Autoimmune chronic active hepatitis (lupoid hepatitis) and primary sclerosing cholangitis in two young adult females

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ABSTRACT: Autoimmune chronic active hepatitis (CAH) and primary sclerosing cholangitis (PSC) are chronic diseases of the hepatobiliary system that have many clinical, immunologic and genetic features in common. Despite these similarities, there are few reports of the two diseases coexisting. Two young women with clinical, biochemical, serologic, radiologic and histologic findings compatible with both autoimmune CAH and PSC are described. The observation that there may be a striking overlap in the features of these two diseases and recent improvements in diagnostic imaging of the biliary tract suggest that the association of these two diseases in the same individual may be more common than is presently appreciated. **Can J Gastroenterol 1988; 2(1): 22-27**

Key Words: *Autoimmune chronic active hepatitis, Inflammatory bowel disease, Primary sclerosing cholangitis.*

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LUPOID OR AUTOIMMUNE CHRONIC active hepatitis (CAH) and primary sclerosing cholangitis (PSC) are chronic diseases of the hepatobiliary system that have many features in common. Both diseases affect young adults and frequently progress to cirrhosis and death from liver failure (1-6). Each is marked by hypergammaglobulinemia (5,7), elevated levels of immune complex-like activity (8,9) and the presence of autoantibodies (5, 10-13). Patients with both disorders have an increased incidence of other 'autoimmune' diseases including inflammatory bowel disease (2, 13-16). Sixty to 80% of patients with autoimmune CAH or PSC are HLA B8 positive, whereas only 20% of the general

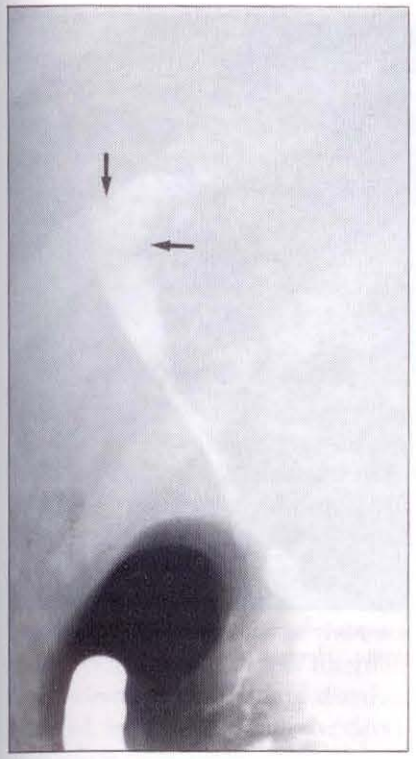

Figure 1) *Endoscopic cholangiogram from case one showing a long stricture of the common duct with slight proximal dilatation and numerous strictures at the level of common duct bifurcation (arrows)*

population possess this haplotype (5,17,18). The high incidence of HLA B8 raises the possibility that the diseases may share common pathogenic mechanisms. The coexistence of autoimmune CAH and PSC would be compatible with this possibility.

Despite the overlapping features of these diseases, there is a paucity of reports documenting their coexistence (6,19). In the present report two patients with features of both autoimmune CAH and PSC are described, emphasizing the problems encountered in establishing these diagnoses.

CASE ONE

A 30-year-old female presented in 1978 with a five week history of abdominal pain and recent onset of jaundice and pruritus. A clinical diagnosis of choledocholithiasis was made and laparotomy was performed. At surgery no stones were found in the biliary tract but the liver was noted to be nodular with prominent lymphadenopathy at the porta hepatis and inflammatory debris in the common bile duct. An operative cholangiogram revealed a distorted common bile duct compatible with sclerosing cholangitis (Figure 1). A liver biopsy demonstrated nonsuppurative obliterative cholangitis.

On further review of the patient's history, she recalled occasional episodes of prolonged nonbloody diarrhea in the recent past. She took no medications other than oral contraceptives and consumed little alcohol. Hashimoto's thyroiditis had been diagnosed at age six.

The patient's family history revealed that her mother had diabetes mellitus, myxedema and pernicious anemia, and her father and paternal uncle had celiac disease.

