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CASE REPORT | LIVER

Autoimmune Hepatitis in a Patient With Common Variable Immunodeficiency

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ABSTRACT

Common variable immunodeficiency (CVID) is characterized by defective immunoglobulin synthesis because of impaired B-cell function. Liver abnormalities including autoimmune hepatitis (AIH) have been described in up to 10% of patients. We report a 27-year-old woman with CVID who presented with liver dysfunction secondary to AIH. AIH is both uncommon and challenging diagnostically in patients with CVID because they have low IgG levels and often have low or undetectable autoantibody levels. Liver biopsy and response to therapy play an important role in establishing the diagnosis. Corticosteroids are the mainstay of therapy, with or without immune modulators.

INTRODUCTION

Common variable immunodeficiency (CVID) is a condition characterized by defective immunoglobulin synthesis because of impaired B-cell function.[1] Liver abnormalities including autoimmune hepatitis (AIH) have been described in up to 10% of patients.[2] AIH is an inflammatory disease of the liver characterized by autoantibodies, hypergammaglobulinemia, and hepatocellular damage with a lymphoplasmacytic infiltrate in portal tracts, at the portal interface, and in the parenchyma on histological examination.[2,3] We report a patient with CVID who presented with liver dysfunction secondary to AIH. This is a challenging diagnosis in patients with CVID because of the deficient immune response, inability to rely on serologic markers, and the histologic overlap with other entities.

CASE REPORT

A 27-year-old Hispanic woman with a medical history of CVID presented with a 1-month history of diffuse abdominal pain, fatigue, poor appetite, nausea, watery/nonbloody diarrhea, and jaundice. She denied the use of alcohol or any home medications. The patient had a history of recurrent hospitalizations for pneumonia and was receiving intravenous immunoglobulin (IVIG) every 3 weeks for CVID treatment. Her last course of antibiotics (piperacillin/tazobactam) was completed 4 months before this hospitalization, and her last IVIG infusion was given 1 month before admission. The patient did not have a history of ascites or any other liver decompensation manifestations before this presentation.

She was afebrile, and physical examination was significant for tachycardia, jaundice, a cachectic appearance, diffuse abdominal tenderness, and evidence of ascites. The patient was alert and oriented with no alteration in mental status throughout her hospitalization. Laboratory results showed a complete blood count with leukocytes of $6.4 \times 10^3/\mu L$, hemoglobin of 10.2 g/dL, platelets of $49 \times 10^3/\mu L$, and an international normalized ratio of 3.1. Her complete metabolic panel was significant for a total bilirubin of 5.3 mg/dL, alkaline phosphatase 819 IU/L, aspartate aminotransferase 1,456 IU/L, alanine aminotransferase 976 IU/L, and albumin of 2.5 g/L. A diagnostic paracentesis showed fluid with a white blood cell count of $314/mm^3$ with 13% of segmented and 55% of lymphocytes and a serum-ascites albumin gradient of 1.4.

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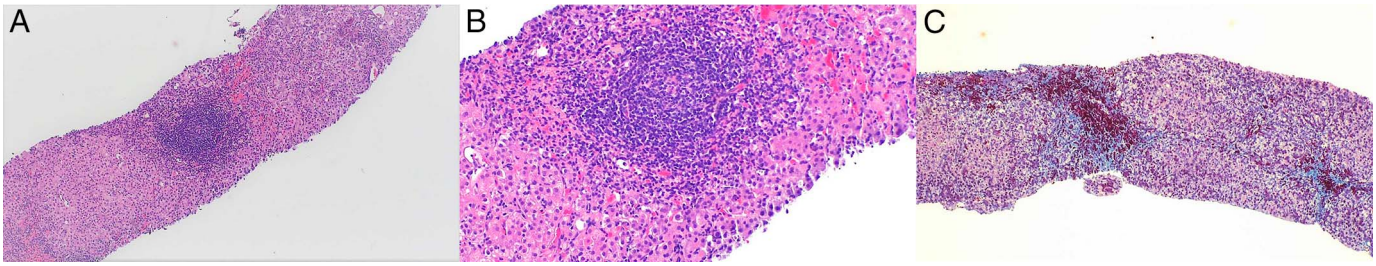

Figure 1. Liver parenchyma showing (A) prominent lymphocytic portal and lobular inflammation (hematoxylin and eosin stain, 20× magnification) and (B) numerous mature lymphocytes and plasma cells. The hepatocytic-portal interface is not identified, consistent with interface hepatitis (hematoxylin and eosin stain, 40× magnification) and (C) septal fibrosis manifested by connective tissue bridges that link portal tracts with other portal tracts, stage 3 (trichrome stain, 20× magnification).

Serology was negative for antinuclear antibody, anti-smooth muscle antibody, anti–liver-kidney microsomal-1 antibodies, and antimitochondrial antibody. Infectious disease workup including hepatitis A, B, C, and E, herpes simplex virus 1 and 2 IgG/IgM, cytomegalovirus polymerase chain reaction, and *Blastomyces* and *Coccidioides* antibodies was all negative. The initial Epstein-Barr virus polymerase chain reaction qualitative was positive. However, serology workup was negative, and histopathology for Epstein-Barr virus was negative. Acetaminophen and alcohol levels were nondetectable. Iron studies and ceruloplasmin were within normal values. The celiac disease antibody panel and human leukocyte antigen (HLA) typing for celiac disease were negative. An abdominal ultrasound with Doppler was negative for thrombosis (hepatic, inferior vena cava, or portal veins). Ultrasound of the abdomen revealed a cirrhotic-appearing liver and moderate volume ascites.

