Associated ulcerative colitis, sclerosing cholangitis, and insulin-dependent diabetes mellitus

MARSHA KAY, MD; ROBERT WYLLIE, MD; WILLIAM MICHENER, MD; MAUREEN CAULFIELD, MD; RITA STEFFEN, MD

■ We report two young men with clinical and laboratory evidence of macroscopic ulcerative colitis, sclerosing cholangitis, and insulin-dependent diabetes mellitus. The first patient presented at age 15 with vomiting, abdominal pain, weight loss, and abnormal liver function test results. Liver biopsy and endoscopic retrograde cholangiopancreatography (ERCP) demonstrated sclerosing cholangitis. Colonoscopy with biopsy revealed ulcerative colitis which responded to sulfasalazine. Diabetes occurred at age 18 and insulin therapy was begun.

The second patient was 19 at presentation with diarrhea, hematochezia, and weight loss. Proctosigmoidoscopy revealed ulcerative colitis, and sulfasalazine led to clinical remission. Three months later he developed diabetes requiring insulin therapy. At age 28, he developed elevated alkaline phosphatase, and ERCP revealed sclerosing cholangitis. At age 37 he expired from adenocarcinoma that metastasized to the liver.

Literature review revealed only one possible case report of this association with microscopic asymptomatic ulcerative colitis in that patient. Statistical analysis suggests that this association is real rather than a chance occurrence. An autoimmune process may be involved and a specific histocompatibility locus antigen (HLA) type may exert a regulatory influence.

■ INDEX TERMS: COLITIS, ULCERATIVE; CHOLANGITIS, SCLEROSING; DIABETES MELLITUS, INSULIN-DEPENDENT ■ CLEVE CLIN J MED 1993; 60:473–478

From the Section of Pediatric Gastroenterology and Nutrition, The Cleveland Clinic Foundation.

Address reprint requests to R.W., Head, Section of Pediatric Gastroenterology and Nutrition, Department of Pediatrics, A120, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

CLINICALLY symptomatic ulcerative colitis, sclerosing cholangitis, and insulin-dependent diabetes mellitus have not previously been reported in the same patient. Although each may be associated with the other, their occurrence in the same individual implies a common susceptibility, perhaps involving the immune system. We have identified two patients with each of these disorders. These two young men were followed up at The Cleveland Clinic Foundation between 1970 and 1992.

PATIENT 1: CASE HISTORY

Patient 1 presented at age 15 years with a chief complaint of abdominal pain and vomiting for 4 months. He denied diarrhea, constipation, hematemesis, hematochezia, melena, fever, and joint, mouth, or skin problems. His medical history was unremarkable. Family history revealed a maternal great uncle and a paternal aunt with diabetes mellitus.

His local physician performed an upper gastrointestinal study with a small-bowel follow-through, which revealed thickening of the duodenal sweep but was otherwise unre-

markable. He was treated with dicyclomine hydrochloride and hydroxyzine hydrochloride without symptomatic relief and was admitted to his local hospital. A blood workup revealed the following values, with normal ranges in parentheses: an amylase level of 310 U/L (23 to 85 U/L), lipase 50 IU/L (4 to 24 IU/L), erythrocyte sedimentation rate 101 mm/hour (0 to 15 mm/hour), platelet count 515 000 (130 to 400 × 10^3), alkaline phosphatase 496 IU/mL (50 to 136 IU/mL), alanine aminotransferase (ALT) 96 IU (10 to 35 IU), aspartate aminotransferase 102 IU (7 to 50 IU), total protein 10 g/dL (6 to 8 g/dL), and globulin 5.5 g/dL (2.3 to 3.5 g/dL). Ceruloplasmin levels were normal. Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) were negative. Tests for antimitochondrial, antinuclear factor, toxoplasmosis, and cytomegalovirus antibodies were negative. Anti-smooth-muscle antibody was positive, with a titer of 1:40 (reference: negative). A liver scan and abdominal ultrasound suggested a mass in the head of the pancreas. Computerized tomography of the abdomen was normal. Exploratory laparotomy revealed intra-abdominal lymphadenopathy and a normal pancreas. Liver biopsy performed during surgery showed widened portal tracts, portal edema and fibrosis, focal ductal proliferation, and neutrophilic infiltration of the bile ducts. Several bile ducts were surrounded by lymphocytic and histiocytic infiltrates and dense fibrotic tissue, consistent with primary sclerosing cholangitis.

