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CASE REPORT

Simultaneous Occurrence of Primary Sclerosing Cholangitis and Autoimmune Chronic Active Hepatitis in a Patient with Ulcerative Colitis

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The prevalence of primary sclerosing cholangitis (PSC) in patients with ulcerative colitis (UC) is reported to range from 2.4% to 7.5% (1–6). In these patients, the presence of abnormal liver enzyme tests, particularly alkaline phosphatase, suggests that PSC is either present or ultimately will develop in most of them (1).

Chronic active hepatitis (CAH) is an uncommon complication of inflammatory bowel disease (IBD) (<1%) (7–9). Many of the patients with combined CAH and IBD reported in the literature did not undergo endoscopic retrograde cholangiopancreatography (ERCP), as this technique was not commonly used at the time the cases were reported. The incidence of CAH, therefore, is probably lower than has been suggested by these reports, as some of these cases may actually have had PSC, which was misdiagnosed as being CAH.

We report the case of a patient with UC that was complicated by the presence of both PSC and CAH. A computer search failed to reveal a similar case.

CASE REPORT

A 30-year-old white male with suspected autoimmune CAH and PSC was referred to the University of Pittsburgh Medical Center in June 1990 for possible liver transplantation (OLTx). His past medical history was remarkable for bloody diarrhea that started in 1984. Colonoscopy as well as multiple colonic biopsies confirmed the diagnosis of ulcerative colitis (UC). He was treated with sulfasalazine and prednisone. During the years 1986–1987, he experienced several relapses of bloody diarrhea accompanied by arthralgia and pleuritis. Abnormal liver injury tests, predominantly alkaline phosphatase and GGTP, were first noted in 1987. Clinically, he was asymptomatic. At that time it was believed that the sulfasalazine accounted for the abnormal tests, but discontinuation of this medication was not followed by any improvement in his liver enzyme levels. In December 1989, he started to complain of weakness, fatigue, loss of appetite, occasional nausea, and mild right upper quadrant abdominal pain. Laboratory tests included the following: bilirubin 5.8 mg/dl, alkaline phosphatase 446 IU/liter, GGTP 340 IU/liter, AST 385 IU/liter, ALT 580 IU/liter, and albumin 2.9 g/dl. ERCP showed mild irregularities in the intra- and extrahepatic bile ducts, which were consistent with PSC (Figure 1). A liver biopsy documented a moderate lymphoplasmocytic inflammatory cell infiltrate in the portal tracts with focal duct infiltration and damage. There was a focal spillover of the inflammatory cells into the surrounding hepatic lobule associated with a mild cholangiolar reaction. Trichrome staining demonstrated perivenular and sinusoidal fibrosis. The patient was treated with prednisone 40 mg/day, which resulted in a clinical improvement. However, despite this therapeutic regimen and the patient's subjective clinical improvement, his liver tests did not improve. In June 1990 he had a second liver biopsy that showed lobular disarray and a portal tract expansion consisting of fibrosis, bile duct proliferation, and a dense lymphoplasmocytic cellular infiltrate. The portal inflammation extended into the hepatic lobules with a typical appearance of piecemeal necrosis (Figure 2A). In addition, a lobular infiltrate of lymphoplasmocytic cells and occasional perivenular infiltrates and fibrosis were evident (Figure

