Primary sclerosing cholangitis

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Abstract

Primary sclerosing cholangitis (PSC) is a chronic, immune-mediated 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, ultimately leading to biliary cirrhosis, portal hypertension and hepatic failure. The cause is unknown but it is closely associated with inflammatory bowel disease (IBD), particularly ulcerative colitis, which occurs in about 70% of patients. Genetic and microbiome studies suggest that PSC/IBD is a distinct disease entity from IBD without PSC. Clinical symptoms of PSC 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, usually magnetic resonance cholangiopancreatography. In symptomatic patients, median survival from presentation to death or liver transplantation is about 12 years, but 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 most common malignancy is hepatobiliary in origin, usually bile duct carcinoma, which is often aggressive. There is no curative medical treatment for PSC. Liver transplantation is the only option in PSC patients with advanced liver disease; 5-year survival after transplantation is 80–90% in most centres. The disease recurs in the donor liver in 30% of patients after 5 years.

Keywords Cholangiocarcinoma; cholestasis; colonic cancer; MRCP; primary sclerosing cholangitis

Key points

- Recent genome-wide association and immunochip studies have shown that a number of genes associated with primary sclerosing cholangitis (PSC) are shared with a several other established autoimmune diseases, strongly indicating that PSC is immune-mediated. PSC patients have a specific microbiome distinct from patients with ulcerative colitis (UC) without PSC. This suggests that PSC/inflammatory bowel disease (IBD) is a distinct disease entity from IBD without PSC
- MRCP is established as the standard method of diagnosing PSC. ERCP is usually reserved for therapeutic procedures such as balloon dilatation in patients with symptomatic, dominant strictures
- Immunoglobulin G4-related sclerosing cholangitis can mimic PSC and should be actively excluded in all suspected patients with PSC
- PSC is a premalignant disease associated with increased incidence of hepatobiliary malignancies and colorectal cancer in patients with associated UC
- Clinical phenotype can determine prognosis; male gender, extrahepatic strictures, dominant strictures, associated UC and high serum alkaline phosphatase are independent predictors of poor prognosis
- Prognostic models have recently been validated for assessing short- and long-term prognosis in PSC. However, none of these models is able to identify individuals at risk of developing cholangiocarcinoma
- There is no proven effective medical treatment in PSC, although studies of new agents are in progress. Liver transplantation is the only treatment option for PSC in patients who develop advanced disease.

Introduction

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, ultimately leading to biliary cirrhosis, portal hypertension and hepatic failure.[1] Cholangiocarcinoma (CCA) 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 aged 25–40 years, although the condition can be diagnosed at any age and has recently become recognized as an important cause of chronic liver disease in children.[2–4] The generally accepted diagnostic criteria are:

- generalized beading and stenosis of the biliary system on cholangiography (Figure 1)
- exclusion of immunoglobulin (Ig) G4-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 for duct fibrosis can be identified. The causes of secondary sclerosing cholangitis are shown in Table 1.

Aetiology

The cause of PSC remains unknown. However, there is a close association with inflammatory bowel disease (IBD), particularly ulcerative colitis (UC). About two-thirds of patients with PSC have coexisting UC, and PSC is the most common form of chronic liver disease in UC. Of patients with UC, 3–10% develop PSC;

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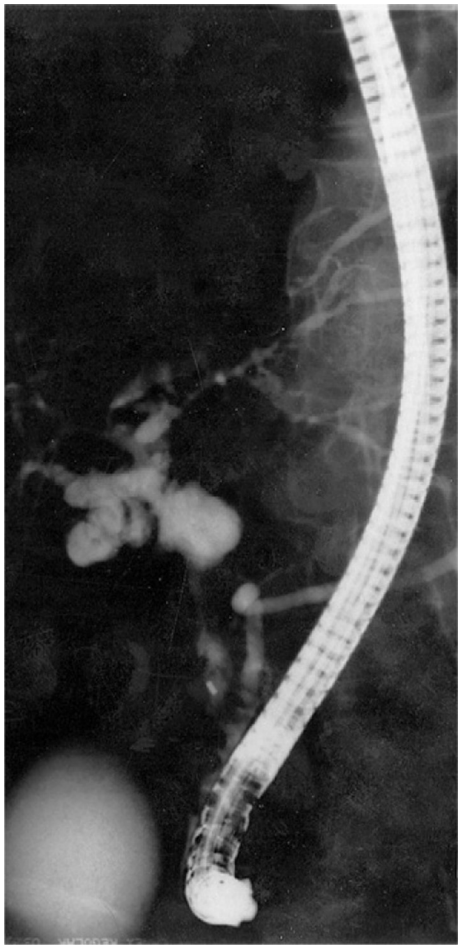

Figure 1 Endoscopic retrograde cholangiopancreatography showing the typical strictured and dilated biliary system diagnostic of sclerosing cholangitis.

