Association between Celiac Disease and Chronic Hepatitis C Virus Infection

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ABSTRACT

Celiac disease affects the proximal small intestine and is caused by a local immune response to dietary gluten. Celiac disease usually presents with chronic diarrhea; however, presentations with elevated hepatic transaminase levels in blood or with iron-deficiency anemia have been described. Celiac disease has been reported to be associated with autoimmune liver diseases. Hepatitis C virus (HCV) can also initiate autoimmune disease process. Therefore, HCV infection and celiac disease may occur together. Here, we describe 4 cases of celiac disease associated with chronic hepatitis C. This small case series indicates that chronic HCV infection and celiac disease are not causally associated.

INTRODUCTION

Celiac disease is a malabsorptive condition of the small intestine that presents clinically with episodic or nocturnal diarrhea, flatulence, and weight loss. It has been increasingly recognized that celiac disease does not always present in the traditional fashion but, instead, may present with elevated hepatic transaminases levels in blood[1,2] or asymptomatically with iron-deficiency anemia.[3] Patients with certain diseases known to be epidemiologically associated with celiac disease may be screened and found to have mildly symptomatic yet clinically important gluten sensitivity. Here, we describe 4 cases of celiac disease associated with chronic hepatitis C.

Case 1

In June 2003, a 42-year-old woman was referred for the evaluation of pallor, chronic diarrhea, and persistent unexplained rise in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). She complained of generalized weakness and fatiguability for 6 years and breathlessness on exertion and loose stools, suggestive of small-bowel diarrhea for 4 months. She also had a history of abortion in 1986 at a local health center and jaundice in 1997 from which she recovered in 2–3 weeks. Physical examination revealed pallor, palpable liver 4 cm below right costal margin, and just palpable spleen. Laboratory evaluation revealed hemoglobin 7.6 g/dL, peripheral blood film showing microcytic and hypochromic red blood cells, and serum ferritin level 4.5 μg/L, suggesting iron-deficiency anemia. Serum AST and ALT levels were 152 U/L (normal 0–40) and 162 U/L (normal 0–35), respectively. Serum bilirubin, alkaline phosphatase, albumin, globulin, and prothrombin time were within normal limits. Screening evaluation for viral etiologies for chronic liver disease showed presence of antibodies to hepatitis C virus (anti-HCV) and absence of hepatitis B surface antigen (HBsAg). Hepatitis C virus ribonucleic acid (RNA) was detectable by real-time polymerase chain reaction, and the HCV RNA genotype was 1b. Her autoimmune markers were negative, and thyroid function tests were normal. Abdominal ultrasound showed mild hepatosplenomegaly without any evidence of portal hypertension. Histopathological examination of liver biopsy showed chronic hepatitis with necroinflammatory score of 5 and stage of 3.[4]

As a workup for chronic diarrhea, her stool routine examination was normal and D-xylose absorption test was abnormal (0.8 g/5 g/5 h). H_2 breath test was suggestive of lactose intolerance. Serum vitamin B_{12} level was 250.36 pg/mL (normal 100–700). Serum antigliadin antibodies (AGA) level was 94.3 units (normal 0.001–10.00). Esophagogastroduodenoscopy revealed mild antral gastritis and atrophic duodenal folds; there were no esophageal varices. Mucosal biopsies from second part of duodenum showed subtotal villous atrophy.

A gluten-free diet with iron and vitamin supplements was initiated for the treatment of celiac disease and iron-deficiency anemia. Her hemoglobin showed a rise from 7.6 g/dL to 12 g/dL, her diarrhea also settled, and she gained weight. Her AGA became negative. She received pegylated interferon-α-2b (80 μg subcutaneously every week)

Keywords: Autoimmune disease, celiac disease, hepatitis C virus infection
Received: 08.06.2011; *Accepted:* 09.06.2011
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Abbreviations: AEA: anti-endomysial antibodies; AGA: antigliadin antibodies; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HLA: human leukocyte antigen; Ig: immunoglobulin; RNA: ribonucleic acid; WBC: white blood cell
doi: 10.1016/S0973-6883(11)60116-3

and ribavirin (1000 mg/day) for hepatitis C for 1 year. Her serum AST and ALT levels normalized and HCV RNA became negative at 24 and 48 weeks. She also attained sustained viral response as her HCV RNA remained negative for 6 months after the completion of therapy.