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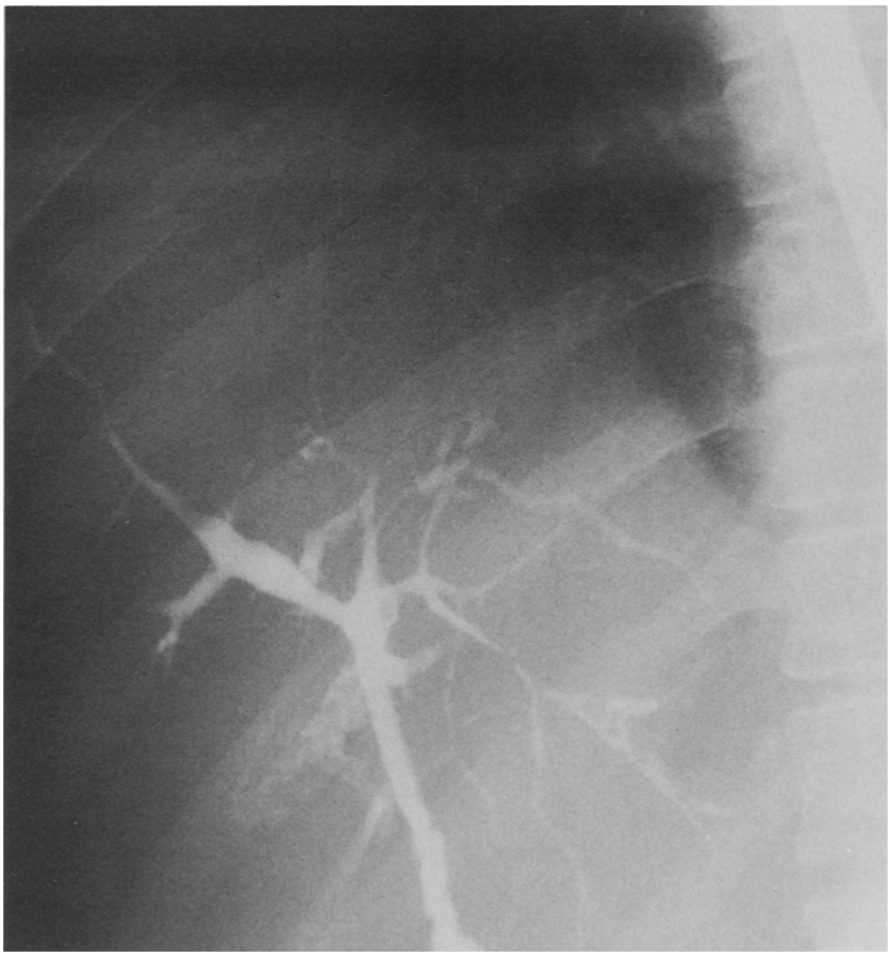

Fig 1. ERCP showing irregularities of the intra and extrahepatic bile ducts.

2B). Several of the interlobular bile ducts also showed inflammatory cell infiltrates and damage with eosinophilic transformation of the epithelial cells (Figure 3). Bridging fibrosis was identified between some of the portal areas. A rhodamine stain revealed deposition of elemental copper in the periportal liver cells suggestive of prolonged cholestasis (Figure 4). Stains for Hepatitis B core and surface antigens were negative.

Physical examination was normal except for mild scleral icterus and the presence of a systolic murmur grade 1/4 at the left sternal border.

Relevant laboratory tests included the following: hemoglobin 10.1 g/dl, hematocrit 32.2%, platelets 512,000/mm^3, white blood cells 5200/mm^3 with normal differential, alkaline phosphatase 375 IU/liter (normal: 40–125), GGTP 614 IU/liter (normal: <65), AST 297 IU/liter (normal: <40), ALT 487 IU/liter (normal: <40), and bilirubin 2.2 mg/dl (normal: 0.5–1.5). Serologic tests for hepatitis A, B, and C where negative. Anti-nuclear antibodies (ANA) were detected as being positive at a dilution of 1:400 (speckled) and anti-smooth muscle antibodies (SMA) were positive at 1:100. Anti-mitochondrial, anti-thyroglobulin, and anti-microsomal antibodies were all negative. His major histocompatibility antigens (HLA) were as follows: A1, B8, Bw6, DR3, DQw2, and DRw52a. A sonogram showed a normal echogenicity of the liver without focal masses and patency of all the hepatic vessels. The spleen was enlarged. A CT scan, with and without contrast, also showed a homogeneous liver without focal lesions. The calculated liver volume was 1675 cc. A diagnosis of combined PSC and CAH was made, and the patient was put on prednisone 40 mg/day and azathioprine 50 mg/day. Because of persistent abnormalities of the liver tests, the dose of azathioprine was increased to 150 mg/day (2 mg/kg), which resulted in a dramatic biochemical response. By October 1990, while on treatment with 150 mg/day of azathioprine and 10 mg/day of prednisone, the patient was clinically asymptomatic and returned to full time work and sport activities. At that time his liver enzymes were: AST 38 IU/liter and ALT 60 IU/liter (Table 1).