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 UC was 171 per 100,000 population and of PSC 6.3 peer 100,000 population. Two recent studies have shown a prevalence of 20 per 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 both PSC and UC are at greater risk of colorectal neoplasia than those with UC alone.

Current evidence suggests that PSC is an immunologically mediated disease, probably triggered in genetically susceptible individuals by acquired toxic or infectious agents that may gain access through the leaky diseased colon. Gut-derived lymphocytes aberrantly 'home' to ligands in the portal tract in addition to gut epithelium. This could be responsible for the association with IBD. Recent studies have shown that PSC patients with and without IBD have a distinct microbiome from UC patients without PSC. These genetic and microbiome studies suggest that PSC/IBD is a distinct disease entity from IBD without PSC.

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

Immunogenic factors

A close link with human leukocyte 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 (AIH)). There is a higher prevalence of *HLA-DR2* and *HLA-DR6* in DR3-negative patients. 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 (ANCAs) have been detected in the sera of about 60–80% of patients with PSC and in about 30–40% of patients with UC 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.

Environmental factors

Cigarette smoking has been recognized as a protective factor against the development of UC. 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 UC alone and was observed in patients with and without IBD. The mechanism of protection in both disorders remains unknown.

Daily caffeine has been shown to be protective in PSC, probably through an antifibrotic mechanism.

Clinical features

The clinical presentation commonly includes fatigue, intermittent jaundice, weight loss, right upper quadrant abdominal pain and pruritus. 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 CCA. IgG4-related sclerosing cholangitis can 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 IBD.

Laboratory investigations

Serum biochemical tests usually indicate cholestasis. However, serum ALP and total bilirubin can 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 ANCAs, 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.

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

Diagnosis

Radiological features: features on endoscopic retrograde cholangiopancreatography (ERCP) are usually diagnostic, comprising multiple irregular strictures and dilatations (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.

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, inevitably leading to biliary cirrhosis. As in PBC, obliterative cholangitis leads to 'vanishing bile duct syndrome'.

Special populations

Small duct primary sclerosing cholangitis

Patients who have a cholestatic pattern on liver biochemistry and have features consistent with a diagnosis of sclerosing cholangitis on liver biopsy but who have a normal cholangiogram are described as having small duct PSC; 6–16% of the PSC population have small duct disease. Small duct PSC occurs more commonly in female patients and in patients with Crohn's colitis. The course of their disease is usually milder than for large-duct disease and a favourable prognosis can be given. To date, no cases of CCA have been reported in small duct disease. Over 10-year follow-up, a quarter of these patients subsequently develop typical changes of large duct PSC on sequential cholangiography.

Autoimmune hepatitis and sclerosing cholangitis (overlap syndrome)

Patients with simultaneous or sequential PSC and AIH have been described. This has been reported more often in children than adults. Overlap should be considered if serum aminotransferase is greater than twice the upper limit of normal and serum IgG is elevated. The diagnostic feature of prominent interface hepatitis is seen on liver biopsy. Immunosuppression appears to be helpful in this selected subgroup, particularly in children.

IgG4-related sclerosing cholangitis

IgG4-related disease is an increasingly recognized multisystem disorder that can involve the pancreas, hepatobiliary system, kidneys, lungs, thyroid, retroperitoneal lymph nodes, salivary glands and aorta.

Some patients with autoimmune pancreatitis (an IgG4-related systemic disease) have biliary strictures similar to PSC (IgG4-related sclerosing cholangitis). In this male-predominant disease, serum IgG4 is variably increased. Importantly, the disease is responsive to immunosuppression with corticosteroids and rituximab.

A retrospective study showed elevated serum IgG4 in a small (9%) proportion of patients with PSC. This untreated subgroup appears to have a more severe disease course with higher bilirubin concentrations and a normal ALP, and shorter time to transplant, than PSC patients with a normal serum IgG4. These patients may really have IgG4-related systemic disease and therefore respond to corticosteroid therapy, but this needs further study.[1,3,4]

Association with other diseases

Many diseases have been associated with PSC, including organ specific autoimmune diseases such as coeliac disease and thyroid disease (Table 2).

