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CASE REPORT | LIVER

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy–Associated Hepatitis

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ABSTRACT

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is an inborn error of immunity, resulting from variation in the autoimmune regulator gene (*AIRE*). Pathogenic variants in the *AIRE* gene result in autoimmunity typically involving endocrine organs with nonendocrine organs less commonly affected. Hepatitis associated with APECED has emerged as a potentially fatal complication with higher reported prevalence in the Americas. We describe a case of a 3-year-old boy presenting with hepatitis from APECED without classical clinical diagnostic criteria. This case highlights the importance of APECED in the evaluation of hepatitis given response to immunomodulator treatment and risk of fulminate liver failure.

KEYWORDS: autoimmune hepatitis; inborn error of immunity; *AIRE* gene

INTRODUCTION

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type 1, is an autosomal recessive inborn error of immunity, resulting from variation in the autoimmune regulator gene (*AIRE*).[1] *AIRE* is a transcriptional regulator, which promotes expression of tissue-specific antigens in the thymus used for negative selection of self-reactive T lymphocytes. Escape of self-reactive T lymphocytes from the thymus in *AIRE* deficiency has been shown to lead to tissue destruction in animal models.[2,3] APECED has been well characterized among European populations with primarily endocrine-related disease manifestations. Classically, APECED results in the triad of chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency. Patients must have at least 2 of the 3 classic manifestations of the disease for diagnosis.[3] We report a case of APECED identified after evaluation for hepatic dysfunction.

CASE REPORT

A 3-year-old White boy with a medical history of chronic thrush, recurrent pulmonary infections, and constipation was transferred to a tertiary-care pediatric hospital in the United States for hepatic dysfunction in the setting of hypoxia because of rhinovirus infection. The patient was admitted to the pediatric intensive care unit and evaluated by the gastroenterology and hepatology service. Initial vital signs were notable for a heart rate between 120 and 129 beats per minute with physical examination showing a drowsy but cooperative child of stated age with no evidence of jaundice, ascites, splenomegaly, or edema. Liver function tests on presentation showed an aspartate aminotransferase of 355 U/L, alanine aminotransferase of 301 U/L, and total bilirubin of 3.1 mg/dL. Additional laboratory evaluation showed positive anti-nuclear antibodies (titer: 1:80) with negative anti-liver-kidney microsomal and anti-smooth muscle antibodies. Hepatitis C serology was reactive; however, hepatitis C nucleic acid amplification was undetectable. A liver biopsy was performed, which showed chronic active hepatitis with 60% steatosis (predominately macrovesicular) and stage 3 fibrosis. Pathology also showed interface hepatitis with isolated clusters of plasma cells (Figure 1). Quantitative hepatic copper was normal with no evidence of excess iron deposition within the liver. Given concern for an immune-mediated process, the patient was evaluated by clinical immunology with genetic testing showing 2 pathogenic variants (c.1249dup and c.967_979del) in the *AIRE* gene consistent with APECED. Flow cytometry showed 1499 CD4 cells/mcL, 969 CD8 cells/mcL, 1634 CD19 cells/mcL, and 482 NK cells/

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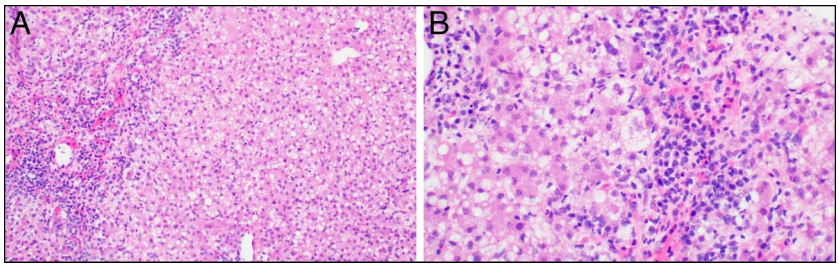

Figure 1. (A) (20×) and (B) (40×) liver biopsy pathology showing chronic active hepatitis with plasma cells. Sections from the specimen show marked lobular and portal inflammation with numerous lymphocytes, histiocytes, neutrophils, eosinophils, and plasma cells. Also seen is marked ductular reaction with largely preserved central bile ducts in each portal triad. Occasional lobular inflammation is associated with hepatocyte proliferation, binucleation, necrosis, and multinucleation. There is moderate steatosis (60%), which is predominantly macrovesicular. Occasional hepatocyte dropouts are seen.

mcL. The patient was treated with prednisone (induction: 2 mg/kg) and transitioned to single-agent azathioprine. Hepatic dysfunction resolved with repeat liver biopsy at 6 months showing decreased plasma cell infiltration and no evidence of fibrosis.

DISCUSSION

Hepatitis is a known nonendocrine entity of APECED with wide clinical severity ranging from asymptomatic liver function elevation to fulminant hepatic failure.[4,5] The pathogenesis of hepatitis in APECED is believed to result from immune-mediated damage with liver biopsy specimens, showing a lymphoplasmacytic infiltrate with interface hepatitis.[6] Many of the classic biomarkers associated with autoimmune hepatitis (ie, anti-nuclear, anti-smooth muscle, and anti-liver-kidney antibodies) have not been shown to reliably correlate with hepatitis associated with APECED; however, several autoantibodies have been associated with APECED-associated hepatitis (APAH) (anti-aromatic L-amino acid decarboxylase, anti-cytochrome P450 family 1 subfamily A member 2, anti-histidine decarboxylase, anti-bactericidal/permeability-increasing fold-containing B1, anti-tryptophan hydroxylase, and anti-21-hydroxylase antibodies). Given these findings, the term APAH has come into recent usage.[5]

APAH has been reported to have a prevalence of 10% among European populations with less than 2% of patients presenting with APAH during the initial diagnosis of APECED. Recent published data indicate the prevalence of APAH to be significantly higher (42%) among American cohorts with less patients in the Americas presenting with the classical clinical diagnostic characteristics of APECED.[3,5]

American APECED patients are typically compound heterozygotes compared with the other well-studied European groups, which typically carry homozygous variants in the *AIRE* gene.[3,4] The largest APAH study to date in the Americas examined a total of 18 patients in the United States. Patients with biallelic c.967_979del113 variants were most likely to have APAH. This American cohort was also noted to have more indolent disease with less evidence of advanced fibrosis.[5] The patient in the case described above presented with heterozygous variants in the *AIRE* gene with more advanced fibrosis on liver biopsy. These genotypic-phenotypic findings highlight the potential for other genetic modifiers accounting for the wide clinical spectrum of disease, which has been seen among siblings with the same gene variant.[7]

Treatment for APAH typically involves immunomodulatory treatment to control disease progression. Azathioprine or 6-mercepatopurine with or without corticosteroids have proven to be the cornerstone of therapy for APAH.[5] The patient in our case was transitioned to azathioprine with both clinical and pathologic response to treatment.

In North America, a large percentage of patients (40%–80%) present with nonendocrine manifestations of disease, leading to a potential delay in diagnosis based on classical clinical features of APECED.[3] These findings highlight the importance of early detection and treatment of APAH in the Americas, given favorable documented response to treatment and concern for fulminant hepatic failure.[5] Given the variable clinical presentation of APECED and limited data on APAH in the Americas, additional clinical information provides valuable guidance for clinicians treating this rare and potentially fatal disease.

DISCLOSURES

Author contributions: Z. Mesbah: literature review and manuscript preparation and is the article guarantor. N. Tiwari: figure acquisition and preparation; pathology analysis and written description; K. Sacco: manuscript review and research supervision.

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