DISCUSSION

The patient under discussion presents two distinct complications of ulcerative colitis: PSC, man-

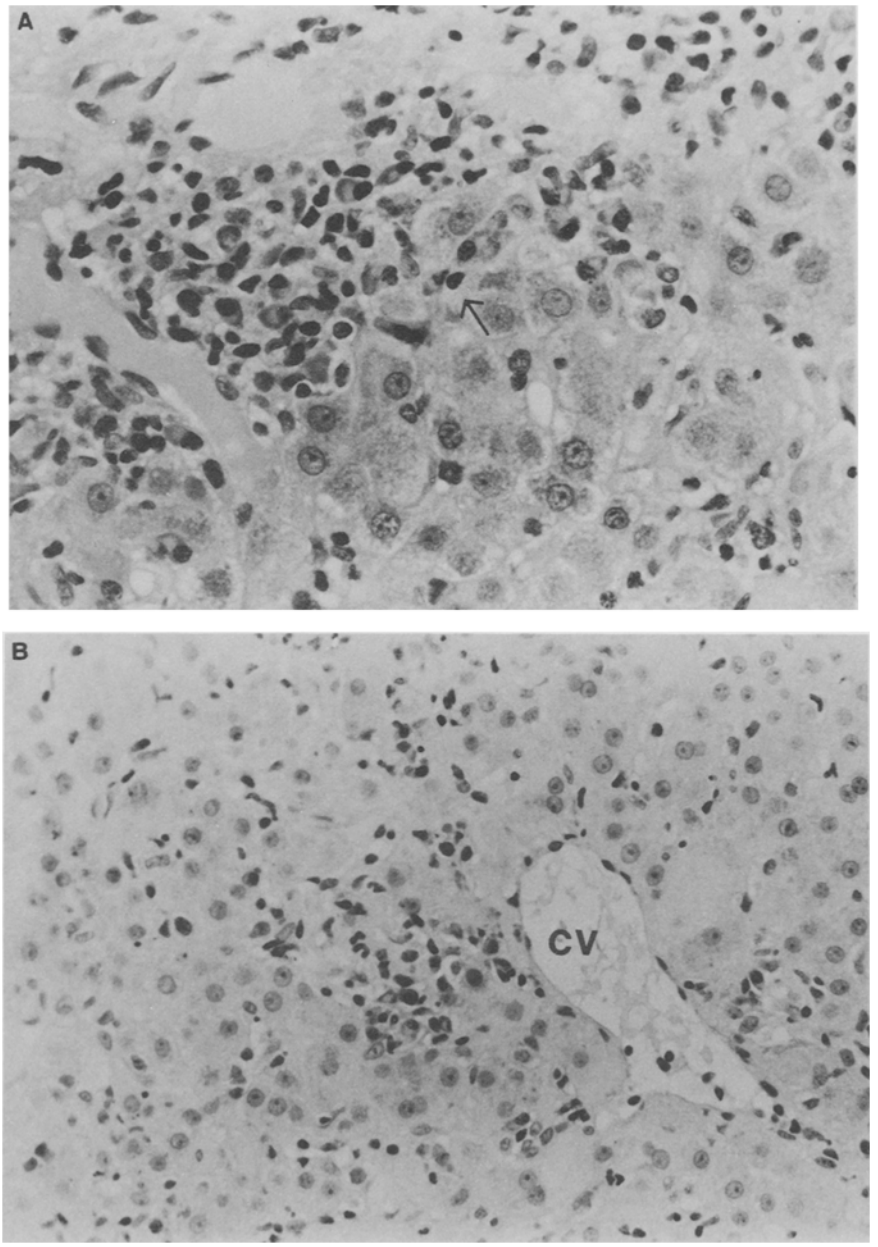

Fig 2. (A) The portal tract shown here (top left) contains a prominent lymphoplasmocytic infiltrate, which spills over the limiting plate into the edge of the lobule (arrow). (B) A lobule from the same biopsy. There is a mild disarray, Kupffer cell hypertrophy, lymphoplasmocytic infiltration, and spoty necrosis. (CV = central vein.)

