective. During the hospital course, he developed acute hepatic encephalopathy and was listed for liver transplantation, but fortunately recovered remaining status 7 (inactive) on the transplant list. With a negative diagnostic evaluation other than his viral infection and hyperdense CD8 T-cells on liver immunohistochemical staining, pediatric acute liver failure (PALF) immune dysregulation phenotype was diagnosed.

KEYWORDS

abnormal liver enzymes, acute hepatitis, coagulopathy, direct hyperbilirubinemia, hyperimmune liver disease, coagulopathy, direct hyperbilirubinemia

1 | INTRODUCTION

Coronaviruses (CoVs) are single-stranded RNA viruses found in a wide variety of animals.[1] Human coronavirus HKU1 (HCoV-HKU1) was the fourth HCoV discovered,[1] first noted in a Chinese adult with pneumonia, and most closely related to a murine hepatitis virus.[2,3] In 2006, HCoV-HKU1 was novel, but retrospective analysis from earlier years found nine out of 851 children in the Western Hemisphere with infection suggesting worldwide distribution.[3] Moreover, two of the nine children developed extrapulmonary conditions: one with seizures, and the other acute hepatitis without liver failure.[3]

HCoV-HKU1, like other CoVs, is associated with an upper and/or lower respiratory tract infection that is indistinguishable from other respiratory viruses.[3] In the early 2000s, upper respiratory tract infections caused by CoVs such as HCoV-OC43 and HCoV-NL-63 were discovered creating moderate clinical impact,[3] but the identification of severe acute respiratory syndrome associated with coronavirus (SARS-CoV) in 2002–2003 led to renewed interest in CoV with HCoV-HKU1.[4] Recently, the seventh HCoV, SARS-CoV-2 emerged in 2019–2022 leading to severe pandemic morbidity and mortality.[5,6]

We report a rare case of HCoV-HKU1 in a patient with pediatric acute liver failure (PALF) with no known respiratory symptoms.

2 | CASE REPORT

An 8-year-old previously healthy boy presented with 1 week of abdominal pain, jaundice, and choluria. At presentation, he had scleral icterus, right upper quadrant tenderness with hepatosplenomegaly, and a distended abdomen. Lungs were clear throughout to auscultation bilaterally, and vital signs were within normal range for age. Laboratory evaluation revealed

TABLE 1 Additional initial laboratory parameters and imaging in the patient.

Laboratory parameters	Value
Infectious	
Blood cultures	No growth
Adenovirus PCR	Negative
Parvovirus PCR	Negative
HSV 1, 2, and 6 PCR	Negative
Hepatitis E IgM/IgG	Negative
Enterovirus antigen PCR	Negative
Cytomegalovirus PCR	Negative
Epstein Barr virus PCR	Negative
Urinalysis	Normal
Human immunodeficiency virus (HIV)	Negative
SARS-CoV-2 PCR	Negative
Respiratory pathogen profile (Including Adenovirus, Coronavirus 229E, Coronavirus NL63, Coronavirus OC43, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A, Influenza A/H1, Influenza A/H1-2009, Influenza A/H3, Influenza B, Parainfluenza virus 1/2/3/4, Respiratory Syncytial Virus, Bordetella parapertussis, Bordetella pertussis, Chlamydia pneumoniae, Mycoplasma pneumoniae)	Negative
Auto-immune	
Antinuclear antibody (ANA)	Negative
Soluble liver antigen	Negative
Antineutrophil cytoplasmic antibody (ANCA)	Negative
Liver–kidney microsomal (LKM) antibody	Negative
LKM-1	Negative
Smooth muscle antibody	Negative
Other	
Triglycerides	158 mg/dL (elevated)
Ferritin	427 µg/L (elevated)
Soluble IL-2 receptor	7812 U/mL (elevated)
Fibrinogen	171 mg/dL (low)
Thyroid studies (TSH/FT4)	Normal
IgG	Normal
IgA	Normal
Alpha-1 antitrypsin phenotype and level	M1M1 phenotype, 196 mg/dL (normal)
Echocardiogram	Normal cardiac anatomy

Abbreviations: IgA, immunoglobulin A; IgG, imunoglobulin G; IL-2, interleukin-2; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome associated with coronavirus 2.

normal hemoglobin and hematocrit with thrombocytosis (platelets of 525,000/µL). He had elevated aspartate aminotransferase (AST) of 4407 units/L and alanine transaminase (ALT) of 2587 units/L with normal serum glucose, albumin, blood urea nitrogen (BUN), and creatinine. Total bilirubin was 19.6 mg/dL with a direct bilirubin fraction of 15.8 mg/dL and gamma-glutamyltransferase (GGT) of 87 U/L. International normalized ratio (INR) was 2.3 with prolonged prothrombin time (PT) of 26.6 s and partial thromboplastin time (PTT) of 37.6 s. Elevated serum ammonia level of 91 µmol/L was noted in the patient with normal mental status.

