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Pediatric Acute Liver Failure Due to Type 2 Autoimmune Hepatitis Associated With SARS-CoV-2 Infection: A Case Report

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Abstract: Although elevated liver enzymes are common in hospitalized children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, pediatric acute liver failure is an uncommon manifestation of COVID-19 disease. We describe the case of a 3-year-old previously healthy female who developed acute liver failure secondary to type 2 autoimmune hepatitis preceded by mild infection with SARS-CoV-2. Testing for viral hepatitis was negative, and the patient did not meet diagnostic criteria for multisystem inflammatory disease in children (MIS-C). A liver biopsy showed acute submassive hepatocyte necrosis with brisk CD3+ T lymphocyte infiltration and no evidence of fibrosis or chronic liver disease. Treatment with high-dose methylprednisolone resulted in rapid normalization of alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR), and ammonia levels, and liver transplantation was avoided. This case highlights a possible association between SARS-CoV-2 infection and subsequent development of autoimmune liver disease presenting with acute liver failure.

Key words: COVID-19, acute liver failure, autoimmune hepatitis

INTRODUCTION

Hepatic involvement is common in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or COVID-19, with abnormal liver biochemistries occurring in 15% to 65% of adult patients (1) and in 6% to 27% of pediatric patients (2). However, severe liver injury, cholestasis, or liver synthetic dysfunction is rare, especially in those without underlying liver disease or without severe systemic disease (1,2). There are two case reports of COVID-19 presenting as isolated acute liver failure, one in a 35-year-old female with known systemic lupus erythematosus (3) and the other in an 11-year-old male (4), although neither report identified a cause of liver failure in addition to SARS-CoV-2 infection. We report the first case of a pediatric presentation of isolated acute liver failure 3 weeks after resolution of mild symptomatic COVID-19 infection. Laboratory and histologic examination was consistent with type 2 autoimmune hepatitis (AIH).

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CASE REPORT

A previously healthy nonobese 3-year-old female presented with fatigue and jaundice. Three weeks prior, she had been diagnosed with SARS-CoV-2 infection by nasopharyngeal polymerase chain reaction (PCR) and experienced mild fever and cough. She received no medications, did not require hospitalization, and symptoms resolved in 5 days. Two weeks later, she developed fatigue, jaundice, and decreased urination, prompting a referral to the emergency department. She was not receiving any medications and had no previous surgeries, underlying chronic liver disease, or other chronic medical conditions. Family history was notable for Hashimoto's thyroiditis and type 1 diabetes mellitus in a first-degree relative. Physical examination was remarkable for scleral icterus, jaundice,

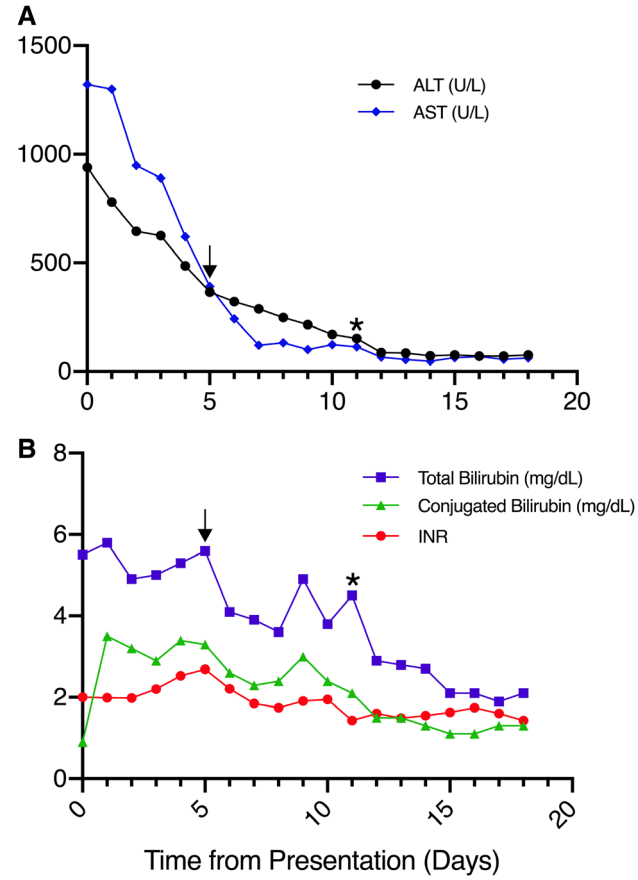

FIGURE 1. Laboratory values from time of presentation (time 0) to 20 days. ALT and AST (A) and total bilirubin, conjugated bilirubin and INR (B) over the first 20 days of illness are shown. Treatment initiation with methylprednisolone is designated with an arrow. *Indicates date of diagnostic liver biopsy. ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio.