ifested histologically by active bile duct destruction, and autoimmune hepatitis, manifested by a dense lymphoplasmocytic portal inflammatory infiltrate, fibrosis, and piecemeal necrosis.

The active ductal destruction and deposition of elemental copper in periportal hepatocytes are consistent with PSC. Although PSC may have morphological features similar to those of CAH (piecemeal necrosis can occur in up to 66% of the patients), the active lobular plasmocytic infiltrate and the perivenular inflammation seen in the case under discussion are somewhat unusual for cases of PSC (10).

The histologic features present in this case are not typical of CAH. Although a nonsuppurative cholangitis may rarely complicate CAH, as has been reported by Ludwig et al (11), it is usually

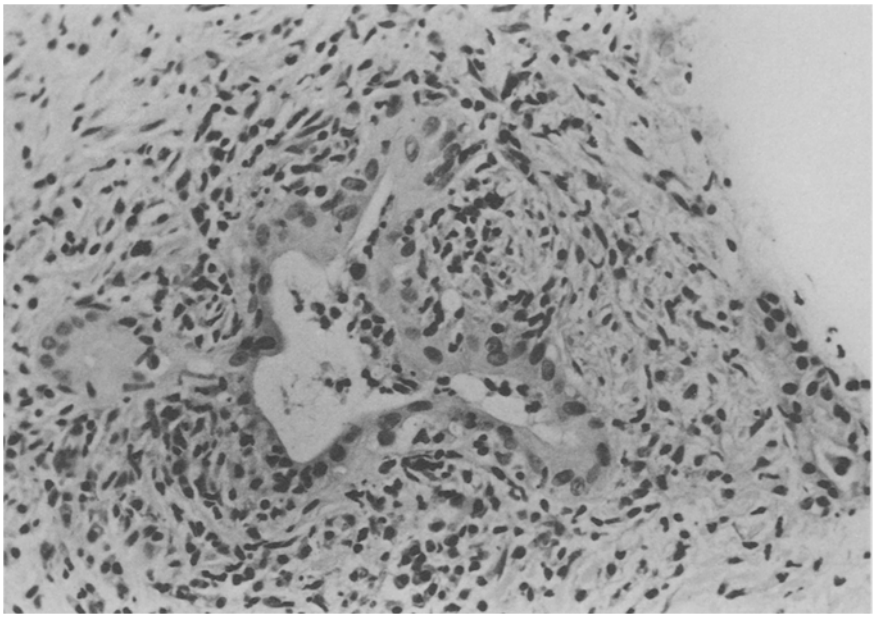

Fig 3. Septal bile duct damage. There is ectasia of the lumen, eosinophilic transformation of the cytoplasm, and intraepithelial as well as intraluminal acute and chronic inflammatory cells. Mild inactive atypia is also present.

nondestructive rather than destructive in nature. In most of their cases with CAH and lymphoidal cholangitis, the number of interlobular and septal bile ducts was not reduced and there was no evidence of duct destruction. In addition, in most patients with a pleomorphic cholangitis characterized by the presence of mixed inflammatory infiltrates in or around the wall of the interlobular and septal bile ducts and by an absence of granulomas or lymphoid aggregates, the bile ductal epithelial cells themselves appeared to be undamaged. These authors emphasized the fact that the presence of a

