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Autoimmune Hepatitis as a Hepatic Manifestation of Common Variable Immunodeficiency: A Case Report

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Abstract

Common variable immunodeficiency (CVID) is one of the most prevalent primary immunodeficiency disorders, characterized by an alteration in the maturation of B lymphocytes. Patients with this condition are redisposed to a higher risk of infections. Despite being an immune deficiency disorder, the prevalence of autoimmune disorders is reported in more than 20% of patients. The likelihood of patients' gastrointestinal tract being affected is relatively low, close to 6%. We present the case of a 22-year-old man with a history of CVID without medical treatment, who presented with upper gastrointestinal bleeding secondary to esophageal varices due to cirrhotic portal hypertension. Infectious and toxic causes of cirrhosis were ruled out. Histological changes compatible with autoimmune hepatitis (AIH) were documented by liver biopsy. The diagnosis of autoimmune diseases is a challenge in the presence of IDCV, we highlight the importance of establishing a timely diagnosis and an intentional search for these conditions to offer timely treatment and avoid late complications.

Keywords

Immunodeficiency, Hepatitis, Liver, Autoimmune

1. Introduction

Common variable immunodeficiency (CVID) is characterized by a disorder in the differentiation of B lymphocytes that creates a predisposition to hypogammaglobulinemia, these conditions lead to an increased risk of recurrent bacterial infections, particularly intestinal and pulmonary in up to 95% of patients affected with this entity [1]. The approximate prevalence of this disorder varies between 1:50,000 - 100,000 of the world population, with a male-female ratio of

1:2. Its diagnosis is usually made in the first decade of life; however, there are case reports of patients diagnosed in the third decade of life [2]. The pathogenesis of CVID has not been delineated clearly; however, mutations in several genes associated with B-cell development, including autosomal-recessive mutations in BAFF-R, CD20, CD19, CD81, CD21, and inducible costimulator, have been found in a small subset of patients [3]. Survival 20 years after the diagnosis of CVID was 64% for males and 67% for females, compared to the expected 92% population survival for males and 94% for females [4]. It is estimated that 25% of patients with CVID have associated autoimmune disorders such as thyroiditis, rheumatoid arthritis, and celiac disease. Liver disorders are rare in the medical literature [5]. Liver disease, including primary biliary cirrhosis and autoimmune hepatitis, which may lead to persistently increased liver enzyme levels, also occurs in CVID. The cause remains unknown, with liver biopsy specimens showing mild periportal changes or granulomas. In one cohort study, 43% of patients had abnormal liver function tests, predominantly increased alkaline phosphatase. Nodular regenerative hyperplasia leading to portal hypertension and cholestasis was found in 14 of 40 subjects in a cohort of subjects who had these abnormalities in liver function tests [6]. Due to the decrease in serum immunoglobulins, the diagnosis of autoimmune diseases is a challenge, since the expression of antibodies is altered and their serum values are normal or decreased, leading to false-negative laboratory reports. We present the case of a 22-year-old Caucasian male patient with liver cirrhosis secondary to autoimmune hepatitis (AIH) with a history of CVID.

2. Case Presentation

A 22-year-old man presented to the emergency department of our hospital with a history of haematemesis. His medical history highlights the history of autoimmune thrombocytopenia diagnosed 12 years ago without treatment or medical follow-up and the diagnosis of IDCV 6 years ago, without treatment for 3 years. He denied a family history of liver disease or immune disorders, drug, alcohol, or tobacco use, or risk exposures for HIV, HBV, or HCV infection. The patient reported that 4 weeks beforehand he had undergone a surgical extraction of fourth molars, later he presented swelling, redness and heat in the left submandibular region, associated with fever not quantified by thermometer for which he received antibiotic treatment (ciprofloxacin*) and non-steroidal anti-inflammatory drugs (ketorolac and diclofenac 2 - 3 tablets per day) with partial improvement of symptoms. Twelve hours before consultation, he started with haematemesis in 3 episodes and hematochezia in 1 occasion. On admission, a blood pressure of 80/50 mmHg and a heart rate of 140 beats per minute stand out, so resuscitation with crystalloids was started, the physical examination revealed the presence of sclera with jaundice, a swollen, erythematous area and local heat in the left submandibular region, flat, symmetrical abdomen, absence of collateral circulation, non-painful hepatomegaly, without changing dullness, and

rectal examination with an examining glove showed traces of bright red blood.

