Case Report

Fulminant Type 1 Autoimmune Hepatitis in a Recently Diagnosed Celiac Disease Patient

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Abstract

Celiac disease (CD) is a small intestine immune-mediated disorder triggered by gluten ingestion in genetically predisposed patients. This condition can also affect many extraintestinal tissues, including the liver.

We report a patient presenting with a marked increase of transaminases at diagnosis of CD. The immune markers for autoimmune hepatitis (AIH) were negative. Following a few months of a strict gluten-free diet (GFD), aminotransferase levels decreased significantly (< 2.5x U/L). The response to GFD suggested that the liver damage was due to a gluten-dependent celiac hepatitis, the most common liver abnormality in CD. Despite the fact that the patient never stopped the GFD, yet, in a few months, the aminotransferase levels raise again to high values (> 50x U/L). At this time, the liver autoantibodies turned to be positive thus confirming the development of a type 1 AIH. The hepatic damage progressed to a late onset liver failure requiring liver transplantation.

Keywords: Antinuclear antibodies, antismooth muscle antibodies, autoimmune hepatitis, celiac disease, liver transplantation

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Case Report

A 53-year-old woman was referred to our hospital for iron deficiency anemia and weakness. CD serology showed a high titer of IgA tissue transglutaminase (tTGA) and antiendomysial antibodies (EmA). Duodenal biopsy displayed a flat mucosa, confirming CD diagnosis. Laboratory tests revealed high aminotransferase levels (AST 13x, ALT 14x U/L). Cholestatic liver enzymes, bilirubin, albumin, g-globulins, and coagulation tests were normal; AIH-related autoantibodies, i.e., antinuclear (ANA), antismooth muscle (SMA), liver-kidney microsomal (LKM), and atypical antineutrophilic cytoplasmic antibodies (pANCA), and B and C viral hepatitis markers were negative. Ultrasonographic examination revealed a liver with irregular profiles and moderate hypertrophy. After four months of GFD, aminotransferases significantly decreased (AST 2.5x, ALT 1.3x), remaining slightly elevated at six months of GFD; tTGA and EmA were consistently negative. During follow-up (scheduled every two months), the patient was admitted to our hospital for jaundice and mild hepatic encephalopathy. Biochemical tests showed highly raised aminotransferase levels (AST 53x U/L, ALT 27x U/L) with acute liver failure (total bilirubin 12.8 mg / dL, direct bilirubin 7.9 mg / dL, INR 2.61). There was a polyclonal hypergammaglobulinemia (total proteins 8.5 g / dL, g-globulins 51 %) with increased IgG (4676 mg/dL). An autoantibody profile detected ANA (1/640 with homogeneous pattern), SMA (1/320 with vessel pattern), and pANCA (1/160) positivity. tTGA and EmA remained negative confirming a strict adherence to GFD. Ultrasonography detected a chronic liver disease excluding signs of biliary obstruction. Clinical profile and laboratory tests before and after GFD are shown in Table 1.

A type 1 AIH was diagnosed and the patient was started on methylprednisolone (1 mg/kg/day).[1] The clinical condition of the patient deteriorated dramatically due to severe coagulopathy and hepatic encephalopathy, rapidly progressing to coma (Figure 1). The patient was immediately referred to surgery for orthotopic liver transplantation. Liver histology showed severe fibrosis with a few remaining hepatocytes. The patient was discharged two months later and currently is in good health.

Discussion

This case report represents a clinical challenge as it was characterized by a marked aminotransferase increase of unknown origin leading to establish a diagnosis of CD; the patient's condition worsened up to liver failure requiring liver transplantation as a result of a fulminant AIH, which occurred despite a strict adherence to GFD and a temporary improvement of aminotransferase levels.

CD is a common (1 % in the general population) chronic immune-mediated disorder of the small intestine triggered by the ingestion of wheat gliadins and/or other cereal prolamins in patients with genetic predisposition.[2] Growing data indicate that CD is a systemic disorder with the involvement of many tissues and organs. The spectrum of liver abnormalities ranges from mild cryptogenic disease up to severe liver damage.[3] Liver blood test abnormalities, characterized by a mild and isolated increase of aminotransferases, have been reported in up to 47 % of adults with classical CD at the time of diagnosis.[4] Conversely, CD has been identified in about 9 % of patients with chronic unexplained hypertransaminasemia, which may be, as it was in our case, the only

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Table 1. Clinical and laboratory values at the first evaluation and at four, six, and eight months of follow- up after GFD

	First evaluation	4 months after GFD	6 months after GFD	8 months after GFD
Symptoms/Signs				
Weakness	Yes	No	No	Yes
Jaundice	No	No	No	Yes
Hepatic encephalopathy	No	No	No	Yes
Laboratory tests				
Hemoglobin (g/dL)	8.5	10.2	10.5	11
AST (x U/L)	13	2.5	4.9	53
ALT (x U/L)	14	1.3	1.2	27
g-GT (x U/L)	0.8	0.7	0.8	1.8
ALP (x U/L)	0.5	0.6	0.6	0.8
Total bilirubin (mg/dL)	1.15	1.2	1.18	12.8
Prothrombin time (INR)	1.1	1.05	1.1	2.61
Total proteins (g/dL)	8.3	8.7	8.5	8.5
Albumin (g/dL)	4.2	4.6	3.9	2.8
Gamma-globulins (g/dL)	1.8	2.2	3.1	4.3
Cholesterol (mg/dL)	221	230	225	205
Autoantibodies				
tTGA(cut-off 16AU)	80.1	15.6	8.7	8.2
EmA IgA (titer)	1 : 80	< 1 : 5	< 1 : 5	< 1 : 5
ANA (titer)	< 1 : 40	Not tested	Not tested	1 : 640
SMA (titer)	< 1 : 40	Not tested	Not tested	1 : 320
p-ANCA (titer)	< 1 : 20	Not tested	Not tested	1 : 160

AST: aspartate aminotransferase; ALT: alanine aminotransferase; g-GT: gamma-glutamintransferase; ALP: alkaline phosphatase; INR: international normalized ratio; tTGA: antitissue transglutaminase antibodies; AU: arbitrary units; EmA: antiendomysial antibodies; ANA: antinuclear antibodies; SMA: antisheer muscle antibodies; p-ANCA: antineutrophilic cytoplasmic antibodies - perinuclear pattern; GFD: gluten-free diet.

