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Concurrent, New-Onset Autoimmune Hepatitis, Celiac Disease, and Hashimoto's Thyroiditis Following COVID-19

A Case Report

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Abstract: Here we describe a 13-year-old adolescent female diagnosed with concurrent autoimmune disorders including Grave disease, Celiac disease, and autoimmune hepatitis within 3 months after infection with severe acute respiratory syndrome coronavirus 2. The patient initially presented to her pediatrician with complaints of epistaxis, cessation of menses, palpitations, and weight loss. Initial evaluation showed evidence of hyperthyroidism, elevated liver enzymes, and abnormal Celiac disease serologies. Additional testing including laboratory tests, liver biopsy, and an upper endoscopy with biopsies confirmed the diagnosis of Grave disease, Celiac disease, and type 1 autoimmune hepatitis. This case highlights the importance of recognizing the risk of autoimmune disorders associated with the novel coronavirus disease 2019.

Key Words: COVID-19, autoimmune hepatitis, Celiac disease

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a pandemic affecting both pediatric and adult patients in a multitude of ways. Early in the pandemic, it became evident that there additionally existed postinfectious complications associated with COVID-19. This is, to the best of our knowledge, the first reported case of a pediatric patient diagnosed with concurrent autoimmune disorders including Grave disease, Celiac disease, and autoimmune hepatitis after COVID-19.

CASE REPORT

A previously healthy, fully immunized 13-year-old female presented in April 2021 with concerns of irregular menses and epistaxis with more recent development of palpitations. The patient experienced menarche approximately 5 months before presentation. She initially had regular menstrual periods for the first 3 months, each lasting approximately 5 to 7 days without complication. Patient was concerned as she had not menstruated for the 2 months preceding the presentation although this was felt to be within normal development. Patient reported frequent nose bleeds in the 2–3 weeks preceding presentation, occurring 4–5 times per day, each lasting about 10 minutes. She had no associated gum bleeding, bruising, petechiae, or night sweats. She had however lost approximately 18 lbs over the past 3 months unintentionally and recently began reporting palpitations at rest. Of note, the patient was found to be positive for SARS-CoV-2 in January 2021 with a mild case of COVID-19 consisting of rhinorrhea and nasal congestion for 2 days, less than 1-month before development of irregular menses, epistaxis, weight loss, and palpitations. The primary care physician noted the patient to be tachycardic and hypertensive on their initial assessment for these symptoms, and thus sent her for blood work for further evaluation.

Initial laboratory results (Table 1) ordered by the pediatrician and by the endocrinologist, to evaluate for the cause of her epistaxis, irregular menses and weight loss, showed normal white blood cell count, anemia (Hemoglobin 11.1 gm/dL and hematocrit 33.6%) with inappropriately low reticulocyte production index (0.8%), platelet 498 k/mm^3, unremarkable basic metabolic panel, elevated alkaline phosphatase 248 IU/L, elevated aspartate aminotransferase (AST) 488 IU/L, elevated alanine transaminase (ALT) 343 IU/L, elevated gamma-glutamyl transferase (GGT) 79 IU/L, normal total bilirubin 1.0 mg/dL, elevated ferritin 137 ng/mL, elevated sedimentation rate (ESR) >129 mm/hour, undetectable C-reactive protein <0.3 mg/dL, elevated INR 1.20 and protime 12.2, markedly low thyroid-stimulating hormone (TSH) 0.01 uIU/mL with elevated free thyroxine (Free T4) 3.99 ng/dL, normal total IgA levels with markedly elevated tissue transglutaminase IgA >100 IU/mL, positive endomysial IgA antibodies, undetectable Epstein-Barr virus (EBV) antibodies, and negative infectious mononucleosis Ab. Patient was urgently referred to endocrinology and was seen the following day.

Patient's lab findings were most consistent with hyperthyroidism with concerns for autoimmune Grave disease versus Hashitoxicosis. Given the concern for Celiac disease and significant elevation in AST/ALT, the pediatric endocrinologist discussed the patient's case with the pediatric gastroenterologist within the same subspecialty clinic who recommended further evaluation including abdominal ultrasound and additional laboratory studies. Methimazole was not started due to possible worsening of elevated transaminases and instead patient was started on propranolol for symptom management.

