Primary sclerosing cholangitis

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Abstract

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease caused by diffuse inflammation and fibrosis that can involve the entire biliary tree. The progressive pathological process obliterates intrahepatic and extrahepatic bile ducts, leading ultimately to biliary cirrhosis, portal hypertension and hepatic failure.

The cause is unknown but it is closely associated with inflammatory bowel disease, particularly ulcerative colitis, which occurs in about 70% of cases. Approximately 5–10% of patients with total ulcerative colitis will have co-existing PSC.

Clinical symptoms include fatigue, intermittent jaundice, weight loss, right upper-quadrant abdominal pain and pruritus. The clinical course of PSC is variable. Serum biochemical tests usually indicate cholestasis; the diagnosis is established by cholangiography.

In symptomatic patients, median survival from presentation to death or liver transplantation is about 12 years. About 75% of asymptomatic patients survive 20 years or more. Median overall survival is 23 years. Overall, 37% of patients die from hepatic failure, while approximately 44% die from cancer – PSC is a premalignant condition. The commonest malignancy is hepatobiliary in origin, usually bile duct carcinoma, which is often aggressive. Patients with associated inflammatory bowel disease may die from colonic cancer or complications of colitis.

PSC has no curative treatment. Medical treatment with the bile acid, ursodeoxycholic acid, may slow progression of the disease and act as a chemoprotective agent against colonic dysplasia. Liver transplantation is the only option in young patients with PSC and advanced liver disease; 5-year survival is 80–90% in most centres. The disease will recur in the donor liver in 30% of patients after 5 years.

Keywords cholangiocarcinoma; cholestasis; colonic cancer; primary sclerosing cholangitis

What's new?

- Recent genome-wide association studies and immunochip studies have shown that a number of genes associated with primary sclerosing cholangitis (PSC) are shared with a number of other established autoimmune diseases, strongly indicating that PSC is immune mediated
- Magnetic resonance cholangiopancreatography is established as the standard method of diagnosing PSC
- Immunoglobulin G4-related sclerosing cholangitis can mimic PSC and should be actively excluded in all suspected patients with PSC

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease caused by diffuse inflammation and fibrosis that can involve the entire biliary tree. The progressive pathological process obliterates intrahepatic and extrahepatic bile ducts, leading ultimately to biliary cirrhosis, portal hypertension and hepatic failure.[1] Cholangiocarcinoma develops in about 10–30% of patients during the course of the disease.[1]

PSC occurs mainly in young men (male:female ratio 2:1); most patients present when aged 25–40 years, though the condition may be diagnosed at any age and has recently become recognized as an important cause of chronic liver disease in children. The generally accepted diagnostic criteria are:

- generalized beading and stenosis of the biliary system on cholangiography (Figure 1)
- exclusion of IgG4-related disease
- absence of choledocholithiasis (or history of bile duct surgery)
- exclusion of bile duct cancer, usually by prolonged follow-up.

The term 'secondary sclerosing cholangitis' is used to describe the typical bile duct changes described above when a clear predisposing factor to duct fibrosis can be identified. The causes of secondary sclerosing cholangitis are shown in Table 1.

Aetiology

The cause of PSC remains unknown.[2] However, there is a close association with inflammatory bowel disease, particularly ulcerative colitis [3] About two-thirds of patients with PSC have co-

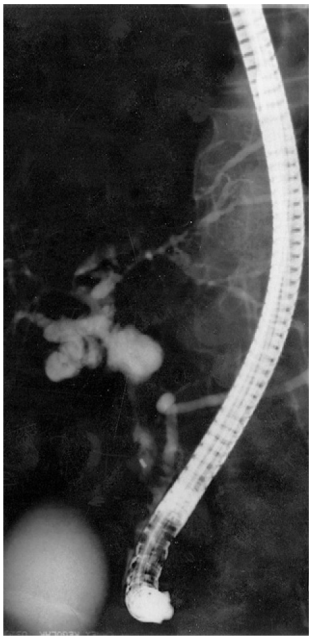

Figure 1 Endoscopic retrograde cholangiopancreatography (ERCP) showing the typical strictured and dilated biliary system diagnostic of sclerosing cholangitis.

