Primary Sclerosing Cholangitis—An Immunologically Mediated Disease?

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Primary sclerosing cholangitis (PSC) is an uncommon, chronic disorder characterized by inflammatory fibrosis usually involving the entire biliary tree. The etiology has been unknown, but PSC is closely associated with ulcerative colitis, which coexists in more than two thirds of patients with PSC. In recent studies 3% to 5% of all patients with ulcerative colitis had PSC.

We propose that PSC is, at least in part, an immunologically mediated disease; it is closely associated with human leukocyte antigens B8 and DR3, and circulating autoantibodies to colon and portal tract are frequently present. The anticolon antibody cross-reacts with enteric Escherichia coli. *The disease may possibly be triggered in susceptible patients with ulcerative colitis by immunization with antigens shared between enteric microorganisms and the biliary system.*

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Primary sclerosing cholangitis (PSC) is an uncommon disease characterized by chronic inflammatory fibrosis usually affecting the entire biliary tree, causing beading and stricturing of the bile ducts.[1] The clinical syndromes associated with PSC range from the classic cholestatic presentation with jaundice, pruritus, fever and abdominal pain to cirrhosis and portal hypertension without predominant cholestatic features.[2] In addition, an increasing number of patients are being diagnosed by cholangiography at an asymptomatic stage following the discovery of an elevated serum alkaline phosphatase level.[3]

Etiology

Previous Hypotheses

The etiology of PSC is unknown. Since the original description of PSC by Delbet in 1924,[4] a number of possible factors have been suggested as having a role in pathogenesis. PSC is closely associated with ulcerative colitis, which is found in about two thirds of patients who have PSC.[2,5] Consequently, Warren and co-workers[6] suggested that chronic low-grade portal infection, which may occur in some patients with ulcerative colitis, leads to chronic biliary tract inflammation and fibrosis. This explanation seems unlikely, for the extent of hepatic histologic change is unrelated to the incidence of portal bacteremia and there is no direct evidence for a causal relationship between portal bacteremia and the development of PSC.[7-9]

A second hypothesis is that PSC associated with ulcerative colitis is caused by a reaction to toxic circulating bile acids arising from the diseased colon.[10] In three recent studies, however, no major abnormality in bile acid metabolism was found in patients who had PSC or ulcerative colitis (or both).[11-13]

Ludwig and associates have suggested that PSC may be caused by a virus,[8] as cholangitis and biliary atresia may be induced in weanling mice, primates and, possibly, also in infants after infection with reovirus type 3.[14] There is no evidence, however, to support this interesting concept.

The same group has also proposed that the excess liver copper found in PSC patients may have a role in either initiating or perpetuating the disease process.[8] The latter suggestion seems more likely, as excess liver copper is found in patients with chronic cholestasis from any cause.

New Hypothesis

In a number of recent studies it has been suggested that genetic and immunologic factors are important in the pathogenesis of PSC. These suggestions lead us to propose that PSC is, like primary biliary cirrhosis, an immunologically mediated disease,[15] possibly triggered in genetically predis-

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ABBREVIATIONS USED IN TEXT
HLA = human leukocyte antigen
PSC = primary sclerosing cholangitis

posed persons by a cross-reaction between antibodies to viral or bacterial antigens in the gut and biliary epithelium.

Evidence

Genetic Factors

In a study of 25 patients with PSC, we found a close association between the human leukocyte antigen (HLA) B8 phenotype and PSC.[16] HLA-B8 was present in 60% of patients with PSC, with and without ulcerative colitis, compared with only 25% of 561 controls. Schrumpf and associates have recently found HLA-B8 in 80% of Scandinavian patients with ulcerative colitis and hepatobiliary disease, most of whom had sclerosing cholangitis.[17] HLA-DR3 was found in 70%.[17] We have confirmed these findings in English patients with ulcerative colitis and PSC.[18] Although the prevalence of HLA-B8 and HLA-DR3 is not increased in a population of patients with ulcerative colitis,[19] it seems that patients with ulcerative colitis unfortunate enough to possess HLA-B8 and HLA-DR3 are at an increased risk for the development of PSC.

Further evidence of the importance of genetic factors comes from Quigley and co-workers who reported the cases of three families in whom ulcerative colitis and PSC developed in two members.[20]

The presence of HLA-B8 and HLA-DR3 has been associated with a number of "organ-specific" autoimmune diseases such as "lupoid" chronic active hepatitis, type I diabetes mellitus, myasthenia gravis and thyrotoxicosis that are associated with the production of autoantibodies.[21] The finding, therefore, of a greatly increased prevalence of HLA-B8 and HLA-DR3 is suggestive that immunologic factors may be involved in the pathogenesis of PSC. This suggestion has been strengthened by a number of recent studies that have shown humoral and cellular immune abnormalities in PSC.