Repeat laboratory results confirmed persistent anemia, thrombophilia, elevated ESR, elevated protein, low albuminemia, elevated alkaline phosphatase, elevated AST/ALT, low TSH, and elevated Free T4. Additional laboratory results were notable for elevated antithyrotropin receptor antibodies 28.20 IU/L and antithyroglobulin antibodies 15.6 (IU/L) as well as negative infectious evaluation including cytomegalovirus, EBV, Hepatitis A, Hepatitis B, and Hepatitis C. Patient had normal alpha-1 antitrypsin level with MZ phenotype, normal ceruloplasmin level, elevated total IgG 6365 mg/dL, positive antinuclear antibody screen with homogenous pattern, absence of

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TABLE 1. Patient laboratory findings during evaluation and in follow-up

	Initial laboratory findings (April 28–29, 2021)	Follow-up laboratory findings (May 3–July 1, 2022)	Range
Hematology			
White blood cell count	10.6	11.4 (H)	4.0–11.0 × 10^3/μL
Hemoglobin	11.1 (L)	12.4	12.0–16.0 gm/dL
Platelet	498 (H)	512 (H)	150–460 × 10^3/μL
Reticulocyte production index	0.8% (L)		1.0%–2.0%
Lactate dehydrogenase	210 IU/L		94–250
Coagulation			
INR	1.2 (H)	1.1	0.9–1.1
Protime	12.2 (H)	11.3	9.2–11.4 second
PTT	26.8		24.3–33.1 second
Chemistry			
Sodium	134	136	133–145 mmol/L
Potassium	4.6	4.3	3.6–5.2 mmol/L
Chloride	100	102	98–107 mmol/L
Bicarbonate	24	26	22–29 mmol/L
BUN	14	10	4–17 mg/dL
Creatinine	0.3	0.5	0.5–0.8 mg/dL
Calcium	9.4	7.5	8.6–10.5 mg/dL
Glucose	100	101	60–99 mg/dL
Total protein	11.6 (H)	7.5	6.2–8.2 gm/dL
Albumin	3.5 (L)	4.1	3.8–5.4 gm/dL
Alkaline phosphatase	248 (H)	125	0–187 IU/L
Gamma-glutamyl transferase	79 (H)	14	5–36 units/L
Aspartate transaminase	488 (H)	23	0–32 IU/L
Alanine transaminase	343 (H)	20	0–33 IU/L
Total bilirubin	1	0.3	0–1.2 mg/dL
Uric acid	6.5		1.6–7.6 mg/dL
Thyroid-stimulating hormone	0.01 (L)	0.16 (L)	1.12–5.01 uIU/mL
Free thyroxine (T4)	3.99 (H)	1.28	1.01–1.63 ng/dL
Immunologic studies			
C-reactive protein	<0.3	<0.3	0–0.5 mg/dL
ESR	>129 (H)	20	0–20 mm/hour
Ferritin	137 (H)		6–70 mg/mL
IgG	6365 (H)	1481	759–1549 mg/dL
IgA	242		58–358 mg/dL
Tissue transglutaminase IgA	>100 (H)	8	0–3 IU/mL
Antithyroid peroxidase Ab	<3		<5.6 IU/mL
Thyrotropin receptor Ab	28.20 (H)		0–1.75 IU/mL
Antithyroglobulin Ab	15.6 (H)		<4.1 IU/mL
Liver/kidney microsomal Ab	<20.1		<20 IU
Antismooth muscle Ab	145 (H)		0–19 IU
Soluble liver antigen Ab	1.1		<20 IU
Antinuclear antibody screen	1:80 POSITIVE Homogeneous pattern		Negative <1:80
Infectious studies			
Cytomegalovirus IgM	<30.0		<30 IU/mL

(Continued)

TABLE 1. (*Continued*).