Further laboratory evaluation revealed a normal serum lipase, a negative toxin screen with a negative serum acetaminophen level, and a normal serum ceruloplasmin level. Infectious studies for hepatitis A, B, and C were negative. The soluble interleukin-2 (IL-2) receptor was elevated. A respiratory pathogen profile was considered due to the diagnostic possibility of a Coronavirus or Adenovirus accounting for the severe acute liver disease in a patient without any respiratory distress.[5–7] The profile proved to be positive for HCoV-HKU1. Additional studies are shown in Table 1. Abdominal ultrasound with Doppler revealed hepatosplenomegaly without intrahepatic biliary ductal dilation. There was mild dilation of the portal vein with the appropriate directional flow and patent hepatic vasculature. There was a nonspecific thickened gallbladder wall (9.6 mm) with edema and trace pericholecystic fluid without gallstones or biliary duct dilation. Liver biopsy (Figure 1A) revealed acute hepatitis characterized by pan-zonal inflammation with a mixed inflammatory infiltrate of lymphocytes, neutrophils, eosinophils, and apoptotic hepatocytes. Hepatocyte injury with associated collagen fiber condensation were noted on trichrome and reticulin stains. No advanced fibrosis was identified. Immunohistochemical stains for CD8 showed approximately 70% CD8-positive T cells. A stain for CD103 demonstrated reactivity in approximately 10% of lymphocytes.

He was treated with 5 mg of Vitamin K daily and Ursodiol 10 mg/kg/dose twice daily for 21 days.

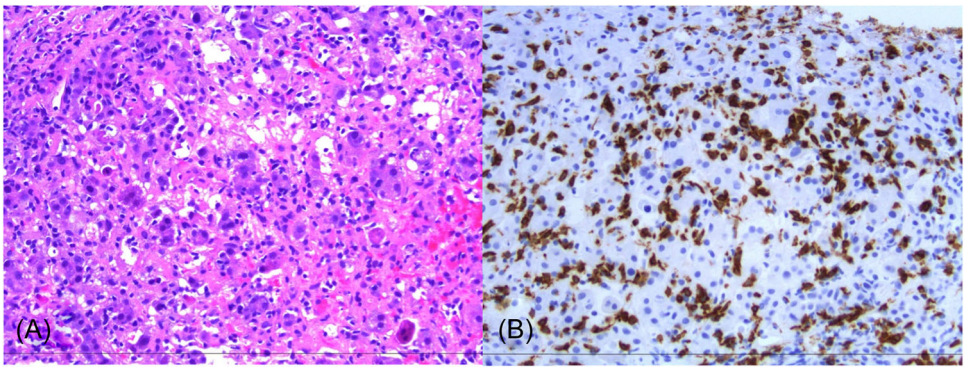

FIGURE 1 Liver biopsy. (A) Acute hepatitis with apoptotic hepatocytes (lower right). Hematoxylin and eosin stain; original magnification ×200. (B) Immunohistochemical stain for CD8 showing hyperdense CD8 + T-cells. Original magnification ×200. Electron micrography images are not available.

Hyperammonemia was treated with Lactulose 90 mL oral divided 3 times daily. Unfortunately, his liver synthetic function deteriorated with worsening INR (5.9), and he developed stage 3 hepatic encephalopathy requiring intubation. Head computed tomography (CT) showed no edema, hemorrhage, or infarct. He was listed for liver transplantation and started Methylprednisolone 10 mg/kg/day for 2 days with subsequent steroid wean and received intravenous antithymocyte globulin 1.5 mg/kg for 4 days as treatment for hyperimmune dysregulation. His clinical course was complicated with ascites requiring intravenous diuretics and 25% albumin infusions (albumin < 3 g/dL). As liver synthetic function normalized, he transitioned to status 7 (inactive) on the transplant list. He remained afebrile throughout his clinical course and was discharged home after 23 days in the hospital.