no hepatosplenomegaly, and normal mental status. Laboratories obtained at the emergency department revealed elevated levels of ALT 939 U/L (normal 0–35 U/L), AST 1321 U/L (normal 15–46 U/L), total bilirubin 5.5 mg/dL, conjugated bilirubin 0.9 mg/dL, and INR (2.0); her ammonia level was 46 µmol/L. The complete blood count (CBC) was unremarkable with a white blood cell count of 12,300/µL, hemoglobin of 11.8 g/dL, and platelet count of 174,000/µL. There was evidence of mild hemolytic anemia with elevated lactate dehydrogenase of 1292 U/L and an undetectable haptoglobin (<3 mg/dL). Both a SARS-CoV-2 nasopharyngeal PCR test as well as anti-SARS-CoV-2 immunoglobulin G (IgG) and immunoglobulin M antibodies were positive. No specific treatment was given for SARS-CoV-2 at this time because of the lack of proven antiviral therapy in this age group. The patient did not fulfill diagnostic criteria for multisystem inflammatory syndrome in children (MIS-C) as she had a normal serum C-reactive protein, erythrocyte sedimentation rate, ferritin, lactate dehydrogenase, creatine kinase, and troponin (5). An abdominal ultrasound with doppler showed diffusely heterogenous hepatic parenchyma consistent with hepatocellular disease, borderline splenomegaly, and normal vasculature. The patient was given 5 mg of oral vitamin K without improvement of her INR and was transferred to our institution given the concern for acute liver failure.

The patient continued to receive intravenous vitamin K and intravenous fluids. Further evaluation for the etiology of her acute liver failure revealed elevated antiliver-kidney-microsomal antibody (anti-LKM) titer of 1:1280, suggestive of type 2 autoimmune hepatitis. Total serum IgG level was normal at 1070 mg/dL. The remainder of her work-up was unremarkable including thorough evaluation for infectious (see Supplemental Digital Content Table 1, http://links.lww.com/PG9/A83), metabolic, and genetic causes. Immunologic evaluation showed a decreased natural killer cell function and increased frequency of CD3+ T-cells, but a normal ferritin and soluble-IL-2