Physical examination showed no peripheral signs of chronic liver disease. The liver and spleen were not enlarged. Laboratory investigations at that time revealed hemoglobin of 12.1 g/100 mL, white blood cell count of 13,200/mm^3 with 60% polymorphonuclear leukocytes. Bilirubin was 3.5 mg/dL (normal, less than 1.4); alkaline phosphatase 946 iu/L (normal, less than 115); and aspartate aminotransferase (AST) 35 iu/L (normal, less than 40). Protein electrophoresis and immunoglobulin quantitation were within normal limits. Antismooth muscle antibody, antimitochondrial antibody and viral hepatitis serology were negative.

The patient was reassessed one year later when she developed bloody diarrhea. Physical examination was unchanged but sigmoidoscopy revealed a granular mucosa with friability. Rectal biopsy was consistent with inflammatory bowel disease, most likely ulcerative colitis, and this was further supported by an air contrast barium enema. A repeat liver biopsy showed evidence of cholangitis with focal portal scarring compatible with early cirrhosis. Endoscopic retrograde cholangiopancreatography (ERCP) showed no evidence of extrahepatic obstruction but the upper portion of the common bile duct was again distorted, suggestive of sclerosing cholangitis. The patient was started on sulfasalazine for ulcerative colitis and did reasonably well for the next year.

She was reassessed in late 1982 for recurrent epigastric pain. Laboratory assessment at that time revealed alkaline phosphatase of 762 iu/L and AST of 366 iu/L. Antinuclear factor was positive at a 1:160 titre and previously negative antismooth muscle

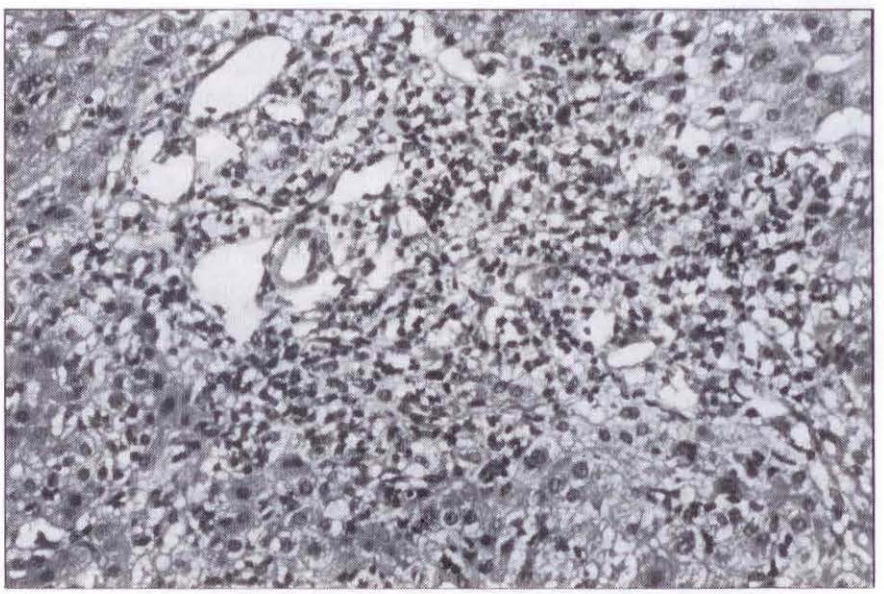

Figure 2) *The portal triads display a moderately heavy infiltrate of lymphocytes and monocytes with piecemeal necrosis at the limiting plate. (Hematoxylin and eosin × 210)*

antibody was now positive at a 1:1280 titre. Hypergammaglobulinemia was also present. A repeat liver biopsy revealed chronic active hepatitis (Figure 2). ERCP revealed further progression of the previous bile duct lesions. The patient was started on corticosteroids which unmasked diabetes mellitus requiring the addition of insulin. Although the patient improved subjectively while on corticosteroids, biochemical improvement was only transient.

Currently the patient is on prednisone 20 mg daily. Bilirubin is 44 μmol/L (normal 2 to 18); alkaline phosphatase 285 iu/L; and AST 464 iu/L. Antimitochondrial antibody remains negative, antismooth muscle antibody positive (1:1280), and antinuclear factor positive (1:1280, diffuse pattern).

