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Primary Biliary Cirrhosis and Adult Celiac Disease

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OVERLAPPING SIGNS and symptoms of two relatively rare disorders, celiac disease and primary biliary cirrhosis (PBC), may result in delays in establishing the diagnosis of both conditions. In a patient with diagnosed celiac disease, persistently abnormal results of liver function tests after symptomatic improvement on a gluten-free diet should arouse suspicion of primary liver disease.

Report of a Case

The patient, a 59-year-old airline pilot, was seen in September 1988 because of persistently abnormal results of liver function tests dating to 1980 and with the chief complaint of intermittent diarrhea and weight loss of 18 months' duration. The patient had 8 to 20 pale, foul-smelling, nonbloody bowel movements daily associated with bloating after meals and borborygmi. On occasion the diarrhea occurred during the night and had not been associated with abdominal discomfort. Despite what the patient perceived as an adequate dietary intake, he had lost about 9 kg (20 lb) during the first six months of his diarrhea. His weight had been relatively stable for a year since then. There had been no fevers, pruritus, or abdominal pain. He did not use laxatives, and he had not traveled outside of the country. He had not had exposure to water suspected of harboring *Giardia* species, nor had he received antibiotics in the past several years.

His medical history was unremarkable other than having persistently abnormal liver function for six years. He had not had previous abdominal operations or radiation exposure. He took no medications other than occasional vitamins, and there was no notable history of alcohol use. He had been a ten pack-year smoker. There was no family history of gastrointestinal diseases. There were no symptoms suggestive of extraintestinal manifestations of inflammatory bowel disease.

On physical examination, he was afebrile, weighed 79 kg (174 lb), was 177 cm (5 ft 10 in) tall, and had no skin stigmata of end-stage liver disease. His abdomen was nontender, and there was no evidence of organomegaly. His stool was pale, grossly fatty, and negative for occult blood. A sigmoidoscopic examination was unremarkable, as was histologic evaluation of rectosigmoid mucosal biopsies. Stool culture and ova and parasite studies were negative. The hemoglobin level was 132 grams per liter (13.2 grams per dl).

Laboratory data since 1982 were reviewed. His alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels had been elevated during that time, minimally at first and gradually rising thereafter (Table 1). The serum bilirubin value was normal. An upper gastrointestinal x-ray study with small bowel follow-through revealed coarsening of duodenal folds, some narrowing of the descending duodenum, and dilatation of the small bowel with a mucosal pattern compatible with sprue. Upper gut endoscopy was then done. Excellent-quality biopsy specimens of small intestine were obtained, revealing total villous atrophy with glandular crypt hyperplasia and intraepithelial lymphocytes consistent with celiac disease (Figure 1). The patient was placed on a gluten-free diet, and his steatorrhea resolved shortly thereafter. His weight had increased 3.2 kg (7 lb), and his subjective feeling of strength was increased. Examination of his stool showed no evidence of fat.

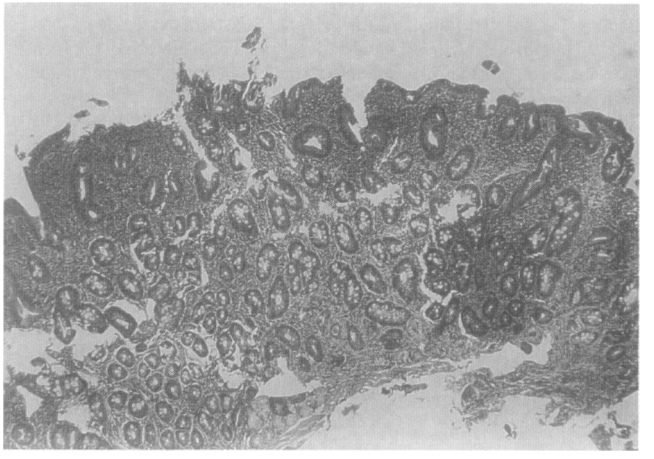

Figure 1.—The small intestine mucosal biopsy shows total villous atrophy. The mucosal glandular crypts have a hyperplastic appearance and are elongated. The lamina propria contains an increased amount of chronic inflammatory cells with an increased number of intraepithelial lymphocytes at the absorptive surface (hematoxylin and eosin stain; original magnification × 25).