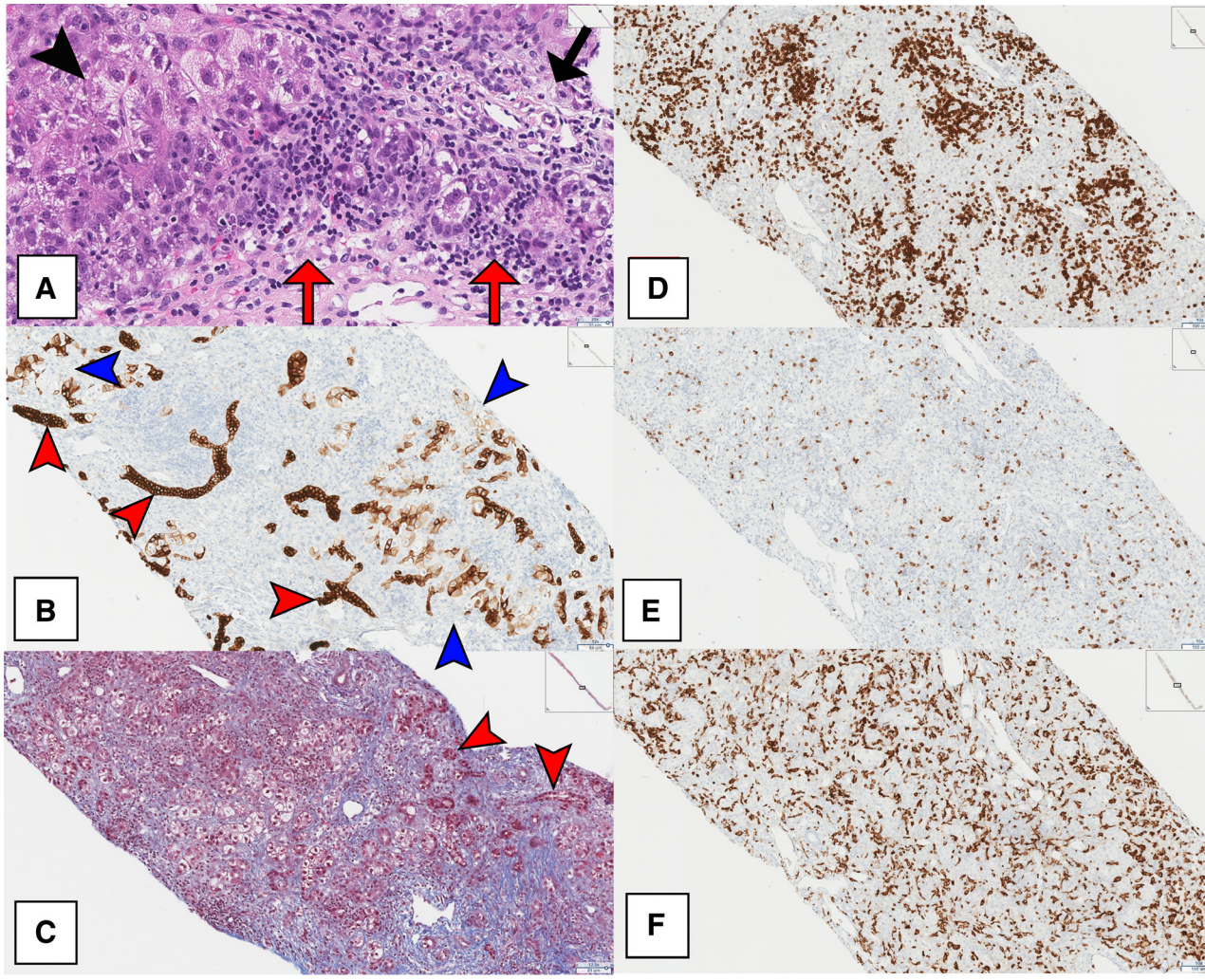

FIGURE 2. Diagnostic liver biopsy highlights massive CD3+ T cell infiltration and acute submassive necrosis. A) Acute submassive hepatocellular necrosis and collapse (black arrow), with replacement fibrosis, regenerative changes, and a mononuclear-predominant inflammation (red arrows), alternate with compensatory hyperplastic regenerative nodules (noninflamed zones, black arrowhead) (H&E stain). B) Remnant bile ducts (red arrowheads), with biphenotypic hepatocytes in lobular parenchyma (blue arrowheads) are evident on CK7 immunostain. C) Trichrome stain highlights massive post-necrotic fibrosis (blue), regenerative hepatocytes (light red), and bile ducts (red arrowheads). D) CD3 immunostain highlights a predominantly CD3+ T-lymphocytic infiltrate. E) CD79a immunostain shows intermixed B-lymphocytes. F) CD163 immunostain highlights numerous intermixed histiocytes and Kupffer cells.