Patient 1 was subsequently referred to The Cleveland Clinic Foundation for further evaluation. Physical examination revealed a height at the 80th percentile and a weight at the 30th percentile. His liver span was 7 cm with no lymphadenopathy. Rectal exam was positive for occult blood. The physical examination was otherwise unremarkable. Laboratory studies demonstrated elevation of amylase to 533 IU (83% salivary origin) (normal range 10 to 135 U/L), and a Westergren sedimentation rate of 62 mm/hour (normal range 0 to 20 mm/hour); the alanine aminotransferase level and platelet count were mildly elevated. Aspartate aminotransferase and alkaline phosphatase values were normal. Hepatitis A (anti-HAV), hepatitis B (HBsAg, anti-HBs), and antimitochondrial antibody studies were negative. Smooth muscle antibody studies were positive, with a titer of 1:10.

Ultrasound of the gallbladder and pancreas revealed a distended gallbladder without biliary duct dilation and a normal pancreas. Esophagogastroduodenoscopy revealed linear erosions in the gastric fundus. Colonoscopy demonstrated diffusely granular mucosa with punctate areas of hemorrhage from the rectum to the cecum consistent with ulcerative colitis. Biopsy revealed diffuse chronic inflammation with crypt abscess formation, and no granulomas. Endoscopic retrograde cholangiopancreatography (ERCP) showed several areas of irregular filling in the common bile duct, common hepatic duct, and intrahepatic ducts consistent with primary sclerosing cholangitis. The pancreatic duct was normal. Repeat liver biopsy demonstrated expansion of the portal tracts with a mixed acute and chronic inflammatory infiltrate, fibrosis with focal areas of pseudo-bile-duct proliferation, hyalinization of connective tissues around preexisting bile ducts, slight ballooning within the liver parenchyma, and bridging between the portal tracts, consistent with sclerosing cholangitis.

The patient's condition was stabilized, and he was discharged on sulfasalazine, 1 g bid. He did well, with a 30-kg weight gain, decreased stool frequency and abdominal pain, resolution of hematochezia, and normalization of liver function tests.

He presented 3 years later with an 8-kg involuntary weight loss over 6 weeks, diminished energy, polydipsia, and nocturia. He was admitted to the hospital. Laboratory examination revealed urinalysis with 30 mg/dL glucose and trace ketones, blood glucose values between 200 and 300 mg/dL (normal range 65 to 110 mg/dL), elevated glycosylated hemoglobin 14.4% (3.5% to 6.5%), and a diminished insulin level 2.5 μU/mL (4 to 24 μU/mL); serum electrolytes, complete blood count, and thyroid function tests were normal.

His condition was stabilized on a regimen of regular and intermediate-acting insulin, and he was discharged. Since discharge, he has regained his lost weight and his liver function tests have remained normal. Histocompatibility locus antigen (HLA) testing was positive for the B8 and DR3 loci. ERCP repeated 2 years later demonstrated irregularity of the common bile duct with a short segmental irregularity and stenosis of multiple intrahepatic ducts. The cystic duct was normal.

PATIENT 2: CASE HISTORY

The second patient was 19 when he presented to our institution in 1970 with a complaint of loose bowel movements for 3 years. He had a 9-kg invol-

untary weight loss over 3 preceding months. A review of systems and his medical history were otherwise unremarkable. A family history revealed a cousin with diabetes mellitus.

Physical exam and vital signs were unremarkable. Proctosigmoidoscopy revealed patchy friability and edema of the colonic mucosa; a barium enema study showed loss of haustral markings and mucosal pattern. A regimen of sulfasalazine was started for the ulcerative colitis. He gained weight, stool frequency diminished, and the proctosigmoidoscopic appearance improved.