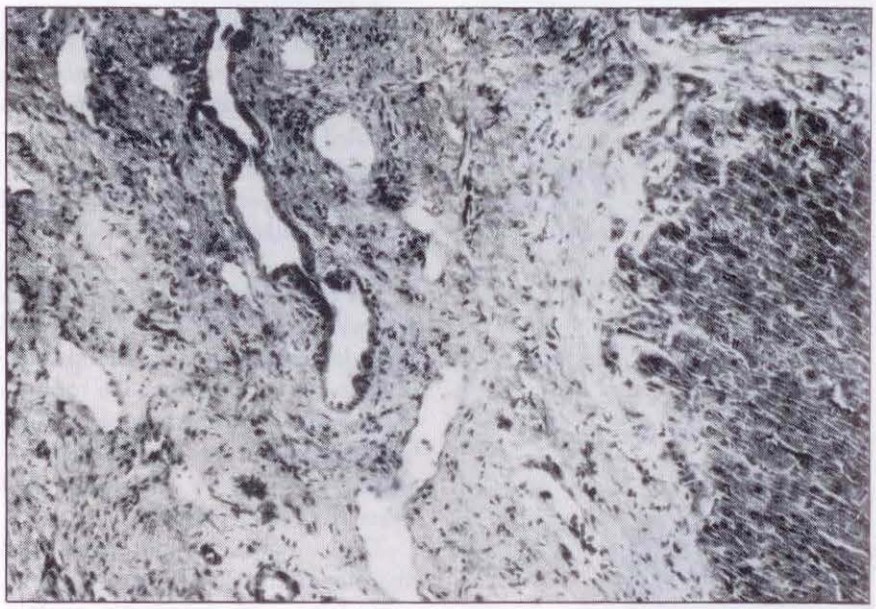

Figure 3) *Sections of liver from case two showing micronodular cirrhosis with extension of the portal inflammatory reaction into adjacent hepatic parenchyma. (Hematoxylin and eosin × 100)*

CASE TWO

An 18-year-old female presented in January 1975 with a six month history of amenorrhea and excessive fatigue. For several weeks her urine had been dark and her stools pale. On physical examination she was found to be icteric and to have multiple spider angiomas over her head and neck, and palmar erythema. Hepatosplenomegaly was present. Laboratory investigations revealed moderate pancytopenia, elevated serum alanine aminotransferase 180 iu/L (normal, less than 36), alkaline phosphatase 690 iu/L, and hypergammaglobulinemia. Antinuclear and antismooth muscle antibodies were both present in the serum (titre equal to or more than 1:80) but antimitochondrial antibodies were not detected. The patient's HLA haplotype was B8. Hepatitis B surface antigen (HBsAg) was negative by radioimmunoassay. Serum α_1 antitrypsin, ferritin, copper and ceruloplasmin levels were within normal limits. The patient had received no medication and did not abuse alcohol. Family history was negative for chronic liver disease but positive for hypothyroidism and juvenile onset diabetes in her mother and sister, respectively. Significant thrombocytopenia and a prolonged prothrombin time precluded a percutaneous liver biopsy.

A tentative diagnosis of autoimmune CAH was made and the patient was started on prednisone 40 mg/day. With initiation of therapy the patient's symptoms resolved and serum aminotransferase levels fell to within normal limits. Serum alkaline phosphatase levels, however, remained elevated at four to five times the upper limit of normal. A percutaneous liver biopsy, nine months later, revealed cirrhosis with areas of piecemeal necrosis of hepatocytes (Figure 3).

One year following presentation the patient complained of vague abdominal pains and diarrhea. Radiology of the gastrointestinal tract failed to demonstrate any mucosal abnormalities. Serum alkaline phosphatase was still elevated at 517 iu/L. An intravenous cholangiogram demonstrated normal filling of the right, left and proximal common bile duct and a gall bladder that was free from stones. The distal common bile duct was not well visualized.

In January 1977, approximately two years following the initial presentation, the patient developed recurrent hematemesis from ruptured gastroesophageal varices. A distal sple-

Figure 4) *Intraoperative cholangiogram from case two showing multiple areas of stricturing (arrows) with only slight proximal ductal dilatation*

norenal shunt was performed. A wedge biopsy of the liver confirmed the presence of cirrhosis with no portal tract features of chronic biliary disease. Following surgery the patient experienced intermittent abdominal cramps and diarrhea. In June 1977 acute pancreatitis developed with an elevation in serum amylase activity. An oral cholecystogram later revealed multiple small radiolucent stones within the gall bladder.