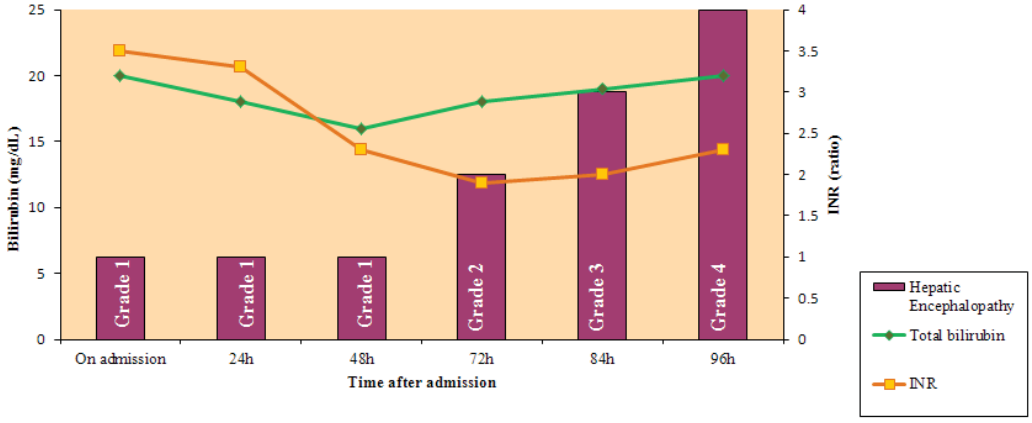

Figure 1. Evolution of hepatic encephalopathy and the main laboratory indexes (i.e., bilirubin and prothrombin time [INR]) of the patient after admission to the hospital.

sign of an atypical CD.[5] Patients treated with GFD respond with a marked improvement or even normalization (usually within six months) of aminotransferases confirming that the liver damage is gluten dependent.[4–7] As occurred in the patient herein reported, CD can coexist with autoimmune liver disorders, e.g., AIH.[3,8,9] GFD may protect CD patients from the development of related autoimmune disorders, including AIH. The reasons why in our patient the GFD was not effective in preventing the occurrence of the AIH remain unclear. Likely, a possible interpretation is that once activated the autoimmune insult to the liver may evolve despite a strict GFD.[8,9] In support of this concept, type 1 diabetes mellitus has been shown to occur in CD patients within 6 to 12 months from the beginning of GFD.[10] Finally, GFD can still significantly improve liver function and clinical manifestations, e.g., ascites and jaundice, in patients with CD-related cirrhosis.[8,11,12]

An important aspect, emerged in the analysis of this case report, pertains to the clinical relationship between gluten-sensitive enteropathy and AIH. Two independent studies based on serologic screening of CD in AIH supported the existence of an immunologic link between gluten-sensitive enteropathy and autoimmune liver damage.[13,14] The prevalence of a biopsy-proven CD in this setting is about 2.8 %.[13] Although not investigated in our patient, the identification of HLA-DR3 and -DQ2 may be a common genetic background in CD and AIH explaining the coexpression of these two conditions.[3,8] Further data are necessary to establish whether a peculiar HLA genotype may play a role in predisposing patients towards CD and AIH.

The pathophysiologic basis as to why the liver can be affected in patients with CD remains poorly explained. One explanation can be found in the abnormalities of the intestinal epithelial barrier, leading to an increased intestinal mucosa permeability, detectable in celiacs with abnormal liver tests. The increased mucosal permeability in CD is supposed to facilitate the transepithelial passage of toxic substances / infective agents which, through the blood stream, can be conveyed to the liver thereby damaging (either directly or via the immune system activation) the hepatobiliary cells.[3,8] Moreover, the small intestinal bacterial overgrowth (SIBO) has been postulated to be a possible cause of liver impair-

ment in CD. The prolonged intestinal transit in untreated CD patients can lead to SIBO with a consequent increase in the bacterial antigen pool and enzymatic production of neoantigens crossing easily a leaky intestinal epithelial barrier.[3,8]

Liver abnormalities are a common extraintestinal manifestation in CD patients ranging from mild hepatic dysfunction to severe liver disease. Cryptogenic liver disease is a quite common diagnostic label applied to a significant number of patients with undefined liver dysfunction. However, before applying this label to patients it is mandatory to exclude CD. GFD is an effective treatment which reverts aminotransferase levels to normal in most CD patients with liver dysfunction; the persistence of elevated aminotransferases after some months of GFD (provided that the patient has a good compliance to the diet) should be regarded as a possible sign of coexisting autoimmune liver disease. Therefore, it is recommended that autoantibodies related to AIH should be sought in CD patients with high aminotransferase levels at the time of diagnosis and during the follow-up, particularly in those with persistent abnormalities of liver enzymes after gluten exclusion. The outcome of liver involvement in CD is generally favorable in most cases since GFD alone or in association with immunosuppressive treatment can significantly improve liver function. In a few cases, however, as demonstrated in the case herein reported, the liver involvement can progress up to a severe organ failure requiring a prompt and more aggressive management in order to save the life of the patient.

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