Nonalcoholic chronic pancreatitis with pancreatic calcification: Presenting manifestation of occult celiac disease

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Celiac disease (gluten-sensitive enteropathy) and chronic pancreatitis with exocrine insufficiency are both relatively frequent causes of impaired nutrient absorption, steatorrhea and weight loss. Occasionally, celiac disease has been associated with diabetes, but coexistence of celiac disease and advanced exocrine pancreatic insufficiency has only rarely been seen (1-7).

Pancreatic calcification is most frequently associated with chronic or persisting pancreatic inflammation which, in North America, is most often attributed to a high intake of alcohol. Atrophy, fibrosis and altered function of the pancreas has been observed in experimental animals treated with diets deficient in protein (8), in adults with protein-energy malnutrition (9), in children with kwashiorkor (10,11) and in some early autopsy studies of patients with celiac disease (12). In addition, pancreatic calcification has been seen with chronic protein malnutrition in the Indian subcontinent and in some African countries (8). Finally, a patient with celiac disease and associated tropi-
cal calcific pancreatitis has recently been described (13).

The present report describes a diabetic female with pancreatic exocrine insufficiency and calcification. Persisting diarrhea and weight loss led to further investigations and, eventually, a diagnosis of celiac disease. In the absence of alcohol use, pancreatic calcification may be the presenting feature of occult celiac disease reflecting the presence of impaired absorption and longstanding severe protein-energy malnutrition.

**CASE PRESENTATION**

A 62-year-old Canadian Caucasian female was referred in 1987 for evaluation of diarrhea and weight loss. Past history included diabetes treated for five years with oral hypoglycemic agents and a prior cholecystectomy for gallstones in 1980. An investigation for diarrhea in 1985 demonstrated anemia with a hemoglobin of 118 g/L (normal 120 to 140), hypoalbuminemia with a serum albumin of 32 g/L (normal 36 to 48) and steatorrhea with a fecal fat of 45.3 g/day (normal less than 7). In addition, endoscopic and barium studies of the upper and lower intestine were normal but pancreatic calcification was noted (Figures 1, 2). Fecal cultures and studies for ova and parasites were negative. Pancreatic enzyme supplements (pancrelipase, to 15 capsules daily) and ranitidine 300 mg daily resulted in a reduction in the fecal fat to 9.1 g/day.

Because of continued diarrhea, weight loss of 14 kg and development of bilateral pitting edema in both lower extremities, the patient was reviewed at University Hospital in January 1987. In spite of pancreatic calcification, there was no prior alcohol use, abdominal trauma, hyperlipidemia, familial history or foreign travel. Laboratory tests revealed (normal ranges in brackets): hemoglobin, 108 g/L (120 to 140); normal white blood cells and platelets; prothrombin time, 16.4 s (10 to 12.5); total protein, 43 g/L (60 to 77); serum albumin, 14 g/L (36 to 48); serum calcium, 7.6 mg/dL (8.6 to 10.6); and serum magnesium, 1.5 mg/dL (1.8 to 2.4). Alkaline phosphatase was 160 IU/L (normal 30 to 110), aspartate aminotransferase was 64 IU/L (normal 5 to 47), total bilirubin was 1.0 mg/dL (normal 0.14 to 1.34) and gamma-glutamyltransferase was 32 (normal 5 to 55). Hepatitis virus serology, antinuclear and antimitochondrial antibodies were negative, and serum ferritin, copper, ceruloplasmin, zinc, amylase and lipase were normal. Measurements of immunoglobulins G, A and M were normal. Urinalysis and 24 h urine protein determination were normal. An abdominal ultrasound confirmed the absence of a gallbladder and the presence of pancreatic calcification. The result of a 72 h fecal fat study on a daily oral intake of 100 g fat was 50.3 g of fecal fat/day. Prothrombin time corrected to 11.8 s with vitamin K administration. With pancreatic enzyme supplements, fecal fat fell to 7.7 g/day (normal less than 7). Liver biopsy showed steatosis and periodic acid-Schiff reagent positive hepatocyte nuclear vacuoles typical of...
glycogen but no inflammation. In particular, changes of alcoholic hepatitis were absent and perivenular sclerosis as well as Mallory’s hyaline were not seen. Small intestinal biopsies revealed a severe ‘flat’ mucosal lesion (ie, crypt hyperplastic villous atrophy) consistent with celiac disease (Figure 3). She was treated with a gluten-free diet, glyburide 10 mg daily, pancrelipase capsules to 15 daily and ranitidine 300 mg daily.

The patient was re-evaluated in May 1987. Energy had improved, edema had resolved and her weight increased by 8 kg. Laboratory investigations revealed resolution of anemia (hemoglobin 125 g/L), hypoproteinemia (total protein 65 g/L) and hypoalbuminemia (serum albumin 38 g/L).