In February 1978 a cholecystectomy was performed. During this surgery the common bile duct was felt and considered to be thickened and fibrotic. An operative cholangiogram revealed multiple strictures of the common bile duct. Proximal to the strictures there was only slight dilatation of the duct (Figure 4). Following surgery intermittent abdominal cramps and diarrhea persisted. In October 1980, she developed severe right upper quadrant pain, fever and chills.

Cholangiograms performed during the subsequent hospitalization revealed multiple strictures and dilatations of intrahepatic and extrahepatic bile ducts as well as multiple stones throughout the biliary tree. Subsequently, pigmented stones were recurrently extracted using nonsurgical techniques. During the course of a biliary drainage procedure (choledochojejunostomy) in December 1980, a third liver biopsy and a biopsy of the common bile duct were obtained. The liver biopsy revealed cirrhosis, nonsuppurative fibrous cholangitis (Figure 5), and the wall of the common bile duct contained dense bands of fibrous tissue compatible with, but not specific for, primary sclerosing cholangitis.

The patient ultimately was discharged with silastic irrigation catheters placed in both the right and the left hepatic ducts. Six months later (seven years following initial presentation) there was an exacerbation of abdominal cramps and diarrhea. Colonoscopy at that time revealed definite mucosal abnormalities in the left colon and multiple biopsies of the involved area revealed crypt abscess formation with accompanying polymorphonuclear leukocyte and round cell infiltration, changes typical of ulcerative colitis. Long term oral sulfasalazine therapy was prescribed for the colitis.

DISCUSSION

Autoimmune CAH is a disease that predominantly affects young females in their second or third decade of life with a second peak in women over the age of 45. Fatigue, nausea and, in the younger age group, amenorrhea are the most common presenting complaints. On physical examination jaundice and an enlarged liver and spleen may be found. Initial laboratory investigations typically reveal mild pancytopenia, elevated serum levels of aminotransferases and hypergammaglobulinemia. Eighty-five percent of patients will be antinuclear antibody positive, and 80% antismooth muscle antibody positive (10). If blood clotting tests permit, a severe chronic aggressive hepatitis, or active cirrhosis will be seen on liver biopsy (7,19). The characteristic histologic feature of autoimmune CAH is active piecemeal necrosis of periportal hepatocytes (3,20). The two patients presented in this report possessed many of the above features. In addition, clinical and serum biochemical indices of the liver disease responded satisfactorily to steroids, a finding entirely consistent with a diagnosis of autoimmune CAH (21).

As demonstrated by these two cases, confirming the diagnosis of both autoimmune CAH and PSC in the same patient can be very difficult. It was particularly difficult to establish the additional diagnosis of PSC in case two. By definition, the diagnosis of PSC should not be made in individuals who have had previous surgery on the biliary tract, documented stones in the intrahepatic or extrahepatic biliary tree, or in individuals who have been followed for an insufficient period of time to rule out a malignancy of the biliary tract (22,23). Complications of biliary surgery, cholelithiasis and cholangiocarcinoma can each lead to the development of a syndrome with clinical, radiological and pathological features that are indistinguishable from that of PSC.