The results of follow-up liver function tests initially were nearly normal in 1989 as well. Despite the resolution of his steatorrhea and gradually increasing body weight, however, liver function test levels began to rise thereafter. In January 1990 his alkaline phosphatase level was 442 units per liter. An antimitochondrial antibody test was positive at a dilution of 1:4,096 (normal $<1:40$). His antismooth muscle antibody test was trace positive at a dilution of 1:64 (normal $<1:40$). A needle liver biopsy was done a month later that showed findings of primary biliary cirrhosis (Figure 2) and precirrhotic bridging fibrosis (Figure 3). The liver biopsy showed no evidence of sclerosing cholangitis. At that time

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
AST = aspartate aminotransferase
PBC = primary biliary cirrhosis

his immunoglobulin M level was 3.29 grams per liter (329 mg per dl) (normal 0.40 to 2.50). Antinuclear antibody, serum copper, and ceruloplasmin levels were normal. Alkaline phosphatase isoenzyme measurements revealed an increased liver fraction. Endoscopic retrograde cholangiopancreatography was not done because of the lack of evidence for cholangitis or inflammatory bowel disease.

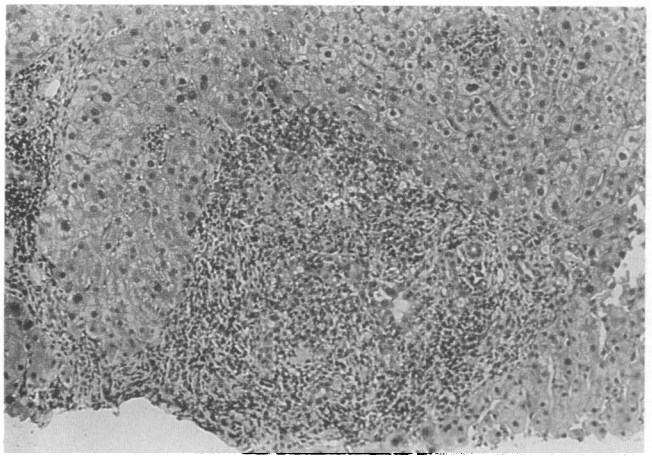

Figure 2.—A liver needle biopsy shows enlargement of the portal area with a prominent epithelioid granuloma. There is an increased number of lymphocytes that impinge on bile ducts and show evidence of glandular destruction. There is no evidence of cholangitis (hematoxylin and eosin; original magnification × 100).

In February 1990, he was placed on a regimen of ursodeoxycholic acid in a dose of 300 mg twice a day in the hope of preventing cirrhosis. Follow-up laboratory data two months later revealed improvement of his liver function test results (Table 1). His alkaline phosphatase level had dropped to 253 units per liter, and his AST and ALT levels were only minimally elevated at 41 and 46 units per liter, respectively. He continues to feel well without evidence of pruritus or other symptoms referable to hepatic dysfunction. Follow-up small bowel and liver biopsies have not been performed to date.

Discussion

Since 1978, there have been 20 case reports of patients—15 female and 5 male—with both celiac disease and PBC.[1-12] Three of these cases were described in letters to the editor.[2,3,10] Once patients were placed on a gluten-free diet—

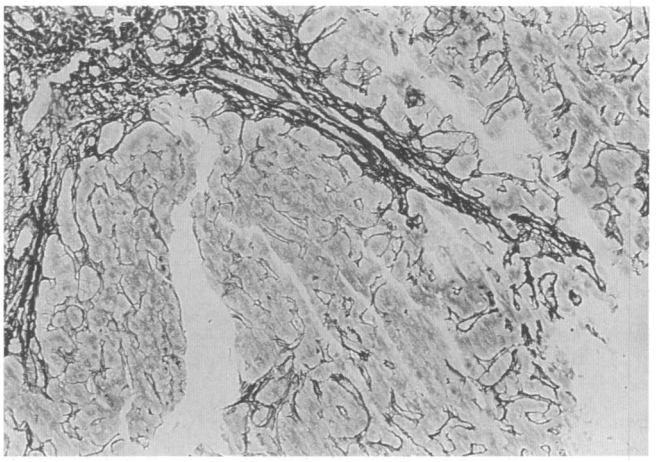

Figure 3.—A reticulin stain of a liver needle biopsy shows moderate portal fibrosis. There is extension of reticulin fibrosis along lobular margins with portal-to-portal bridging (original magnification × 100).

reported in 11 patients[1,5,8,11]—their diarrhea usually resolved but the results of liver function tests remained unchanged. In one patient, pruritus developed after small bowel mucosal damage healed.[1] The effect of a gluten-free diet on liver function test results in three cases was not reported.[2-4] Olsson and co-workers reported that of 26 consecutive patients with PBC, 5 had intestinal villous atrophy.[5] Three of these five patients were male. Four had positive antismooth muscle antibody tests, and one was positive for antinuclear antibody. HLA-B8 was present in three.