	Initial laboratory findings (April 28–29, 2021)	Follow-up laboratory findings (May 3–July 1, 2022)	Range
Epstein-Barr virus capsid IgM	<36.0		<36 IU/mL
Epstein-Barr virus capsid IgG	<18.0		<18 IU/mL
Epstein-Barr virus nuclear antigen Ab	<18.0		<18 IU/mL
Infectious mononucleosis Ab	NEGATIVE		NEGATIVE
Hepatitis A IgM	NEGATIVE		NEGATIVE
Hepatitis B surface antigen	NEGATIVE		NEGATIVE
Hepatitis B Core Ab	NEGATIVE		NEGATIVE
Hepatitis C Ab	NEGATIVE		NEGATIVE
Tuberculous cellular blood spot	NEGATIVE		NEGATIVE
Miscellaneous studies			
25 OH-vitamin D	45.5	33.8	20–50 ng/mL
Ceruloplasmin	35		16–45 mg/dL
Alpha-1 antitrypsin	130		100–188 mg/dL
Antitrypsin phenotype	MZ		

H = high; L = low.

liver/kidney microsomal antibodies and markedly elevated smooth muscle antibodies 145 IU/mL. Limitations to the evaluation include adenovirus polymerase chain reaction (PCR), parvovirus B19 PCR, and Hepatitis E virus PCR were not performed and IgG subtypes were not obtained. Ultrasound of the liver showed normal liver parenchyma and hepatobiliary system. Patient underwent upper endoscopy as well as percutaneous liver biopsy consistent with diagnoses of Celiac disease (Fig. 1) and autoimmune hepatitis (Figs. 2, 3) on pathology respectively. Taking all this into consideration, the patient had a simplified autoimmune hepatitis score of 8 points, indicating a likely diagnosis of type I autoimmune hepatitis.

Patient was started on prednisone 40 mg daily as well as a strict gluten-free diet at the time of diagnosis. At the 2-week follow-up, the patient was noted to have an improvement in her AST 61 IU/L, ALT 99 IU/L, and ESR 110 mm/hour although GGT remained elevated. At 1-month follow-up, the patient was started on ursodiol, azathioprine, and methimazole. Liver enzymes (AST and ALT) persistently improved and normalized at 7 months, GGT normalized at 7 months, ESR normalized at 4 months then fluctuated with mild elevation for another 4 months before normalizing again, and tissue transglutaminase IgA normalized at 14 months (Table 1). Eighteen months after initial presentation, the patient was asymptomatic and stable on a regimen including azathioprine 75 mg, ursodiol 300 mg daily, prednisone 5 mg daily, and methimazole 5 mg daily. Prednisone was discontinued at the 12- and 18-month marks, but due to a bump in liver enzymes and ESR, the low dose was restarted. Plan to discontinue prednisone and ursodiol again at the 2-year mark. Labs showed essentially normal CBC with differential, ESR, liver function panel, TSH, and Free T4.

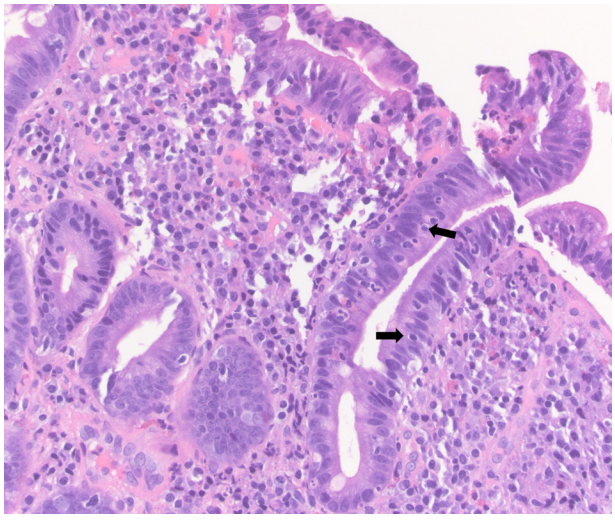

FIGURE 1. High power magnification (40×): H&E section of duodenal biopsy showing chronic moderately active enteritis and increased villous surface intraepithelial lymphocytes (black arrows).