Although patient two had surgical exploration of the common bile duct

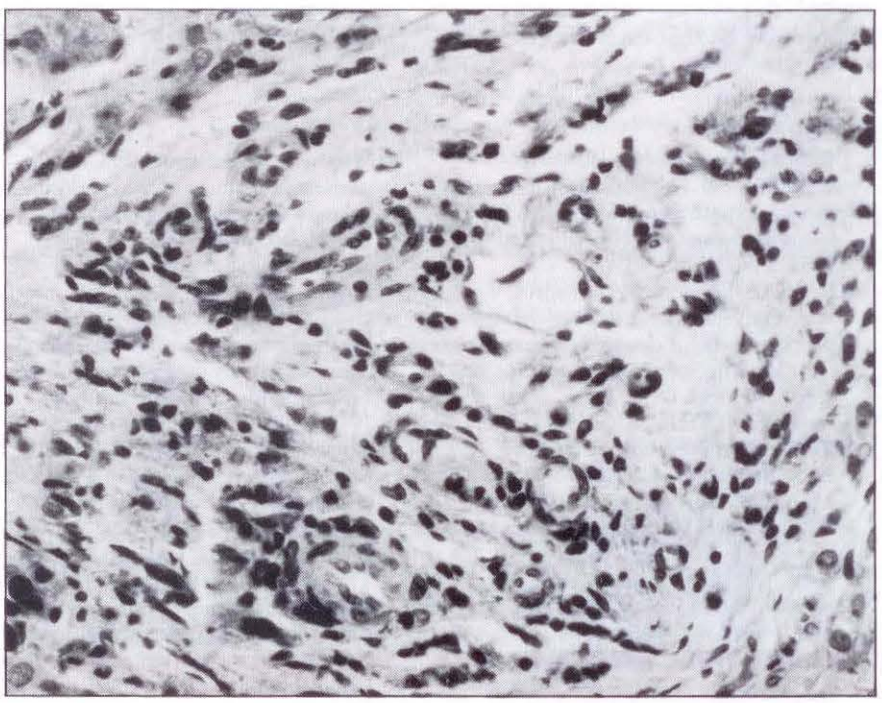

Figure 5) *The wedge biopsy of liver from case two showing nonsuppurative fibrous cholangitis, obliteration of bile ducts and marked periportal bile stasis with focal aggregates of acute inflammation. (Hematoxylin and eosin × 100)*

and intrahepatic stones documented by cholangiography, it is necessary to consider the timing of these events in relation to the patient's overall course. At the time of initial presentation, three years prior to common duct surgery and five years prior to the demonstration of intrahepatic lithiasis, serum alkaline phosphatase level was already six times the upper limit of normal and remained markedly elevated, being unaltered by the initiation of corticosteroids. Moreover, the first accurate radiologic examination of the patient's biliary tract (performed at the time of cholecystectomy and thus just prior to exploration of the common bile duct and two years prior to intrahepatic stone formation) demonstrated strictures of the proximal common hepatic duct, the right and left hepatic ducts and smaller intrahepatic radicles. Finally, the histologic extent of the sclerosing process seen in the 1980 biopsy of the common bile duct and the subsequent documentation of chronic idiopathic ulcerative colitis are additional findings supporting a diagnosis of PSC in this patient (12,26).

There are several possible explanations why PSC has not previously been described in patients with autoimmune CAH and vice versa. One major reason may be that each of these diseases has until recently been associated with a relatively short median survival time (autoimmune CAH 3.3 years [27]; PSC 6 years [28]). Thus the likelihood of a second disease appearing during the relatively brief course of the primary one was quite remote. Prolongation of survival of patients with autoimmune CAH with corticosteroids (23) and improvements in ability to diagnose PSC at an earlier stage (through the advent of multichannel biochemical testing of serum and more accurate biliary imaging techniques) (5) have extended the known survival period for both diseases, thereby enhancing the likelihood of both diseases being detected in the same individual.

A second reason, and one that is particularly relevant to case two, involves the incidence of hepatic stone formation in patients with hepatic cirrhosis. Many patients with autoimmune CAH, by the time of presentation will already have histologic evidence of established cirrhosis on liver biopsy (1,3,4). Because hepatic cirrhosis can be associated with the production of pigment gall stones by the liver (29,30), cases of sclerosing cholangitis could inadvertently be attributed to intrahepatic lithiasis rather than to a primary sclerosing process. Early cholangiography, in a patient with autoimmune CAH and cholestatic features or cryptogenic cirrhosis, would likely diminish the frequency with which PSC is overlooked in these patients (5).

The results of a report by Shepherd and colleagues (12) provide indirect evidence that PSC may coexist with autoimmune CAH more often than has previously been appreciated. In their study, greater than 80% of chronic ulcerative colitis patients with abnormal liver enzyme tests had cholangiographic changes consistent with PSC. Thus, a significant portion of patients with chronic ulcerative colitis and autoimmune CAH would presumably have evidence of PSC, were cholangiography performed.

Typically, the liver diseases associated with inflammatory bowel disease follow the onset of bowel signs or symptoms. In the two patients described in the present report the opposite was observed. Whether this finding might serve to identify individuals in whom autoimmune CAH and PSC are likely to coexist remains to be determined. A persistently elevated serum alkaline phosphatase following an otherwise prompt biochemical response to the initiation of corticosteroids might further suggest the coexistence of these disorders (31-33).

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