ABSTRACT

Common variable immunodeficiency (CVID), a condition characterized by impaired antibody production, is paradoxically associated with various autoimmune disorders. The most common causes of liver disease in patients with CVID are nodular regenerative hyperplasia, granulomatous infiltration of the liver, and chronic viral hepatitis. We present a case of autoimmune hepatitis in a patient with CVID.

INTRODUCTION

Common variable immunodeficiency (CVID) is a heterogeneous group of immunodeficiency disorders associated with impaired antibody production and reduced immunoglobulin levels. Chronic liver disease is frequently observed in patients with CVID. In the largest study published to date, Ward et al determined that 47 of 108 patients with CVID had abnormal liver biochemistries for at least 6 months. Liver biopsies performed in 16 of the patients revealed that 13 had nodular regenerative hyperplasia, 6 were positive for hepatitis C serology, and in the remaining 28, the liver enzyme abnormalities remained unexplained.

Autoimmune hepatitis (AIH) is a chronic liver disease characterized by a loss of tolerance against self-liver antigens. AIH is subdivided according to antibody presence. Type 1 AIH is characterized by antinuclear antibody or smooth muscle antibody positivity. Type 2 AIH is characterized by positive antiliver kidney microsomal type 1 antibodies, antiliver cytosol type 1 antibodies, and/or antiliver kidney microsomal type 3 antibodies. AIH is associated with increased hepatocellular liver enzymes, elevated serum immunoglobulin G (IgG) levels, and low levels of C3 and C4. Histologic features include piecemeal necrosis, lymphoplasmacytic inflammatory infiltrates, lobular hepatitis, central zone necrosis with perivenulitis of the central vein, and lymphoid follicles. The diagnosis of AIH is established by the presence or absence of a combination of these features, as outlined by the International Autoimmune Hepatitis Group (IAIHG). To date, there have been only 2 reports describing AIH in patients with CVID. However, in neither of the reports did the authors indicate whether their patients satisfied the IAIHG criteria. We present a case of IAIHG-supported AIH in a patient with CVID.

CASE REPORT

A 44-year-old woman with CVID being treated with monthly intravenous immunoglobulin (IVIG) presented to the hospital with jaundice in January of 2017. Risk factors for acute and chronic liver disease were absent. Her physical examination was significant for jaundice and increased numbers of spider nevi. Hepatocellular liver enzymes were markedly elevated, with peak aspartate aminotransferase and alanine transaminase levels of 1355 IU/L and 279 IU/L, respectively. Cholestatic liver enzymes were only mildly elevated, with an alkaline phosphatase of 177 IU/L and a gamma-glutamyltransferase of 219 IU/L. A transjugular liver biopsy revealed severe hepatocellular injury with confluent necrosis, parenchymal necrosis, and lobular inflammation suggestive of acute hepatitis. The hepatic venous pressure gradient was 11 mm Hg, compatible with portal hypertension. An extensive workup for the causes of liver disease was performed. The results included a positive smooth muscle antibody at a titer of 1:80, an elevated serum IgG level at 19.8 g/L, and low C3 and C4 levels at 0.76 and 0.06 IU/L, respectively. Serology for hepatitis A, B, C, cytomegalovirus, and...
Epstein-Barr virus were negative. Itraconazole treatment for a previous aspergillosis infection was discontinued. She received no immunosuppression at this time.

In April of 2017, she was readmitted to hospital with a recurrence of features in keeping with acute liver injury. Magnetic resonance cholangiopancreatography suggested the presence of cirrhosis. She was treated with a rapidly tapering course of prednisone, which resulted in normalization of the liver biochemistry abnormalities. Unfortunately, she developed steroid-induced myopathy and the steroids were discontinued. Shortly thereafter (November, 2017), she was again readmitted with jaundice, markedly elevated hepatocellular enzymes, and a prolonged prothrombin time. A repeat liver biopsy revealed lymphocytic infiltrates with interface activity and plasma cells. She was treated with glucocorticoids and quickly transitioned to azathioprine. Her liver enzymes and liver function normalized and remains stable currently while on azathioprine alone.

DISCUSSION
Diagnostic criteria for AIH were first published by the IAIHG in 1993. These criteria include 13 categories and 29 possible grades. To simplify the diagnostic process, “simplified” diagnostic criteria were developed and published in 2008. These criteria included only 4 categories: positive autoimmune markers, high serum IgG levels, compatible liver histology, and the absence of viral hepatitis.

As illustrated in this case, meeting the simplified criteria for AIH in patients with CVID can be challenging. The impaired humoral response of these patients often results in their inability to develop autoimmune markers. In addition, serum IgG levels can be low, as a reflection of the disease, or high in the setting of recent IVIG treatment. Finally, viral hepatitis markers may be present because of passive transmission of positive serology with IVIG infusions. Owing to the above concerns, in this case, we used the more extensive IAIHG criteria for diagnosing AIH, and by virtue of a score of 23 (albeit in the setting of IVIG treatment), the diagnosis was firmly established. The patient’s course of frequent relapses off immunosuppressive treatment, complete response when such treatment was initiated, and the absence of evidence for nonviral causes of acute or chronic liver disease further supported the diagnosis. In addition to serving as the first clearly established case of AIH in association with CVID, this report underscores the challenges in establishing a diagnosis of AIH in patients with CVID.

Although more cumbersome, the results also favor the use of the original or revised rather than simplified IAIHG criteria for diagnosing AIH in patients with CVID.

In conclusion, this case highlights the importance of remaining clinically suspicious for autoimmune liver disease in patients with CVID presenting with liver enzyme abnormalities or evidence of hepatic synthetic dysfunction. This is especially true given the relative frequency of autoimmune disorders in patients with CVID. It also demonstrates the challenges in establishing a diagnosis of AIH in patients with CVID.

DISCLOSURES
Author contributions: G. Pollock wrote the manuscript and is the article guarantor. A. Sharma and M. Gy edited the manuscript.

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