A case of celiac disease was reported in a 69-year-old man who had a history of PBC followed by dermatitis herpetiformis.[8] After a year on a gluten-free diet, the jejunal biopsy appearance had almost returned to normal and the skin problems had almost completely disappeared. In a study of the prevalence of PBC in a Swedish population, two patients were found to also have celiac disease complicated by osteomalacia.[9] In 1986, a case of celiac disease and PBC was reported in a woman who had presented initially with diarrhea that responded to a gluten-free diet, but her liver function test results did not return to normal.[11] Seven years later, ascites, jaundice, and hepatosplenomegaly developed. A postmortem liver biopsy showed PBC. The most recent case of PBC and celiac disease was in a woman who was also found to have renal tubular acidosis in association with Sjögren's syndrome.[12]

Primary biliary cirrhosis is a rare chronic disease of unknown etiology, primarily affecting middle-aged women, that is characterized by inflammation and necrosis of intrahepatic bile ducts.[13] It may be associated with autoimmune syndromes—Sjögren's syndrome, seronegative arthritis, progressive systemic sclerosis, and thyroiditis.[12] Its onset is

TABLE 1.—*Historical Laboratory Data*

Serum Laboratory Test	*1982*	*1985*	*1988*	*1989* *Feb/July*		*1990* *Jan/Apr*	
Aspartate aminotransferase, units/liter*	76	54	128	69	64	113	41
Alanine aminotransferase, units/liter*	135	83	144	90	101	133	46
Serum alkaline phosphatase, units/liter†	152	158	422	228	329	422	253
Serum total bilirubin, μmol/liter (mg/dl)‡	7 (0.4)	7 (0.4)	12 (0.7)	--	--	10 (0.6)	--

*Reference range, < 40 units/liter.
†Reference range, 35 to 65 units/liter.
‡Reference range, 0 to 26 μmol/liter (0.0 to 1.5 mg/dl).

usually insidious. Asymptomatic patients without physical abnormalities are often diagnosed on the basis of laboratory abnormalities alone.[14] Malabsorption may occur, which has been shown to be due to intraluminal bile acid deficiency.[15] Pruritus and skin pigmentation are considerably less prominent in men initially, but survival is similar among men and women.[16]

Celiac disease is a rare disease of the small intestine that is characterized by villous atrophy of the cryptic hyperplastic type and malabsorption. It is caused by hypersensitivity to cereal, grains, and storage proteins (gluten or a substance derived from gluten, gliadin) found in wheat, barley, and rye. Celiac disease generally occurs either as a disease limited to the gastrointestinal tract or in conjunction with dermatitis herpetiformis.[8] It has also been associated with autoimmune diseases, including thyrotoxicosis, diabetes mellitus, fibrosing alveolitis, and chronic active hepatitis.[17]

Liver function disturbances in adult patients with celiac disease are not unusual and are generally thought due to nonspecific reactive hepatitis or fatty infiltration. Moreover, osteomalacia resulting from malabsorption may cause elevated alkaline phosphatase levels. An association of primary sclerosing cholangitis and celiac disease was noted in three men who had chronic cholestatic liver disease that led to endoscopic cholangiopancreatography; these men had fibrous or inflammatory cholangitis on liver biopsy.[18] Hagander and colleagues found nonspecific histologic evidence of liver injury in 16% and abnormal results on liver function tests in 39% of patients with celiac disease.[19] Elevated aminotransferase activities usually decreased substantially after a gluten-free diet was instituted. In theory, nonspecific morphologic hepatic changes should resolve once a patient is treated.

Behr and Barnert discussed current theories regarding a common cause of PBC and celiac disease.[11] One theory concerns the formation of immune complexes with a common antigenic basis, which mediate tissue damage. To date, however, no specific antigen has been identified nor is there general acceptance that PBC is an immune complex disease. A second theory postulates a diminished function of suppressor T cells in patients with PBC and celiac disease, which permits effector cytotoxic lymphocytes to attack a modifying antigen, that is, gluten.[20] These effector cells would recognize and attack a patient's own histocompatibility antigens. This theory requires that the recognized antigens are either present in high concentration in biliary epithelial cells or that they are modified in some way.[21]

The case reports outlined here suggest that concomitant celiac disease and PBC may occur more often in men than would be expected based on the incidence of PBC in men. The eventual occurrence of both disorders may be more common than is generally realized, if patients are tested carefully and observed for a long enough period of time. We recommend for patients with either of these two diseases that they be observed not only to assess their condition and response to treatment of the recognized problem, but also to look for signs and symptoms of the other disease. In particular, patients with intestinal malabsorption due to celiac disease should have periodic liver enzyme tests because persistent abnormal results may be the only clinical manifestation of liver disease.

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