Primary biliary cirrhosis in HLA-identical twin sisters

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HJ FREEMAN, RJ BAILEY. Primary biliary cirrhosis in HLA-identical twin sisters. *Can J Gastroenterol* 1994;8(2):88-91. Human leukocyte antigen (HLA)-identical twin sisters with chronic liver disease were evaluated. Both had a childhood history of transient jaundice suggestive of a possible infectious cause. Subsequent studies in both siblings at age 51 years revealed antimitochondrial antibody-positive primary biliary cirrhosis. This report documents HLA-identical twins with primary biliary cirrhosis, providing added evidence for a genetically determined abnormal immune response in this liver disorder, possibly to a specific viral or other environmental factor.

Key Words: *Antimitochondrial antibodies, Heritable liver diseases, Human leukocyte antigens (HLA), Identical twins, Primary biliary cirrhosis*

Cirrhose biliaire primaire chez des jumelles HLA-identiques

RÉSUMÉ : Des jumelles HLA-identiques (anticorps leucocytaire humain) atteintes de maladie hépatique chronique ont été examinées. Les deux présentaient des antécédents de jaunisse transitoire durant l'enfance, signalant une cause infectieuse possible. Des examens subséquents chez les deux sœurs, à l'âge de 51 ans, ont révélé la présence d'une cirrhose biliaire primaire positive à l'égard d'anticorps antimitochondriaux. Ce rapport fait état de cirrhose biliaire primaire chez des jumelles HLA-identiques, ajoutant des preuves à l'appui d'une prédisposition génétique à une réponse immunitaire anormale dans le cas de cette maladie hépatique, possiblement attribuable à un facteur viral spécifique ou autre facteur environnemental.

PRIMARY BILIARY CIRRHOSIS IS A chronic progressive liver disease characterized by the destruction of intrahepatic bile ducts and portal inflammation leading to cirrhosis (1).

The etiology of this disorder is unknown, but its clinical features, association with autoimmune phenomena and the detection of multiple immunological abnormalities have resulted in the

concept that primary biliary cirrhosis is an autoimmune-related liver disease (2). The immunological abnormalities described in this condition include circulating immune complexes (3), abnormalities of suppressor cell modulation of T cell proliferation (4) and of immunoglobulin production by B cells (5), and a defect in the activity of the CD4+, Leu8+ populations (inducer of suppressor cells) in the regulation of immunoglobulin production (6,7). Bile duct damage may be mediated by abnormalities of cellular immunity (8) and aberrant major histocompatibility complex (MHC) class II antigen expression in the bile ducts, together with portal tract inflammation comprising predominately CD8+ cytotoxic suppressor cell populations (9). In recent years, an increased incidence of immunological abnormalities has also been observed in the relatives of patients with primary biliary cirrhosis (10-13). Indeed, it has been recommended that the detection of antimitochondrial antibodies in the absence of overt clinical or biochemical disease markers in kindred of patients with primary biliary cirrhosis should arouse suspicion of the disease (14). The familial occurrence of primary biliary cirrhosis has also been occasionally recorded (15-20). In one of these earlier reports from 1973, twin sisters were described with childhood jaundice and later development of primary biliary cirrhosis (20). Although

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specific genetic markers were not defined in that study, the observation of human leukocyte antigen (HLA)-identical twin siblings with this disorder in the present report provides strong support for the hypothesis that development of primary binary cirrhosis is due to a genetically based abnormality of the immunological response.

CASE PRESENTATIONS

Case 1: A 51-year-old female was referred to the University Hospital in Vancouver, British Columbia, in April 1983 for investigation of abnormal liver chemistry tests. In 1976, fatigue and jaundice were reported. Liver biopsy could not be done in her community hospital because she did not agree to blood transfusions for religious reasons should a bleeding complication occur. At that time, a clinical diagnosis of 'chronic hepatitis' was made; she was placed on prednisone 40 mg daily, gradually tapered to 10 mg daily with apparent resolution of her jaundice. She also had multiple joint arthralgias but no history of alopecia, xerostomia, oral ulcers, skin rash or Raynaud's phenomenon. The patient was the first of two twins delivered full term; she had measles, mumps, chickenpox and possibly rubella in childhood. Her past history also revealed a transient episode of jaundice at age 10 years; at that time, her identical twin sister (see case 2) had a similar temporary episode of jaundice. In 1970, the patient's liver was reported to be 'normal' at a cholecystectomy done for cholelithiasis. There was no history of biopsy-proven liver disease reported in other family members but the mother had a nonalcohol-associated form of chronic liver disease and one paternal uncle had died of nonalcohol-associated 'cirrhosis'. Examination revealed joint swelling and tenderness of her knees, ankles, elbows, and small joints in her hands and feet. Liver and spleen were not palpable and there was no lymphadenopathy. Peripheral stigmata of chronic liver disease were not detected.

Laboratory investigations revealed: hemoglobin, 127 g/L (normal 120 to 160); white blood cell count, 8400 (normal 4000 to 11,000); erythrocyte

sedimentation rate, 62 mm/h (normal 0 to 20); prothrombin time, 10.0 s (normal 10.0 to 12.5); total bilirubin, 16 μ mol/L (normal 2 to 23); alkaline phosphatase, 520 U/L (normal 30 to 110); alanine aminotransferase (ALT), 85 U/L (normal 3 to 36); and aspartate aminotransferase (AST), 69 U/L (normal 5 to 47). Antimitochondrial antibodies were positive in a titre of 1:640. Total proteins were 77 g/L (normal 60 to 77), with a serum albumin of 29 g/L (normal 35 to 50) and total globulins of 49 g/L (normal 18 to 42). Immunoglobulin (Ig) quantitation revealed an elevated serum IgM of 4.65 g/L (normal to 2.5). Serological tests for hepatitis A and B viruses, cytomegalovirus, herpes simplex virus, toxoplasmosis, rubella and Epstein-Barr virus were negative. Stools for ova, parasites and bacteria were negative. An abdominal sonogram confirmed an absent gallbladder. HLA typing revealed A2, A3, B18 and Bw44.