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Causes of secondary sclerosing cholangitis

- Previous bile duct surgery with stricturing and cholangitis
- Bile duct stones causing cholangitis
- Intrahepatic infusion of 5-fluorodeoxyuridine
- Insertion of formalin into hepatic hydatid cysts
- Insertion of alcohol into hepatic tumours
- AIDS (probably infective as a result of cytomegalovirus or *Cryptosporidium*)
- IgG4-related sclerosing cholangitis

Table 1

existing ulcerative colitis, and PSC is the most common form of chronic liver disease found in ulcerative colitis. Of patients with ulcerative colitis, 3–10% develop PSC; the prevalence is greater in those with substantial or total colitis than in those with distal colitis alone. In a Swedish study, the prevalence of ulcerative colitis was 171/100,000 population and of PSC 6.3/100,000 population.[3] Two recent studies have shown a prevalence of 20/100,000 in male PSC patients. The prevalence of PSC is lower in patients with Crohn's colitis (about 1%); this may be related to the lesser colonic involvement in patients with Crohn's disease. Patients with PSC and ulcerative colitis are at greater risk of colorectal neoplasia than those with ulcerative colitis alone.

Current evidence suggests that PSC is an immunologically mediated disease, probably triggered in genetically susceptible individuals by acquired toxic or infectious agents, which may gain access through the leaky diseased colon. Gut-derived lymphocytes aberrantly 'home' to ligands in the portal tract in addition to gut epithelium.[4] This may be responsible for the association with inflammatory bowel disease.

Immunogenic factors

A close link with human leucocyte antigen (HLA) haplotype A1 B8 DR3 DRW 52A has been identified. This haplotype is commonly found in association with other organ-specific autoimmune diseases (e.g. autoimmune hepatitis).[2] The prevalence of *HLA-DR2* and *HLA-DR6* is greater in patients who are DR3-negative. Genome-wide association studies and immunochip studies have shown an association with a number of genes shared with other autoimmune diseases, as well as genes associated with the bacterial composition of the colon.

Studies show humoral and cellular abnormalities in PSC. Perinuclear antineutrophil cytoplasmic antibodies (ANCA) have been detected in the sera of about 60–80% of patients with PSC and in about 30–40% of patients with ulcerative colitis alone. The antibody is not specific for PSC and is found in other chronic liver diseases. The antigen in the neutrophils is probably nuclear in origin, but it is unclear whether the presence of the antibody has any pathogenic significance.

Smoking

Cigarette smoking has been recognized as a protective factor against the development of ulcerative colitis.[2] In contrast to its contributory role in primary biliary cholangitis (PBC), smoking may also protect against the development of PSC. This protective effect was more marked in patients with PSC than with ulcerative colitis alone and was observed in patients with and without inflammatory bowel disease. The mechanism of protection in both disorders remains unknown.

Clinical features

The clinical presentation commonly includes fatigue, intermittent jaundice, weight loss, right upper-quadrant abdominal pain and pruritus.[5] Attacks of acute cholangitis are uncommon, and usually follow instrumental biliary intervention. Physical examination is abnormal in about 50% of symptomatic patients; the most common findings are hepatomegaly and/or splenomegaly. Presentation with jaundice is uncommon and it is often associated with the presence of underlying cholangiocarcinoma. IgG4-related sclerosing cholangitis may also present with jaundice, and should be actively excluded by serology and/or histological assessment.

Many patients with PSC are asymptomatic at diagnosis, which is made incidentally when a persistently raised serum alkaline phosphatase (ALP) is discovered in an individual with inflammatory bowel disease.

Laboratory investigations

Serum biochemical tests usually indicate cholestasis. However, serum ALP and total bilirubin may vary widely in individual patients during the course of the disease (e.g. increasing during acute cholangitis, decreasing after therapy) and sometimes fluctuate for no apparent reason. Modest elevations in serum alanine/aspartate aminotransferase are usually seen, whereas hypoalbuminaemia and clotting abnormalities are found only at a late stage.

In addition to ANCA, low titres of antinuclear and smooth muscle antibodies have been found in PSC, but these have no diagnostic significance and antimitochondrial antibodies are absent. IgM concentrations are increased in about 50% of symptomatic patients and elevations of IgG are found in about one-third of adult patients tested.

The serum IgG4 concentration should be measured in all patients with suspected PSC as a modest elevation is detected in about 12–20% of PSC patients and is associated with a worse outcome.

Diagnosis

Radiological features: features on endoscopic retrograde cholangiopancreatography (ERCP) are usually diagnostic, comprising multiple irregular stricturing and dilatation (Figure 1). However, there is a risk of cholangitis and/or pancreatitis after ERCP. Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive method of imaging the biliary tree and has become established as the standard diagnostic method.[6]

Pathological features: histological examination of the liver is not required if radiological findings support the diagnosis. The characteristic early features of PSC are periductal 'onion-skin' fibrosis and inflammation, with portal oedema and bile ductular proliferation resulting in expansion of the portal tracts. Later, fibrosis spreads, leading inevitably to biliary cirrhosis. As in