3. Diagnostic Support

Anemia, thrombocytopenia, altered liver biochemistry with mild hypertransaminasemia, a cholestatic pattern, and a prolonged INR were documented in the admission laboratories. The endoscopic study showed the presence of large esophageal varices according to the Baveno classification (Figure 1(A)) and mild portal hypertensive gastropathy, for which he received endoscopic therapy with the collation of 3 ligature bands. As part of the diagnostic approach, hepatoportal Doppler ultrasound was performed, reporting data of diffuse cirrhosis-type liver disease, portal hypertension, splenomegaly, and ascites (Figure 1(B) and Figure 1(C)). Chronic viral infectious processes were ruled out. ANA was documented at 1:1200 and the rest of the antibodies were negative (Table 1). Due to the association with autoimmune diseases and because the rest of the studies performed were negative, a percutaneous liver biopsy was performed, which reported F2-3 fibrosis on the Metavir scale, interface hepatitis, associated with lymphoplasmacytic infiltrate, integrating a diagnosis of AIH (Figure 1(D) and Figure 1(F)).

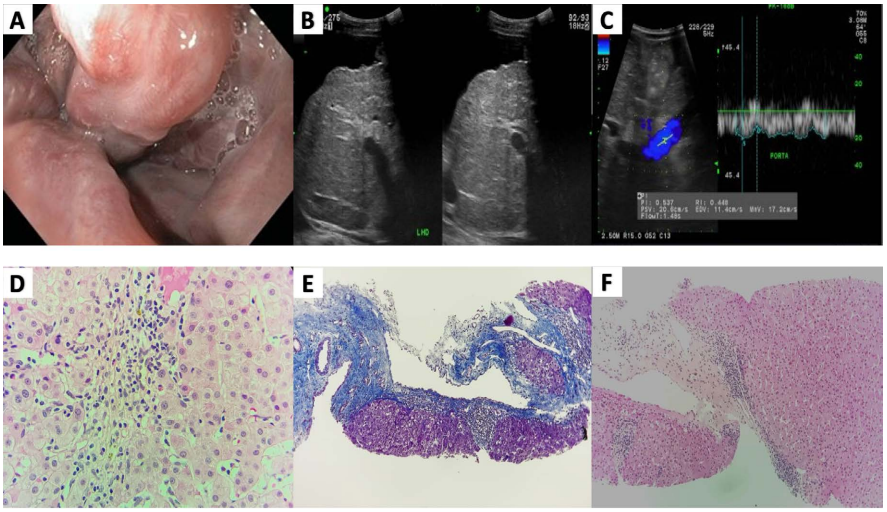

Figure 1. (A) Esophagogastroduodenoscopy shows the presence of at least 3 venous vascular pathways greater than 5 mm, in the esophagus with the presence of hematocystic points that run to the esophagogastric junction. (B) Liver ultrasound image showing the right lobe with lobulated and defined contours, with a heterogeneous parenchyma at the expense of a generalized and diffuse increase in its echogenicity with a pseudonodular pattern and perihepatic free fluid. (C) Doppler ultrasound image showing a portal vein with an inspiration caliber of 14 mm, with hepatopetal flow, maximum peak velocity of 20.6 centimeters per second and calculated congestive index of 0.08. (D) H&E 40× showing the hepatic parenchyma with pseudoacinar transformation. (E) 10× with Masson's trichrome showing expansion of the portal spaces by fibroconnective tissue that binds them together and forms a nodular pattern with evidence of fibrosis bridges from one portal space to another. (F) 20× with H&E shows interface area between portal space and hepatic lobule with increased lymphoplasmacytic cells which focally infiltrate hepatocytes.

Table 1. Main findings laboratory investigations.