Three months later he presented with polydipsia, polyuria, and involuntary weight loss. He was diagnosed as having diabetes mellitus, and a regimen of intermediate-acting insulin was begun; his weight subsequently returned to normal.

Three years later, he had an episode of scleral icterus, anorexia, acholic stools, and night sweats. He had no history of fever, recent foreign travel, intravenous injections, or exposure to hepatitis. The physical examination revealed jaundice with hepatomegaly but was otherwise unremarkable. Laboratory examination demonstrated an alkaline phosphatase of 165 U/L (20 to 110 U/L), bilirubin 6.2 mg/dL (0.3 to 1.5 mg/dL), aspartate aminotransferase 1070 U/L (7 to 40 U/L), elevated gamma globulin, and a prolonged prothrombin time of 14 seconds (control value, 12 seconds). Tests for antimitochondrial and anti-smooth-muscle antibody were negative, as were hepatitis studies. Liver biopsy revealed diffuse lymphocytic infiltration with scattered eosinophils, diffuse lobular disarray, and some areas of scarring consistent with chronic active hepatitis. He was treated with azathioprine, and his jaundice resolved within 4 months. Azathioprine treatment was discontinued within 3 years.

Nine years after the initial evaluation, he was admitted to the hospital because of an elevated alkaline phosphatase concentration of 550 U/L (20 to 110 U/L). Other liver function tests were normal. ERCP revealed an irregular contour and caliber of the common bile and intrahepatic ducts consistent with sclerosing cholangitis. He was discharged, with follow-up visits every 4 to 6 months.

Seventeen years after the initial presentation, he was admitted because of right upper quadrant abdominal pain, fever, and dyspnea on exertion. After extensive evaluation, he was found to have adenocarcinoma metastatic to the liver, presumed to have originated from dysplastic lesions in the colon. Despite chemotherapy, he died 7 months later at age 37. HLA typing was not done.

DISCUSSION

The association of ulcerative colitis and sclerosing cholangitis has been well documented, but not in combination with insulin-dependent diabetes mellitus. We have been unable to find any reports linking these three disorders, either in the same patient or in first-degree relatives, and this was one of our reasons for investigating the apparent association.

Neither patient demonstrated convincing evidence of pancreatitis as the etiology of insulin-dependent diabetes mellitus; neither was on a medication shown to cause pancreatitis; and neither had a clinical episode resembling pancreatitis prior to the development of diabetes. Patient 1 was found to have an amylase elevation on the basis of salivary amylase. The pancreatic fraction of amylase was normal, ERCP revealed a normal pancreatic duct, and ultrasound of the pancreas was unremarkable. Despite progression of his sclerosing cholangitis, the appearance of his pancreatic duct remained normal on ERCP.

Patient 2 had no documented episodes of amylase elevation. He developed diabetes 9 years before the diagnosis of sclerosing cholangitis. Diagnostic ERCP demonstrated a normal pancreatic duct and no evidence of pancreatitis.

There have been many theories offered to explain the etiology of these three disease processes. Evidence exists to support an immunologic basis for each.[1–8]

Ulcerative colitis

Ulcerative colitis may represent a genetically determined response that is immunologically mediated.[8] The antigen may be an environmental factor, bacterium, or virus that cross-reacts with, or induces a response in, the cellular constituents within the host's gastrointestinal tract.[8] Evidence to support this hypothesis includes high titers of circulating antibodies to colonic epithelial cells in some patients with ulcerative colitis.[8] Circulating lymphocytes from patients with ulcerative colitis may be cytotoxic to colonic epithelium, and serum of patients with ulcerative colitis can cause normal lymphocytes to be cytotoxic.[8,9]

Other data supporting an immunologic origin of ulcerative colitis includes the work of Duerr and

other authors who have reported the presence of perinuclear antineutrophil cytoplasmic antibodies in patients with ulcerative colitis and in patients with sclerosing cholangitis.[10–13] These antibodies have been found in the sera of up to 60% of a group of patients with ulcerative colitis.[10] These antibodies do not appear to correlate with disease activity and may occur in patients who have primary sclerosing cholangitis who have undergone a colectomy.[10,12] However, these antibodies are not unique to ulcerative colitis and may be found in patients with collagenous colitis of idiopathic origin.[10] They have also been found in patients with other autoimmune liver diseases but not in patients with nonautoimmune obstructive bile duct disorders.[11,13] The antigen against which they are directed and their clinical significance have not yet been determined, but their presence appears to support an autoimmune etiology of these disorders.