3 | DISCUSSION

Prior publications have highlighted patient response to immunosuppressive therapy, primarily corticosteroids, in cases of indeterminate PALF.[8,9] Indeterminate PALF has been historically hypothesized to be a response to primary immune-mediated liver injury in the setting of immune dysregulation.[10–12] Viral infection is suspected to have provoked immune dysregulation as our patient had a negative diagnostic evaluation in the setting of hyperdense CD8 T-cells on liver immunohistochemical staining and an elevated soluble IL-2 receptor (Figure 1B and Table 1, respectively).[13,14] Previous studies have revealed hepatic involvement in other CoVs, such as SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2.[5,6,15–17] Pediatric acute liver failure has recently been associated with adenovirus serotype 41 in a few of these children.[6,7] However, more research is needed to determine the incidence and mechanisms of extrapulmonary manifestations of HCoV-HKU1 infection.

In conclusion, to our knowledge, this is the first report of a patient with PALF secondary to HCoV-HKU1 infection. The report highlights a case of pediatric liver failure immune dysregulation phenotype based on appropriate laboratory, immunologic, and histopathologic studies to rule out other viral, metabolic, immunologic, or congenital diseases. In this setting, prompt recognition and aggressive management of acute liver failure with immunosuppression may lead to favorable outcomes.

ACKNOWLEDGMENTS

The authors have no funding to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The patient of the case report and their parents are aware of the intent to publish and have agreed to it. We have obtained signed informed consent and have archived it.

ORCID

Arun Ajmera https://orcid.org/0009-0007-2640-8070

REFERENCES

1. Woo PCY, Lau SKP, Yip CCY, Huang Y, Yuen KY. More and more coronaviruses: human coronavirus HKU1. *Viruses*. 2009; 1:57-71.
2. Woo PCY, Lau SKP, Chu CM, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. *J Virol*. 2005;79: 884-895.
3. Esper F, Weibel C, Ferguson D, Landry ML, Kahn JS. Coronavirus HKU1 infection in the United States. *Emerging Infect Dis*. 2006;12:775-779.
4. McIntosh K. Coronaviruses in the limelight. *J Infect Dis*. 2005;191:489-491.
5. Antala S, Diamond T, Kociolek LK, Shah AA, Chapin CA. Severe hepatitis in pediatric coronavirus disease 2019. *J Pediatr Gastroenterol Nutr*. 2022;74:631-635.

6. Kelgeri C, Couper M, Gupte GL, et al. Clinical spectrum of children with acute hepatitis of unknown cause. *N Engl J Med*. 2022;387:611-619.
7. Gutierrez Sanchez LH, Shiau H, Baker JM, et al. A case series of children with acute hepatitis and human adenovirus infection. *N Engl J Med*. 2022;387:620-630.
8. DiPaola F, Grimley M, Bucuvalas J, et al. Pediatric acute liver failure and immune dysregulation. *J Pediatr*. 2014;164:407-409.
9. McKenzie RB, Berquist WE, Nadeau KC, et al. Novel protocol including liver biopsy to identify and treat CD8+ T-cell predominant acute hepatitis and liver failure. *Pediatr Tranplant*. 2014;18:503-509.
10. Bucuvalas J, Filipovich L, Yazigi N, et al. Immunophenotype predicts outcome in pediatric acute liver failure. *J Pediatr Gastroenterol Nutr*. 2013;56:311-315.
11. Antoniades CG, Berry PA, Wendon JA, Vergani D. The importance of immune dysfunction in determining outcome in acute liver failure. *J Hepatol*. 2008;49:845-861.
12. Alonso EM, Horslen SP, Behrens EM, Doo E. Pediatric acute liver failure of undetermined cause: a research workshop. *Hepatology*. 2017;65:1026-1037.
13. Chapin CA, Burn T, Meijome T, et al. Indeterminate pediatric acute liver failure is uniquely characterized by a CD103+ CD8+ T-cell infiltrate. *Hepatology*. 2018;68:1087-1100.
14. Kulkarni S, Chapin CA, Alonso EM, Rudnick DA. An update on pediatric acute liver failure. *Clin Liver Dis*. 2022;26:461-471.
15. Alsaad KO, Hajeer AH, Al Balwi M, et al. Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection - clinicopathological and ultrastructural study. *Histopathology*. 2018;72:516-524.
16. Chau TN, Lee KC, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology*. 2004;39:302-310.
17. Cates J, Baker JM, Almendares O, et al. Paediatric acute hepatitis of unknown aetiology: a national surveillance investigation in the USA during 2021 and 2022. *Lancet Child Adolesc Health*. 2023;7:773-785.

How to cite this article: Ajmera A, Pernicone PJ, Patel N, Benabe SH. Coronavirus HKU1 infection and development of pediatric acute liver failure with immune dysregulation phenotype. *JPGN Rep*. 2024;5:204-207. doi:10.1002/jpr3.12065