Esophagogastroduodenoscopy showed mild gastritis, and there were no esophageal or gastric varices. Duodenal biopsies were obtained and were negative for celiac disease. The colonoscopy was normal. A percutaneous liver biopsy showed prominent lymphocytic portal and lobular inflammation, numerous plasma cells in the lymphocytic infiltrate, and trichrome stain highlighted stage 3 fibrosis by the Batts-Ludwig system (Figure 1).[4] No hepatocyte rossetting or biliary changes were seen.

Based on biopsy and clinical findings, the patient was diagnosed with AIH/cirrhosis and started on prednisone 60 mg daily with a slow taper over 6 months. IVIG therapy was restarted. Liver transplant was discussed, but declined by the patient. However, aminotransferases and total bilirubin trended down (Table 1). Azathioprine 50 mg daily was started on the third month of tapering prednisone. At a 6-month follow-up, the patient has shown significant clinical improvement.

DISCUSSION

CVID is the most common symptomatic primary immune deficiency disease and is characterized by profound hypogammaglobulinemia.[1] Recurrent infection are a common presenting feature. Inflammatory and autoimmune complications have an overall prevalence of about 25%. Gastrointestinal manifestations are common, with a prevalence ranging from 20% to 60%, and may be the dominant disease manifestation in a subset of patients.[2] The most common gastrointestinal symptom is chronic persistent diarrhea.

Liver involvement is seen in 10% of patients with CVID.[2] Patients with liver involvement may remain asymptomatic or have fatigue, nausea, vomiting, jaundice, pruritus, ascites, edema, hepatomegaly, splenomegaly, and esophageal varices.[4] Nodular regenerative hyperplasia is the most common lesion observed in the liver of CVID patients and can lead to chronic cholestasis, noncirrhotic portal hypertension, or the appearance of cirrhosis.[5,6] Hepatitis C is now rarely seen but was a complication of IVIG infusions in the past. Primary biliary cholangitis (PBC) and AIH leading to persistently elevated liver enzymes can occur in CVID.[7]

Table 1. Bilirubin and aminotransferases at admission and trend throughout the 6-month treatment

	Admission	2 weeks[a]	1 month	2 months	3 months	4 months	5 months	6 months
Bilirubin	5.3	11.8	16.3	7.0	4.3	1.8	1.3	1.1
ALP	819	458	331	281	338	478	504	496
AST	1,456	1,353	707	67	67	116	118	94
ALT	976	805	672	46	52	100	111	93

Laboratory values 4 months before admission were bilirubin 0.3, ALP 357, AST 30, and ALT 68.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Treatment with prednisone was started 2 weeks after admission.

The diagnosis of AIH requires a constellation of findings including the presence of autoantibodies, elevated serum IgG, absence of certain findings, and a compatible liver biopsy.[8] These patients have low IgG levels and often have low or undetectable autoantibody levels, so 2 of the key diagnostic criteria may be absent. As in this case, the diagnosis may be based on the absence of alternative diagnoses, liver histology, and response to immunosuppression. However, autoantibody-negative AIH has been previously described, and it is possible that the lack of autoantibodies in our patient was not related to underlying CVID.[8]

To the best of our knowledge, there are only a few reported cases of CVID patients with AIH in literature.[9,10] Although there are no pathognomonic histological features in AIH, there are some characteristic features that have been observed in patients before treatment. These features include hepatocellular damage with a lymphoplasmacytic infiltrate in portal tracts, at the portal interface, and in the parenchyma. The number of plasma cells, severity of hepatitis, and extent of damage to bile ducts can vary. Some of these features overlap with other entities, especially PBC making it difficult to diagnose.[11] Our patient had no histologic features of PBC (cholangitis, cholestasis, or granulomas). As per the American Association for the Study of Liver Diseases guidelines, the revised original scoring system of the International Autoimmune Hepatitis Group Scoring for AIH was used for diagnosis in our case. The biopsy showed portal interface and parenchymal lymphoplasmacytic inflammation.

Management of AIH in CVID lacks general consensus. Treatment is individualized and based on clinical status, comorbid conditions, disease activity and severity, and previous treatment response. Intravenous replacement of immunoglobulin and infection management are the main treatment goals for CVID. Corticosteroids are the mainstay of AIH therapy, with or without immune modulators. In a similar case, use of budesonide at 3 mg/kg resulted in resolution of AIH. Ursodeoxycolic acid may be used if biliary dysfunction is present on biopsy.[10] Liver transplant seems to be a viable option in end-stage liver failure. However, recent studies have shown mixed results with poor prognosis in some patients.[12,13] Occurrence of AIH in CVID is an uncommon and clinically challenging diagnosis with limited data available on how to manage these patients. In this case report, we emphasize the complexity in diagnosis and treatment of liver disease in CVID patients. Liver biopsy and response to therapy play an important role in establishing the diagnosis. Early diagnosis is critical to prevent progressive liver damage.

DISCLOSURES

Author contributions: K. Myneedu and LO Chavez wrote the manuscript and approved the final manuscript. NL Sussman, M. Michael, A. Padilla, and MJ Zuckerman revised the manuscript for intellectual content and approved the final manuscript. MJ Zuckerman is the article guarantor.

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