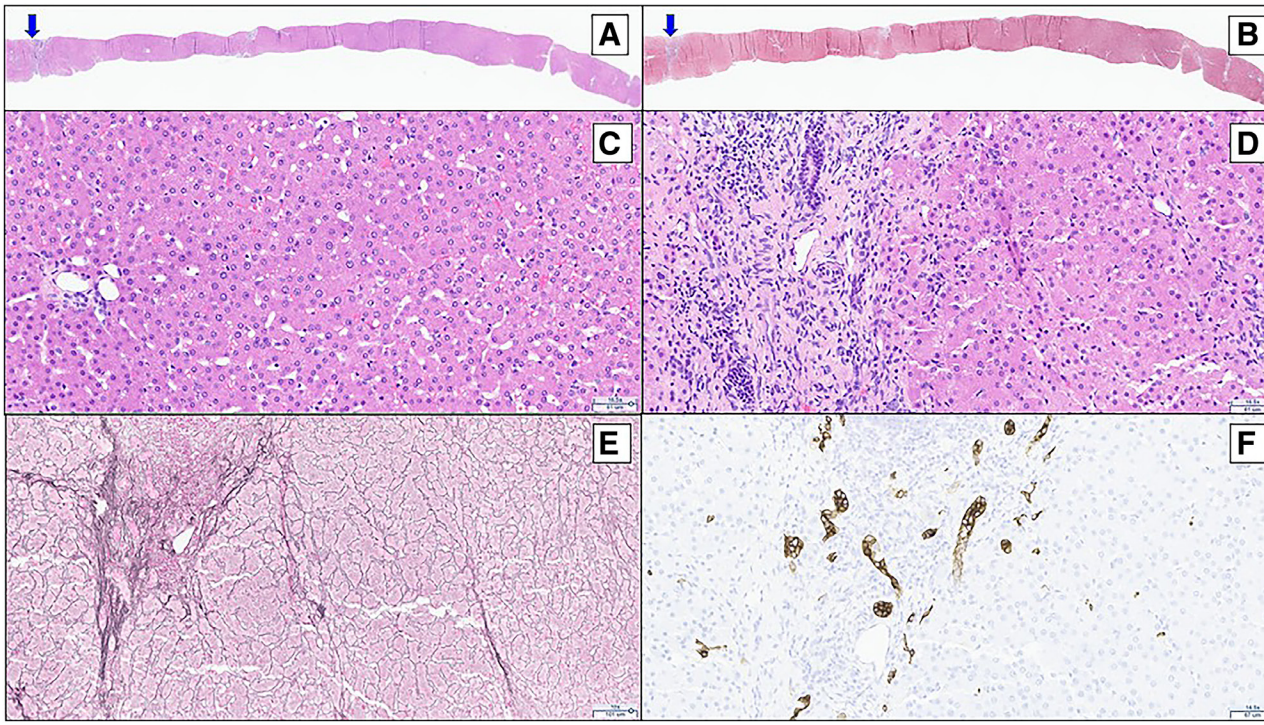

FIGURE 3. Follow-up liver biopsy shows minimal residual inflammation after 1 year. In follow-up, the liver needle core biopsy showed impressive resolution, as apparent at scanning low power (A,C: H&E, **B**: Trichrome) and representative high power image with a single focus of mild persistent inflammation (D, H+E; arrow from A), architectural collapse (E; reticulin stain), and ductular reactivity (F; CK7 stain).

receptor. The patient had a worsening coagulopathy (INR 2.7), cholestasis (conjugated bilirubin of 3.8 mg/dL), and hyperammonemia to 317 μmol/L along with altered mental status consistent with hepatic encephalopathy grade I–II. She was evaluated for liver transplantation and received intravenous methylprednisolone (2 mg/kg/day) as well as rifaximin and lactulose. This resulted in rapid improvement of AST and ALT levels, bilirubin, INR, and ammonia (Figure 1). A liver biopsy showed acute submassive hepatic necrosis, lobular collapse, and an intense mixed inflammatory infiltrate, consisting primarily of $CD3^+$ T lymphocytes (Figure 2). She was discharged on hospital day 18. With resolution of cholestasis, azathioprine was initiated (1 mg/kg/day) as steroid-sparing maintenance immunosuppression for type 2 AIH. She has had resolution of her clinical symptoms and normalization of her ALT (19 U/L) and AST (29 U/L), bilirubin and INR. A liver biopsy 1 year later confirmed marked histologic improvement with only focal residual portal/periportal inflammation and focal architectural changes (Figure 3).

DISCUSSION

SARS-CoV-2 infection commonly affects the liver, manifesting as elevated serum aminotransferase levels (1). Isolated severe liver dysfunction is considered rare and has been reported only in those with multiorgan dysfunction or underlying chronic liver disease, which the patient described herein did not have (6,7). To our knowledge, only two cases of isolated fulminant hepatic failure related to SARS-CoV-2 infection have been reported (3,4) and here we describe the first pediatric case of isolated acute liver failure in a previously healthy child due to type 2 AIH following mild SARS-CoV-2 infection. Fortunately, the patient had excellent response to high-dose steroids followed by maintenance immunosuppressive therapy with azathioprine.

The etiology of liver injury associated with SARS-CoV-2 continues to be elucidated with evidence mounting that an immune-mediate inflammatory response likely plays a significant role (1). Additionally, AIH involves complex interplay between genetic, immunologic, and environmental factors, with an infectious or viral trigger thought to play a role in disease development (8). SARS-CoV-2 has been associated with the development of several autoimmune diseases, including AIH and type 1 diabetes in adults (9). Similarly, SARS-CoV-2 vaccination has also been associated with development of AIH in adults (10), suggesting the possibility that molecular mimicry between viral spike protein and liver antigens may trigger COVID-associated autoimmune liver disease. Although it is impossible to directly prove that SARS-CoV-2 infection caused AIH in this patient, the temporal association of infection with subsequent liver failure cannot be ignored. This case highlights a rare but important phenomenon and emphasizes the importance of clinician diligence to evaluate for underlying causes of liver injury in patients presenting with isolated severe hepatic dysfunction during and following SARS-CoV-2 infection.

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The parents signed written consent for the publication of their child's information in this case report.

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