In spite of her improved clinical state and laboratory tests, a small intestinal biopsy showed no morphological change. In February 1988, diarrhea recurred but poor gluten-free diet compliance was evident. Hemoglobin was 108 g/L and serum albumin was 20 g/L while other blood tests were normal. A barium radiographic study of upper gastrointestinal tract was normal with no radiological evidence of lymphoma. A computed tomography abdominal scan showed some fatty infiltration in the liver and pancreatic calcification. Thyroid studies revealed serum triiodothyronine (T3) levels of 0.9 and 0.7 nmol/L (normal 1.2 to 2.8) and serum thyroxine (T4) levels of 92 and 76 nmol/L (normal 58 to 154) while thyroid antibodies were positive at a dilution of 1:6400. Small intestinal biopsies showed no improvement. A strict gluten-free diet was urged. By October 1988, her bowel habit was normal and her weight had increased by a further 10 kg. Laboratory studies were normal including: hemoglobin (148 g/L), prothrombin time (11.0 s), serum albumin (41 g/L), serum iron, ferritin, folic acid, vitamin B12, carotene, calcium, phosphate, magnesium, alkaline phosphatase, aspartate aminotransferase and gamma-glutamyltransferase. An abdominal ultrasound showed pancreatic calcification but fatty infiltration of the liver had resolved. Biopsies of the small intestine showed morphological improvement with reappearance of the villi, and biopsies of the gastric mucosa were normal with none of the features of lymphocytic gastritis (14) or mucosal glandular atrophy. A repeat fecal fat study on a 100 g fat gluten-free diet with supplemental pancreatic enzymes was 5 g fat/day.

Subsequent follow-up laboratory studies (hemoglobin, white blood cell count, carotene, iron and iron binding capacity, red cell folate, vitamin B12, calcium, total protein and serum albumin) in April 1989, April 1990, April 1991, May 1992 and September 1993 have been normal. Repeated small intestinal biopsies at each of these visits revealed villi while gastric and colonic biopsies in May 1992 were normal with no epithelial lymphocytosis (15).

DISCUSSION

The patient described in this report initially presented with weight loss and steatorrhea. Chronic pancreatitis with pancreatic calcification that responded to pancreatic enzymes was diagnosed. In the presence of steatorrhea, it was believed that severe pancreatic insufficiency was responsible (16). However, in spite of supplemental pancreatic enzymes, further weight loss developed along with hypoalbuminemia and peripheral edema. Further studies led to detection of occult celiac disease that was responsive to a gluten-free diet. This report further emphasizes the need to establish firmly the cause or causes for impaired nutrient absorption and weight loss in patients with steatorrhea. In celiac disease, it has long been recognized (1) that an incomplete clinical response to a gluten-free diet may be due to occult pancreatic disease. Conversely, as in the present report, a poor clinical response to pancreatic enzyme supplements in a patient with chronic pancreatic insufficiency, even with calcific pancreatitis, should lead to re-evaluation and exclusion of a possible superimposed small intestinal cause for impaired absorption and steatorrhea, such as celiac disease.

Pancreatic exocrine insufficiency in patients with small intestinal disease may lead to steatorrhea through a number of possible mechanisms. First – and possibly more frequent than is appreciated – impaired elaboration and/or release of pancreatic stimulating hormones from diseased proximal small intestine may result (17). Previous quantitative immunocytochemical studies from our laboratory demonstrated significant alterations in the numbers of entero-endocrine cells in proximal small intestinal biopsies from seven celiac patients compared with five nonceliac controls (18). In particular, a complete absence of mucosal secretin cells in biopsies from celiac patients was noted (18). Studies with test meals in celiac patients also suggested that impaired secretion of cholecystokinin-pancreozymin (and, consequently, pancreatic enzyme stimulation) and intraluminal dilution of pancreatic lipase rather than lipase deficiency per se contributes to steatorrhea in some patients with celiac disease (19). Second, a deficiency of amino acids may result, in part, from impaired small intestinal transport of amino acids and this deficiency could result in a diminution in the precursors available for pancreatic enzyme synthesis (4). Third, protein malnutrition per se may result in structural changes in the pancreas, including acinar cell atrophy and pancreatic fibrosis (12,19) with resultant impairment in pancreatic exocrine function.

Although studies of pancreatic pathology with chronic alcohol use have revealed pancreatitis with calcification as the cause of exocrine failure (20), the present report emphasizes that other causes, in addition to chronic alcohol use, should be considered, including celiac disease with severe malabsorption and concomitant protein deficiency. In an earlier report (7) a woman of Russian origin was described with celiac disease and chronic calcific pancreatitis but no information was provided on alcohol consumption. In a recent report from India (13) tropical calcific pancreatitis was associated with celiac disease in a patient who did not consume alcohol. The authors suggested that the celiac disease may have contributed to the development of calcification of the pancreas.

In the present report, chronic calcific pancreatitis was documented in an
elderly patient who did not consume alcohol and had no foreign travel or familial history of pancreatic disease; in this patient, calcific pancreatitis, possibly due to her protein deficient state,

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