Case 2

A 32-year-old woman presented with history of awareness of mass in left upper abdomen, recurrent episodes of mild fever, and generalized weakness since 13 years of age. She complained of frequent large volume of loose stool and abdominal distension for 1½ months. She also had a history of loose stools lasting for few weeks, l8 years ago; she used to have 9–10 episodes/day associated with bloating sensation, passage of undigested food particle, and nocturnal episodes. She received oral iron and vitamin supplementation. She also received blood transfusion twice in 1996 and then in 2002 for anemia. She had an abortion 1 year ago for nonviable fetus of 2 months. She had jaundice in 1996, which lasted for few weeks; however, she was not investigated for this episode of jaundice. Physical examination revealed pallor, nonpalpable liver with a liver span of 10 cm, palpable spleen 6 cm below left costal margin, and moderate ascites.

Laboratory evaluation showed a serum hemoglobin 3.9 g/dL, total white blood cell (WBC) 1200/mm^3, platelets 81,000/mm^3, peripheral blood film showing microcytic and hypochromic anemia, and serum ferritin <15 µg/L. Serum AST and ALT levels were 113 U/L and 243 U/L, respectively; serum alkaline phosphatase was 391 U/L (normal 143–340), serum bilirubin 0.9 mg/dL, and prothrombin time 18 seconds (control 12). Screening evaluation for viral etiologies for chronic liver disease showed positive anti-HCV antibodies and detectable HCV RNA. She tested negative for HBsAg. Her ascites fluid revealed high serum-ascites albumin gradient, normal WBC counts, and sterile culture. An abdominal ultrasound showed small liver with irregular surface, heterogenous echotexture, gross splenomegaly with dilated portal and splenic veins, and ascites. Esophagogastroduodenoscopy showed grade 3 esophageal varices. Sulfur colloidal hepatic scan was suggestive of cirrhosis. She did not receive treatment for hepatitis C as she was suffering from decompensated cirrhosis of liver with a Child Turcotte Pugh's score of 9.

She was worked up for small-bowel diarrhea, which revealed normal routine stool examination, normal serum vitamin B_{12} level, and abnormal D-xylose absorption test. Serum immunoglobulin (Ig) A anti-endomysial antibody was positive. Mucosal biopsies from distal part of duodenum showed subtotal villous atrophy.

A gluten-free diet with iron and vitamins supplements was initiated for the treatment of celiac disease and associated iron-deficiency anemia. Her hemoglobin showed a rise from 3.9 g/dL to 11.5 g/dL; diarrhea also settled.

Case 3

A 32-year-old man presented with a history of easy fatigability, anemia requiring multiple blood transfusions, and intermittent episodes of small-bowel diarrhea since childhood. His hemogram was suggestive of iron-deficiency anemia. Liver function test showed elevated AST (85 IU/L) and ALT (49 U/L), and normal serum bilirubin, albumin, and prothrombin time. His AGA and antitissue transglutaminase antibodies were positive, and biopsy from second part of duodenum showed partial villous atrophy with increased intra-epithelial lymphocytes. He tested positive for anti-HCV antibody but negative for HBsAg. His serum HCV RNA was positive. Esophagogastroduodenoscopy showed grade 2 esophageal varices. Ultrasound was suggestive of cirrhosis of liver with portal hypertension.

He was treated with a gluten-free diet with iron and vitamin supplements for the treatment of iron deficiency anemia and celiac disease. He is maintaining hemoglobin of 11 g/dL. The patient was not willing treatment for chronic hepatitis C.

Case 4

A 32-year-old man presented to the outpatient clinic with intermittent episodes of watery, non-bloody diarrhea from 4 to 5 years. He also complained of generalized weakness and fatigability. The patient had anemia since childhood, requiring hematinics and blood transfusions. He was incidentally detected to be positive for anti-HCV antibody. On examination, he appeared to be malnourished. There was no icterus. Examination of abdomen revealed hepatosplenomegaly, with liver span of 14 cm and spleen being palpable 4 cm below the left costal margin.