Sclerosing cholangitis

Sclerosing cholangitis may also be an autoimmune phenomenon, although other etiologies including genetic factors and infections have been proposed.[1,3,6,7,14,15] There are at least two alternate autoimmune theories.[4,7] One is that antibodies in the systemic circulation are deposited in the bile ducts, where they react with bile duct antigen and produce inflammation and fibrosis.[4] Another postulated mechanism is that circulating antibody and antigen combine to form a circulating antigen-antibody complex which is deposited in the bile ducts and which results in inflammation and fibrosis.[6]

Evidence supporting an immunologic etiology includes abnormal immunoglobulin levels in both the serum and bile of some patients with sclerosing cholangitis.[4,7] Bodenheimer studied the serum of 24 patients, 7 with sclerosing cholangitis (16 of whom also had ulcerative colitis) and found that circulating immune complexes were present in 80% of patients, regardless of their inflammatory bowel status.[7] In our second patient, immunoglobulin levels were markedly elevated, predominantly of the IgG class, possibly reflecting this process.

Recent literature also suggests an abnormality of circulating T cells in patients with sclerosing cholangitis. Kilby et al[16] have reported a patient with ulcerative colitis and sclerosing cholangitis whose T-cell suppressor activity was decreased to 33% compared with a mean activity of 82% ± 4% (mean ± standard error) for their laboratory. Other authors have reported a decreased number of circulating suppressor T cells (CD8) with a consequent increase in the CD4/CD8 ratio, but with conflicting results of functional in vitro studies.[16–18]

Insulin-dependent diabetes mellitus

There also appears to be an autoimmune component to insulin-dependent diabetes mellitus.[5,19,20] Between 60% and 80% of affected individuals have circulating antibodies to islet cells at the time of diagnosis and anti-insulin antibodies may be present before the administration of exogenous insulin.[5,19,20] Once diagnosed, our patients' insulin requirements were persistent and were not altered by dosage adjustments in their other medications. Individuals with diabetes mellitus may also have defects in their functional suppressor cells.[19]

The HLA link

The association of these three diseases may be a clue to understanding their pathogenesis. Ulcerative colitis and sclerosing cholangitis have been previously shown to occur together.[1,2,6–8,14,15] Though only 4% of patients with ulcerative colitis have sclerosing cholangitis, up to 70% of patients with sclerosing cholangitis have ulcerative colitis.[4,15,21,22] Sclerosing cholangitis may antedate the development of ulcerative colitis, as was seen in our first patient.[4,22] These two diseases are not commonly seen in patients with insulin-dependent diabetes mellitus.[5,22] Upon literature review, we found only one possible case supporting this association, and in that patient, the ulcerative colitis was microscopic and without clinical symptoms.[14]

The HLA system may represent the link between these three disorders. Certain HLA types appear to be more frequent in each disease.[2–5,19–22] Schrumpf has studied the prevalence of HLA types in patients with sclerosing cholangitis and ulcerative colitis.[2] Of the patients with hepatobiliary disease, 80% had ERCP-confirmed sclerosing cholangitis. Eighty percent were positive for HLA-B8 (compared with 25% of controls), and 70% were positive for HLA-DR3 (compared with 19% of controls), both statistically significant. Of the group without hepatobiliary disease, 32% were positive for HLA-B8 (not significant), and 35% were positive for HLA-DR3 (significant). He also demonstrated an increased incidence of HLA-DR3 and HLA-B8 in patients with pancolitis who were young at disease onset.[2] Our first patient was positive for HLA-DR3 and HLA-

B8. He also had pancolitis at disease onset. Unfortunately, HLA typing was not available for our second patient.