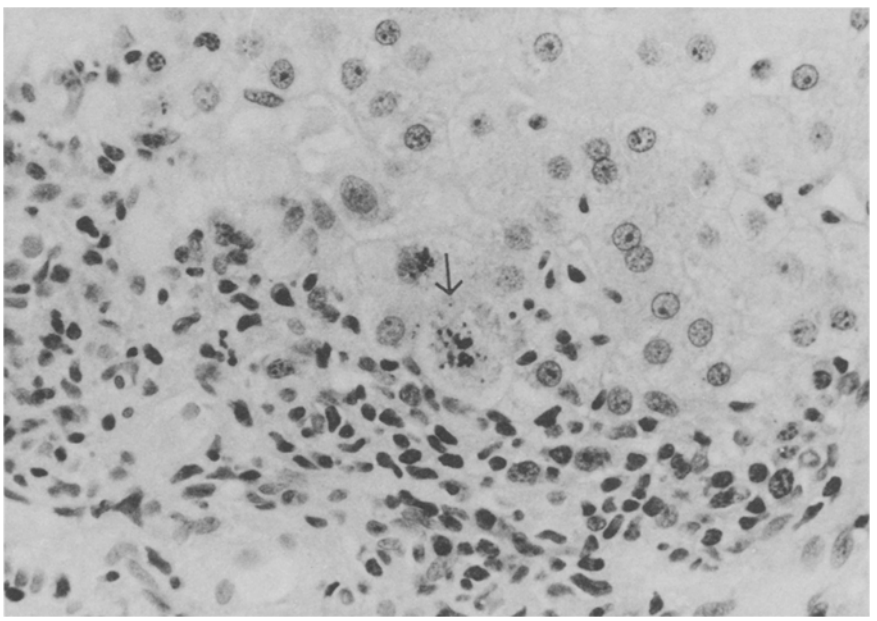

Fig 4. The deposition of copper-associated protein in hepatocytes at the edge of the limiting plate on the orcein stain (arrow) supports the cholestatic nature of the disorder.

TABLE 1.

	Date and treatment			
	12/89, before treatment	*6/90, prednisone (40 mg/day)*	*7/90, prednisone (40 mg/day) + azathioprine (50 mg/day)*	*10/90, prednisone (10 mg/day) + azathioprine (150 mg/day)*
ALT (IU/liter)	580	487	396	60
AST (IU/liter)	385	297	231	38

pleomorphic cholangitis is not sufficient to distinguish patients with CAH from patients with either PSC or PBC (11). In the present case, it well might be that the destructive bile duct lesions are the result of CAH rather than PSC. However, the diagnosis of PSC was established by the typical findings on the ERCP.

HLA typing and autoantibodies profile can not be used to distinguish between PSC and CAH. HLA types A1, B8, and DR3, as well as ANA and SMA, can be found in >50% of patients with either disease (12–18). In the present case, however, the high titers of both ANA (1:400) and SMA (1:100) and the speckled pattern of the ANA are more consistent with autoimmune CAH than with PSC.

The most important evidence supporting the presence of autoimmune CAH in the present case is the significant clinical and biochemical response to prednisone and azathioprine. Within several months of treatment, AST and ALT levels almost normalized: 38 IU/liter and 60 IU/liter, respectively. This dramatic response to corticosteroids with or without azathioprine is very unlikely to occur in patients with PSC (19).

PSC and autoimmune CAH can occur simultaneously in patients with ulcerative colitis. Treatment of the "hepatitis" component with drugs that are not helpful in PSC, such as glucocorticoids and/or azathioprine, may result in significant clinical improvement.

SUMMARY

The simultaneous occurrence of PSC and autoimmune CAH in a patient with ulcerative colitis is described. Although each disease is a well documented complication of UC, their combination has never been reported. The diagnosis of PSC was based on typical findings on ERCP and liver biopsy and that of CAH was based on typical findings on liver biopsy supported by HLA typings and a remarkable response to a combination of glucocorticoids and azathioprine. The difficulties in establishing the diagnosis and the management of such patients are discussed.

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