Investigations showed hemoglobin 11.7 g/dL. Liver function tests showed elevated AST (85 U/L) and ALT (49 U/L), total serum bilirubin 0.6 mg/dL, albumin 5.8 g/L, and globulin 3.7 g/L. His autoimmune workup was negative. Antibody to tissue transglutaminase was elevated to 74.00 U/mL. Duodenal biopsy taken from second part of duodenum showed partial villous atrophy and intra-epithelial lymphocytes. Iron workup showed iron-deficiency anemia. D-xylose absorption test was abnormal (0.8 g/5 g/5 h). Esophagogastroduodenoscopy revealed 3 columns of grade 2 esophageal varices. No varices were seen in the gastric region. Ultrasound of abdomen showed parenchymal disease of the liver with splenomegaly. Collaterals at splenic hilum were seen along with evidence of lienorenal shunt. Liver biopsy was not done due to unwillingness of the patient for the procedure.

This patient was simultaneously suffering from chronic hepatitis C, the diagnosis of which was supported by positive antibody for hepatitis C, elevated transaminases, serum HCV RNA levels of 4.2 million IU/mL and genotype-3.

The patient was put on gluten-free diet, and his hemoglobin improved from 11.7 g/dL to 14.2 g/dL. He was later

started on treatment for hepatitis C with pegylated interferon-α-2b 80 μg/week subcutaneously and ribavirin 1000 mg/day. The therapy was continued, and the patient achieved end-of-treatment response after 24 weeks of treatment. With the treatment for celiac disease and hepatitis C, the patient started gaining weight. His symptoms resolved. The transaminases were down to the normal values. The patient's last tissue transglutaminase antibody was 0.79 U/mL, and he also achieved sustained viral response after 1 year of therapy for hepatitis C.

DISCUSSION

The prevalence of celiac disease in patients with chronic liver disease is at least 1.5%, which is 15 times higher than that in the general population.[5] Celiac disease has been reported in 5% of the patients with autoimmune hepatic disease.[6] The association of hepatitis C and celiac disease has been reported earlier.[7–12] The association between HCV and celiac disease can be causal or a coincidental finding. HCV has been identified to cause secondary autoimmune processes in other parts of the body, including development of antinuclear antibodies, mixed cryoglobulinemia, lichen planus of the skin and mouth, and Sjogren's syndrome. Therefore, HCV infection also may have an increased prevalence of celiac disease, which is also an autoimmune disease.

Hepatitis C virus can initiate autoimmune disease process.[13,14] Viral infections have been suspected for many years to act as pathogenetic triggers for the immunologic reactions of celiac disease in genetically predisposed individuals.[14] Thus, hepatitis C is a potential candidate for stimulating this phenomenon. Furthermore, a solitary case report has shown that the cell-mediated inflammatory response to the HCV may involve T cells restricted to human leukocyte antigen (HLA)-DQ2, the class II HLA allele linked to celiac disease.[15]

Hepatitis C virus is a blood-borne pathogen, which is the most common cause of posttransfusion hepatitis worldwide. Blood transfusion in many of patients with celiac disease for anemia might have led to HCV infection. We believe that 3 of our patients might have acquired HCV infection during blood transfusion for anemia due to celiac disease, while the other patient might have acquired HCV in 1986 when she had abortion and underwent dilatation and curettage. Therefore, a coincidental rather than a causal relationship is more likely between celiac disease and HCV infection in our patients. Recently, Thevenot et al[16] conducted a multicenter prospective study to determine the prevalence of celiac disease in a large population of HCV-infected patients consecutively tested for the presence of IgA and IgG AGA and IgA anti-endomysial antibodies (AEA). The prevalence of celiac disease in HCV-positive patients was 0% (95% confidence interval: 0–0.59%); this was not higher than that in general population. In a cross-sectional study, Hernandez et al[17] also did not find increased prevalence of celiac disease in patients with HCV infection.

Interferon treatment has been shown to be associated with onset of celiac disease. There are reports of patients in whom treatment with interferon-α for hepatitis C led to celiac disease.[17–24] This suggests that interferon-α may precipitate the development of celiac disease in susceptible individuals. This is consistent with the known fact that interferon-α may precipitate or worsen autoimmunity in some individuals. Hence, physicians should be aware that celiac disease is an autoimmune disease that may become evident after the commencement of interferon-α therapy in patients with chronic hepatitis C. Routine screening of celiac disease in HCV patients is not warranted; however, the presence of celiac disease should be considered in the setting of clinical deterioration during or after interferon-α therapy. In our cases, none of the 4 individuals received interferon treatment prior to diagnosis of celiac disease, thus ruling out this possibility completely.

This small case series indicate that chronic HCV infection and celiac disease are not causally associated.

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