The two antigens also occur with an increased prevalence in patients with insulin-dependent diabetes mellitus. From 92% to 98% of Caucasians with insulin-dependent diabetes mellitus have either HLA-DR3 or HLA-DR4, compared with 30% to 60% of nondiabetic individuals.[5,23] Individuals with insulin-dependent diabetes mellitus also have an increased prevalence of HLA-B8.[5,19] Schrumpf and other authors have postulated that the HLA-B8 antigen is a genetic marker of a defect in the suppressor effect of T cells, which has also been postulated in diabetes.[2,5,16] Having such a defect would allow an environmental antigen to trigger an autoimmune process in susceptible individuals, with subsequent inflammation and disordered tissue function.[5,8]

Based on age-adjusted incidence rates of ulcerative colitis, sclerosing cholangitis, and insulin-dependent diabetes mellitus, and based on the prevalence of HLA antigens in the population, we were able to calculate the probability of these three diseases and the HLA-B8 and HLA-DR3 antigens occurring in the same individual. The age-adjusted incidence of ulcerative colitis in Caucasian men is 2.92 per 100 000 (.0000292, or 2.92×10^{-5}).[24] The incidence of childhood-onset insulin-dependent diabetes mellitus in US Caucasians is 17 per 100 000 (.00017, or 1.7×10^{-4}.[25] No incidence data are available for sclerosing cholangitis, but for persons with ulcerative colitis the lifetime risk is approximately 4%, so the estimated incidence is 0.12 per 100 000 (.0000012, or 1.2×10^{-6}.[26] The prevalence of HLA-B8 or HLA-DR3 positivity in Caucasians is approximately 20%.[2] Assuming that all three diseases and the HLA antigens B8 and DR3 occur independently, the probability of all three diseases and the specified HLA type occurring in a given individual is 1.19×10^{-15}.

Approximately 457 children with ulcerative colitis were diagnosed at The Cleveland Clinic Foundation during a 30-year survey period.[27] The rate of 1 out of 457 (.0022, or 2.2×10^{-3}) indicates that the occurrence of all three diseases with a specific HLA antigen are not independent. If the second patient for whom HLA typing was not available is included in the analysis, the probability of these three disorders occurring independently without the specified HLA type would be 5.95×10^{-15}, as compared with the actual rate of 2 out of 457 patients (.0044, or 4.4×10^{-3}). Therefore, the probability of occurrence appears to be greater than chance alone.

The association of ulcerative colitis, sclerosing cholangitis, and insulin-dependent diabetes mellitus has not been established. These diseases may share a common defect in immune surveillance, T-cell suppression, or linkage disequilibrium with regard to HLA or some other etiology.[5] Their occurrence in the two individuals presented in this report may reflect this common origin.

ACKNOWLEDGMENT

The authors would like to thank Lata Paranandi, MSHP, of the Department of Biostatistics and Epidemiology for assistance with statistical analysis.