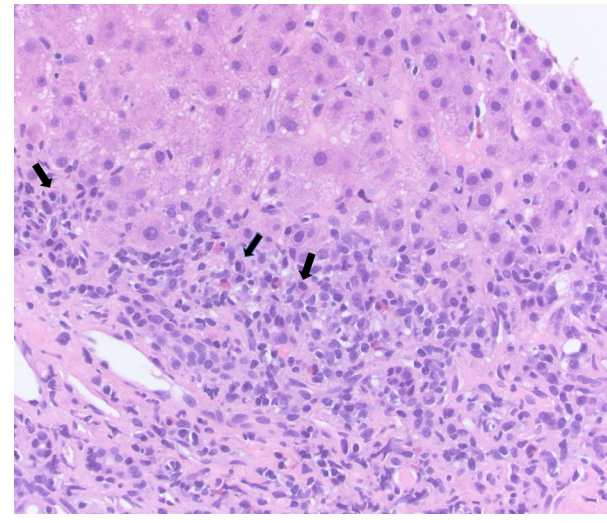

FIGURE 2. High power magnification (40×); H&E section of liver biopsy showing dense plasma cell-rich infiltrate (black arrows) with interface hepatitis.

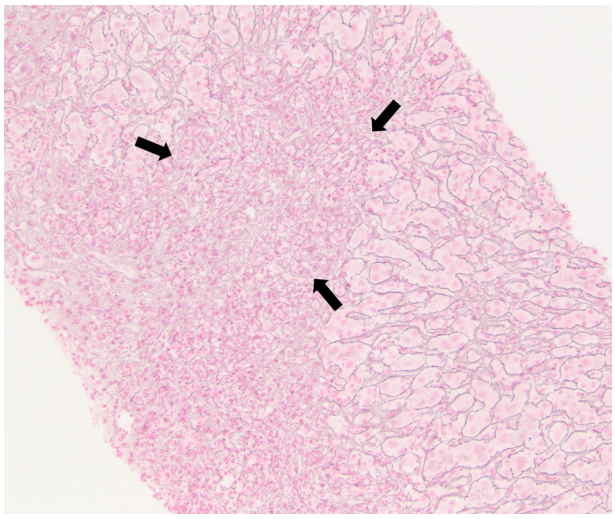

FIGURE 3. Low power magnification (20×): reticulin stain of liver biopsy showing absence of reticulin network in areas of inflammation and necrosis (black arrows).

DISCUSSION

In this case, we describe a previously healthy adolescent female who presented with new simultaneous onset of 3 autoimmune conditions, Grave disease, Celiac disease, and type 1 autoimmune hepatitis within 3 months of COVID-19 infection. While Grave disease (1) and Celiac disease (2) have been previously described as possible post-COVID-19 complications, this is, to the best of our knowledge, the second reported case of a patient diagnosed with autoimmune hepatitis as proven by biopsy after COVID-19. The first was a 3-year-old previously healthy female who developed acute liver failure secondary to type 2 autoimmune hepatitis in the setting of mild COVID-19 (3).

Autoimmune disease is the product of a dysregulated immune system recognizing self-antigens as foreign, characterized by the presence of autoantibodies and pro-inflammatory cytokine production, resulting in end-organ damage and the development of clinical symptoms. This is believed to occur when a genetically predisposed individual is exposed to an environmental trigger. While an environmental trigger for autoimmune hepatitis has not been identified, several viral candidates including rubella, EBV and the hepatotropic viruses A, B, and C have been named (4). A variety of mechanisms have been proposed in the role of viral infection and autoimmunity including molecular mimicry, bystander activation, and superantigens (5). SARS-Cov-2 has been shown to share some characteristic features with other viruses that trigger autoimmunity and several studies have reported autoantibodies in patients with COVID-19 including antinuclear antibodies, anticytoplasmic neutrophil antibodies, anti-Ro/SSA, rheumatoid factor, and antiphospholipid (6–8). These autoantibodies may arise from a predominantly extrafollicular B cell response that is more prone to generating autoantibody-secreting B cells. Some of the said antibodies have been further associated with worse clinical prognosis and the development of severe respiratory symptoms. The wide variability in autoantibodies produced in the setting of COVID-19 supports an excessive inflammatory response to the virus in such a way as a superantigen often behaves.

This case highlights yet another autoimmune disease associated with COVID-19. Given the clinical course of this patient, clinicians should have a low threshold to perform and repeat laboratory studies evaluating for autoimmune disorders in patients following COVID-19.

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Informed consent was obtained by the patient's parent/legal guardian for this case report. All identifying information has been removed.

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