Humoral Immune Abnormalities

Like primary biliary cirrhosis,[15] a disease with which it shares many features, symptomatic primary sclerosing cholangitis is characterized by hypergammaglobulinemia, often with a disproportionate elevation of serum IgM levels.[2]

Although characteristically absent, smooth muscle antibody and antinuclear factor are found in some patients with PSC.[2] These antibodies are usually present only in a low titer and may simply represent a nonspecific result of parenchymal liver damage. We have recently shown, however, that at least two other specific serum autoantibodies are present in PSC patients with ulcerative colitis.[22,23] In our studies 62.5% of patients with ulcerative colitis and PSC have circulating anticolon antibodies compared with only 17% of patients with ulcerative colitis alone.[22] The anticolon antibody did not cross-react with human liver and was not associated with the presence of the HLA-B8 phenotype.[22] We were also able to demonstrate a separate antibody to portal tracts, probably to proliferating bile ductules, from human obstructed liver in the serum of 53% of patients with PSC and ulcerative colitis.[23] This antibody was present in only one patient with ulcerative colitis alone and, interestingly, was closely associated with the HLA-B8 phenotype.[23] The antibody was not found in the serum specimens of 20 patients with extrahepatic bile duct obstruction or 20 with primary biliary cirrhosis. Studies in organ-specific autoimmune disease such as type I diabetes mellitus and pernicious anemia have shown a correlation between serum cytotoxic activity and surface-reactive but not cytoplasmic autoantibodies.[24,25] Further studies are needed in PSC patients to determine whether the portal tract antibody is cytoplasmic, cytotoxic or both.

Additional evidence for the importance of humoral mechanisms in the development of PSC comes from a study by Bodenheimer and colleagues.[26] These workers found elevated circulating immune-complexlike material by at least one method (of two used in the study) in 16 of 20 patients who had PSC with and without ulcerative colitis compared with controls with and without colitis. Immune complexes have also been found in the bile of PSC patients.[27] However, elevated levels of serum immune complexes are not specific for PSC and are found in cases of various liver diseases.[26] Further studies are needed to characterize the nature of the antigen and antibody components of the complexes, which may simply represent an epiphenomenon. It is possible, however, that antibodies against hepatobiliary antigens, such as we have recently described, may form immune complexes in the liver, which play a direct role in tissue injury.

Cellular Immune Abnormalities

Few studies of the cellular immune system have been carried out in PSC. McFarlane and associates found an inhibition of leucocyte migration in response to biliary antigens in patients with PSC, suggesting that their lymphocytes may react with specific antigens in biliary epithelial cells.[28] Similar changes were observed in cases of primary biliary cirrhosis and chronic active hepatitis but not in other forms of cholestatic liver disease.

Schrumpf and co-workers studied T-cell subsets in 11 patients with ulcerative colitis and PSC.[17] They could not find any abnormality in total T-cell numbers or in the ratio of helper to suppressor cells, compared with normal controls.[17]

It is likely, however, that there will be some abnormality in T-cell function in patients with PSC. It has been shown in patients with dermatitis herpetiformis and in normal controls that the HLA-B8 and -DR3 antigens are associated with a low number of Fc-receptor-bearing T cells and a functionally defective Fc-receptor function.[29]

Relationship With Ulcerative Colitis

On the evidence presented it seems likely that PSC is an immunologically mediated disease. How then to explain the close association with ulcerative colitis?

It has been suggested that immunologically mediated diseases are the result of an interplay between independent, antigen-nonspecific defects and antigen-specific defects.[15] The HLA-B8- and HLA-DR3-linked gene is in some way responsible for an antigen-nonspecific increase in immune responsiveness[21] and the disease specificity in PSC must reside in some other non-HLA-linked, genetic or environmental influence somehow linked to ulcerative colitis. The situation may be analogous to the association of ankylosing spondylitis with ulcerative colitis. Although the prevalence of HLA-B27 is not increased in ulcerative colitis, in patients with ulcerative co-

litis and HLA-B27 there is a higher risk for ankylosing spondylitis developing than in controls.[30] There is evidence of antigenic cross-reactivity between HLA-B27-positive lymphocytes and antigens present on *Klebsiella pneumoniae*.[31] It is postulated that this may result in disease by either the production of microbial antibodies that also have an "antiself" activity or that *Klebsiella* antigens may bind to the HLA complex, rendering it susceptible to immune attack.[30] As previously discussed, approximately one fifth of patients with ulcerative colitis have circulating anticolon antibodies, which are not seen in normal controls.[22] The colonic antigen is probably a mucopolysaccharide located in the cytoplasm.[32] It shares determinants with a heterogenetic antigen that is a constituent of most Enterobacteriaceae strains,[33] including *Escherichia coli* O14, which has been shown to cross-react with the colon antigen.[34] The significance of anticolon antibodies in the pathogenesis of ulcerative colitis is unclear, as they are not directly cytotoxic to human colonic cells in tissue culture.[35] They may act, however, by invoking antibody-dependent cell-mediated cytotoxicity against colonic epithelium in cases of ulcerative colitis.[36] The distinct portal tract antibody in PSC may also represent a cross-reacting antibody to an enteric microorganism. This antibody, in genetically predisposed patients with and without ulcerative colitis with HLA-B8, HLA-DR3 and heightened immune responses, could also play a role in the development of PSC through the variety of direct or indirect immunologic mechanisms already discussed.

Implications for Therapy

Symptomatic PSC is a severe, debilitating disease usually culminating in death from progressive liver failure or bile duct carcinoma.[2,5] Current medical therapy is unsatisfactory.[9] If our hypothesis is correct, then immunosuppressive agents such as corticosteroids or cyclosporine administered either singly or in combination may be beneficial at an early stage. We and others have stated that corticosteroids should not be used in cases of long-standing PSC because of the hazards of corticosteroids accentuating osteoporosis in patients with cholestasis.[2,5,9] There has been no controlled trial, however, and it is possible that patients with early disease may benefit from a regimen of corticosteroids.[37] Cyclosporine is a new immunosuppressive agent that may prove to be of benefit in PSC, although in view of its numerous side effects it should be studied only in a carefully controlled and monitored clinical trial.

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