REFERENCES

1. **Silber GH, Finegold MJ, Wagner ML, et al.** Sclerosing cholangitis and ulcerative colitis in a mother and her son. J Pediatr Gastroenterol Nutr 1987; 6:147–151.
2. **Schrumpf E, Fausa O, Forre O, Dobloug JH, Ritland S, Thorsby E.** HLA antigens and immunoregulatory T cells in ulcerative colitis associated with hepatobiliary disease. Scand J Gastroenterol 1982; 17:187–191.
3. **Alberti-Flor JJ, Jeffers L, Schiff ER.** Primary sclerosing cholangitis occurring in a patient with systemic lupus erythematosus and diabetes mellitus. Am J Gastroenterol 1984; 79:889–891.
4. **Alberti-Flor JJ, Avant GR, Dunn GD.** Primary sclerosing cholangitis. South Med J 1985; 78:173–177.
5. **Skyler JS, Rabinovitch A.** Etiology and pathogenesis of insulin dependent diabetes mellitus. Pediatr Ann 1987; 16:682–692.
6. **Wiesner RH, Ludwig J, LaRusso NF, MacCarty RL.** Diagnosis and treatment of primary sclerosing cholangitis. Semin Liver Dis 1985; 5:241–253.
7. **Bodenheimer HC, LaRusso NF, Thayer Jr WR, et al.** Elevated circulating immune complexes in primary sclerosing cholangitis. Hepatology 1983; 3:150–154.
8. **Kirschner BS.** Inflammatory bowel disease in children. Pediatr Clin North Am 1988; 35:189–208.
9. **Shorter RG, McGill DB, Bahn RC.** Cytotoxicity of mononuclear cells for autologous colonic epithelial cells in colonic diseases. Gastroenterology 1984; 86:13–22.
10. **Duerr RH, Targan SR, Landers CJ, et al.** Anti-neutrophil cytoplasmic antibodies in ulcerative colitis. Gastroenterology 1991; 100:1590–1596.
11. **Duerr RH, Targan SR, Landers CJ, et al.** Neutrophil cytoplasmic antibodies: a link between primary sclerosing cholangitis and ulcerative colitis. Gastroenterology 1991; 100:1385–1391.
12. **Zauli D, Baffoni L, Cassani F, et al.** Antineutrophil cytoplasmic antibodies in primary sclerosing cholangitis, ulcerative colitis and autoimmune diseases. Gastroenterology 1992; 102:1088–1095.
13. **Klein R, Eisenburg J, Weber P, et al.** Significance and specificity of antibodies to neutrophils detected by Western blotting for serological diagnosis of primary sclerosing cholangitis. Hepatology 1991; 14:1147–1152.
14. **Alberti-Flor JJ, Kalemeris G, Dunn GD, Avant GR.** Primary sclerosing cholangitis associated with massive intra-abdominal lymphadenopathy. Am J Gastroenterol 1986; 81:55–60.

15. **Sheperd HA, Selby WS, Chapman RW, et al.** Ulcerative colitis and persistent liver dysfunction. Q J Med 1983; 208:503–513.
16. **Kilby AE, Krawitt EL, Albertini RJ, et al.** Suppressor T-cell deficiency in primary sclerosing cholangitis. Dig Dis Sci 1991; 36:1213–1216.
17. **Whiteside TL, Lasky S, Si L, et al.** Immunologic analysis of mononuclear cells in liver tissues and blood of patients with primary sclerosing cholangitis. Hepatology 1985; 5:468–474.
18. **Lindor KD, Wiesner RH, Katzmann JA, et al.** Lymphocyte subsets in primary sclerosing cholangitis. Dig Dis Sci 1987; 32:720–725.
19. **Christy M, Deckert T, Nerup J.** Immunity and autoimmunity in diabetes mellitus. Clin Endocrinol Metab 1977; 6:305–332.
20. **Palmer JP.** Insulin autoantibodies: their role in the pathogenesis of insulin dependent diabetes mellitus. Diabetes Metab Rev 1987; 3:1005–1015.
21. **Schrumpf E, Fausa O, Kolmannskog F, Elgjo K, Ritland S, Gjone E.** Sclerosing cholangitis in ulcerative colitis. Scand J Gastroenterol 1982; 17:33–39.
22. **Chapman R, Marborgh B, Rhodes J, et al.** Primary sclerosing cholangitis: a review of its clinical features, cholangiography, and hepatic histology. Gut 1980; 21:870–877.
23. **Lernmark AK, Li S, Baekkeskov S, Chrisyie M, Michelsen B.** Islet specific immune mechanisms. Diabetes Metab Rev 1987; 3:959–980.
24. **Calkins BM, Lilienfeld AM, Garland CF, et al.** Trends in incidence rates of ulcerative colitis and Crohn's disease. Dig Dis Sci 1984; 29:913–920.
25. **Diabetes Epidemiology Research International Group.** Secular trends in incidence of childhood IDDM in 10 countries. Diabetes 1990; 39:858–864.
26. **Olsson R, Danielsson A, Jarnerot G, et al.** Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. Gastroenterology 1991; 100:1319–1323.
27. **Michener W, Caulfield M, Wyllie R, et al.** Management of inflammatory bowel disease: 30 years of observation. Cleve Clin J Med 1990; 57:685–691.