TEST NAME	RESULT	REFERENCE RANGE
Hemoglobin	7 gr/dL	14 - 16 gr/dL
Hematocrit	21.6%	40% - 48%
Mean corpuscular volume	85 fL	75 - 100 fL
Platelet count	56,000/mm^3	150,000 - 400,000/mm^3
Leukocytes - Total	7230/mm^3	3500 - 10,000/mm^3
Alkaline phosphatase |	237 UI/L	40 - 160 UI/L
Gama-glutamyltransferase	160 UI/L	8 - 60 UI/L
Transaminase ALT	48 UI/L	29 - 33 UI/L
Transaminase AST	37 UI/L	29 - 33 UI/L
Bilirrubin - Total	2.0 mg/dL	0.3 - 1.2 mg/dL
Albumin	3.1	3.5 - 5 gr/dL
INR	1.45	0.9 - 1.1
Serum creatinine	0.74 mg/dL	0.7 - 1.2 mg/dL
IgG	146 mg/dL	800 - 1500 mg/dL
IgM	18.1 mg/dL	45 - 150 mg/dL
Antinuclear antibodies	1:1200	<1:40
Anti-smooth muscle antibodies	1:40	<1:80
Antimitochondrial antibodies	<1:40	<1:40
HIV	Negative	Negative
HBsAg	Negative	Negative
HCV antibodies	Negative	Negative

4. Treatment and Follow-Up

Upon admission, the patient was initially treated with intravenous omeprazole and terlipressin in accordance with the international management guidelines for gastrointestinal bleeding of non-variceal and variceal origin for 5 days [7] [8]. An upper endoscopy was performed that revealed large esophageal varices, which were treated with ligation. Secondary prophylaxis was started with non-selective beta-blockers and endoscopic follow-up at 8 weeks for the second ligation session [7]. After 7 days of hospitalisation, the patient was feeling better. There were no further episodes of haematemesis. On discharge, it was decided to start treatment with prednisone 40 mg/day and after 2 weeks azathioprine was added at 2.5 mg per kilo without presenting hematological side effects [9]. Currently with prednisone 5 mg/day and azathioprine 150 mg/day, in his follow-up he has not presented elevated transaminases and does not present cholestasis. He will receive a liver ulltrasound every 6 months to assess for hepatocellular carci-

noma and continues to receive intravenous immunoglobulin once a month.

5. Discussion

IDCV is a rare disorder, and its pathophysiology is complex and poorly understood. Its main characteristic is hypogammaglobulinemia resulting from alterations in the differentiation of B lymphocytes. It has been established that gastrointestinal disorders are found in 6% - 20% of patients with this entity, the most common being celiac disease and liver disorders that range from nodular regenerative hyperplasia to cirrhosis [10] [11].

It has been described that patients with CVID and hypertransaminasemia may have characteristics of AIH, since despite being an immunodeficiency disorder, up to 25% of patients have autoimmune diseases [6]. Previous studies have established a prevalence of episodes of non-B and non-C hepatitis in patients with CVID of approximately 41%, generally in patients older than 30 years [4] [12]. The diagnosis of HAI in this context is complex, because the criteria for its diagnosis require high levels of IgG, which are decreased in patients with IDCV [13] [14]. Antibody expression is usually altered, giving false negative results, so in the appropriate clinical context, histological findings and the presence of hypertransaminasemia should lead to suspicion of AIH [10]. In our case, the decision to perform a liver biopsy was based on the absence of a cause of advanced liver disease. The most common liver involvement in patients with CVID includes elevated levels of transaminases and alkaline phosphatase, nodular regenerative hyperplasia (NRH) or liver cirrhosis. NRH is defined as hepatocellular nodules less than 3 mm in diameter, not surrounded by marked fibrosis, however, histological findings on biopsy are consistent with AIH due to the presence of interface hepatitis and lymphoplasmacytic infiltrate [14].

Despite this, there are reports in which, after the administration of intravenous immunoglobulins for the treatment of IDCV, patients recover their immune response, raising IgG and serum antibody figures [1]. The use of steroids increases the risk of developing infectious processes, however, given the HAI activity data, they should be initiated for its management [10].

Patients with CVID paradoxically experience a higher risk of developing autoimmune disorders, because they share a pathophysiological basis that involves alterations in the function of B lymphocytes [5]. Given the vast array of pathology these patients can suffer from, a broad differential diagnosis is necessary when approaching a patient with CVID. A deliberate search should be made in order to offer treatment, prompt medical care and avoid late complications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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