A surgical wedge liver biopsy was done in March 1983. The liver had a nodular appearance. The biopsy showed overall preservation of hepatic architecture but with apparent nodularity and areas of portal fibrous bridging. Most striking was an intense portal infiltrate of inflammatory cells, including large numbers of plasma cells and lymphocytes with occasional eosinophils and neutrophils. In some portal areas, lymphoid follicles with germinal centres and rare, poorly defined granulomas were present. In many areas, the inflammatory infiltrates were centred around small, reactive bile ductules. Some portal areas showed preservation of interlobular bile ducts with minimal associated inflammation. There was a diffuse, mild infiltrate of mononuclear cells with increased prominence of Kupffer cells. The remainder of the lobules showed focal loss of hepatocytes with occasional poorly formed granulomas. These features were characteristic of primary biliary cirrhosis and consistent with recently described features of 'granulomatous cholangitis' (21).

The patient's subsequent clinical course was complicated by deteriorating liver function, portal hypertension

with varices, ascites and gastrointestinal hemorrhage, marked bone demineralization and osteoporosis as well as vertebral compression fractures. Liver transplantation was declined on religious grounds. Progressive liver failure and encephalopathy developed, with death in 1988.

Case 2: A 51-year-old female, twin sister to case 1, presented to Royal Alexandra Hospital in Edmonton, Alberta, in August 1983 with recurrent hematemesis. Examination revealed hepatic and splenic enlargement while upper gastrointestinal endoscopy showed large esophageal varices, but there was no active bleeding. Laboratory investigations revealed: hemoglobin, 92 g/L; erythrocyte sedimentation rate, 56 mm/h; prothrombin time, 10.9 s; total bilirubin, 37 μ mol/L; alkaline phosphatase, 1580 U/L; AST, 175 U/L; total proteins, 59 g/L; albumin, 32 g/L. Quantitation of serum immunoglobulins revealed increased IgM to 7.65 g/L. Antimitochondrial antibodies were positive to a titre of 1:640. Hepatitis A and B serological studies were negative. HLA typing revealed A2, A3, B18, Bw44 and Cw5. Liver biopsy (percutaneous), done in June 1984, revealed lymphoid hyperplasia in the portal triad regions with a mononuclear portal infiltrate consisting mainly of lymphocytes and plasma cells. Rare eosinophils and neutrophils were present. Well formed granulomas were not seen. As in case 1, inflammatory infiltrates appeared to be centred on reactive bile ductules while, in other areas, interlobular bile ducts were preserved. In addition, portal fibrosis was evident. The features in this biopsy were also consistent with primary biliary cirrhosis.

Because of recurrent esophageal bleeding episodes, a distal splenorenal shunt for portal hypertension was done in June 1984. Ascites developed in July 1984 requiring diuretics. In March 1985, xerostomia and xerophthalmia were recorded; arthralgias in her knees, shoulders, neck, ankles and hips were first described in October 1985. Because of deteriorating liver function, liver transplantation was offered in April 1986 but declined for religious reasons. Her clinical course became

complicated by osteoporosis with rib and vertebral fractures followed by progressive liver failure, encephalopathy and death in 1988.

DISCUSSION

In 1973, Chohan (20) recorded twin sisters with clinical, biochemical, immunological and histological features consistent with primary biliary cirrhosis. In their report, both patients had a history of a concurrent episode of transient jaundice at five years old, followed over two decades later by more florid features of primary biliary cirrhosis; the genetic identities of these two twin sisters was not defined.

In the present report, the twin sisters had a very similar clinical course. Transient childhood jaundice, suggestive of a possible infective cause, was followed by a long asymptomatic phase and the eventual clinical presentations of both patients only months apart in different teaching hospital centres. Both twins had primary biliary cirrhosis, and HLA identity was confirmed, providing sup-

port for the hypothesis that this disease has, at least in part, a genetically determined basis. As these individuals were not separated from each other at birth, it is not possible to exclude environmental factors in the pathogenesis of the disease in these twin siblings.

The familial occurrence of primary biliary cirrhosis in two or more family members has been recorded previously elsewhere (15-19). Given that this is a rare disease seen primarily in women, these other studies have also provided some evidence to support the hypothesis that the disorder has an inherited basis. In addition, a very high prevalence of seroimmunological abnormalities has been recorded in patients with primary biliary cirrhosis and their relatives without evidence of liver disease (10-14). Initial studies examined HLA and ABO blood group antigens; the differing results (22-26) failed to identify a specific genetic marker suggestive of a definitive link for this disease. More recent studies, however, have renewed

interest in a possible immunogenetic role for the MHC in the pathogenesis of primary biliary cirrhosis.

Genes of the MHC region on human chromosome 6 code for at least three classes of proteins: first, class I gene products (ie, HLA-A, -B and -C) which are cell surface molecules involved in cell recognition; second, class II gene products (ie, HLA-DR, -DQ and -DP) that act as receptors for antigen presentation on immunocompetent cells; and third, class III gene products that comprise components of the complement system (ie, C2, factor B, C4A and C4B). As a high degree of genetic polymorphism is evident for most gene products, some recent studies have further evaluated their relationship in primary biliary cirrhosis with some intriguing results. For example, reported positive associations with HLA DR3 as well as DRw8 are being explored (24,27-30); these studies, if confirmed, may identify specific gene product risk factors for different forms of genetically based liver disease.

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