Dysplasia and cancer

Patients with total UC have an increased risk of colorectal cancer, associated with longevity of disease and the extent of colitis. The risk of colonic dysplasia and colorectal cancer is enhanced in those with coexistent PSC. Thus, patients with UC and PSC should undergo regular annual surveillance colonoscopy once the diagnosis of PSC is made. This risk continues after liver transplantation and increases with time.

CCA complicates the clinical course in 8–30% of adult patients with PSC and can develop in either the intra- or extrahepatic bile ducts. In one-third of patients with PSC who develop CCA, the cancer is identified within 1 year of diagnosis of their PSC. The incidence of CCA is approximately 0.5–1.5% per year in those with large-duct PSC.

The symptoms of CCA are non-specific and include jaundice, weight loss, abdominal pain and, rarely, recurrent cholangitis.

Diseases associated with PSC

- ulcerative colitis
- Crohn's colitis
- Chronic pancreatitis
- Coeliac disease
- Thyroid disease
- Angio-immunoplastic lymphadenopathy
- Histiocytosis X
- Autoimmune haemolytic anaemia
- Rheumatoid arthritis
- Immunodeficiency states

Table 2

Early detection of CCA is difficult. Unfortunately, computed tomography, ultrasonography and MRCP have poor sensitivity for detecting CCA. An elevated CA19-9 concentration (>200 U/litre) and weight loss as well as presence of a dominant bile duct stricture are suggestive of malignancy. However, CA19-9 has no role in cancer surveillance in PSC as it can be elevated in benign biliary disease and in other malignancies, including of pancreas, colon and stomach, and gynaecological cancers.

CCA can be indistinguishable on cholangiography from a benign dominant stricture; diagnosis is difficult, and brush cytology and endoscopic biopsy may be needed. Survival is poor, with a median time to death of 7 months from diagnosis. Most patients are treated palliatively, which can include biliary stenting and photodynamic therapy.

Other hepatobiliary malignancies, particularly carcinoma of the gallbladder and hepatocellular carcinoma, are frequently seen in PSC. The risk of pancreatic carcinoma can also be increased in PSC.

Management of complications

Management of cholestasis: symptomatic patients often have pruritus, which is best managed initially with colestyramine. Refractory pruritus can be treated with rifampicin or the opioid antagonist naltrexone.[5] Fat-soluble vitamin replacement is necessary in jaundiced patients. Metabolic bone disease, usually osteoporosis, is a common complication of advanced PSC.

Biliary strictures: dominant strictures of major bile ducts can develop in patients with PSC and can cause biliary obstruction and severe cholestasis and predispose to CCA. ERCP can be used for balloon dilatation to treat dominant strictures, providing relief of symptoms and possibly leading to improved survival without transplant.

Recurrent bacterial cholangitis: this is rare in PSC in the absence of previous biliary interventional procedures. It should be treated by immediate administration of broad-spectrum antibiotics such as ciprofloxacin. Prophylaxis using oral quinolones can decrease the frequency of episodes in individuals with recurrent attacks.

Biliary stones: choledocholithiasis probably occurs secondary to chronic bacterial contamination of bile, and the stones are characteristically small, brown, bile-pigment stones. Stones and sludge can be removed by therapeutic ERCP.

Medical treatment

Medical therapies, including immunosuppressive agents and anti-fibrotic therapy, have proved disappointing in the treatment of PSC. Some antibiotics such as metronidazole and vancomycin have shown promise but further studies are required to confirm efficacy.

Ursodeoxycholic acid (UDCA) is a naturally occurring bile acid that improves abnormalities of liver biochemistry in PSC, but its effect on survival remains controversial. A recent randomized controlled study employing higher doses (25–30 mg/kg) in patients with advanced PSC was halted prematurely because of greater need for liver transplant and death in the UDCA group.

A number of new agents, including novel bile acids, anti-fibrotic treatments and biological agents targeting integrins, are currently being evaluated in clinical trials in PSC patients.

There is little evidence that corticosteroids are beneficial in PSC, except for the minority of patients with 'overlap syndrome' who have features of both PSC and AIH.

Prognosis

The estimated median survival from diagnosis to death or liver transplant is 22 years in all patients with PSC. Patients who are asymptomatic at diagnosis, most of whom develop progressive disease, have a mean survival rate of 88% at 5 years and >70% at 16 years after diagnosis. Those who are symptomatic at diagnosis have a shorter survival. Clinical phenotype may determine prognosis: male gender, the presence of extrahepatic strictures, dominant strictures, associated UC and high serum ALP are all independent predictors of poor prognosis.

A serum bilirubin concentration that is persistently raised for >3 months from diagnosis is an independent risk factor correlating with poor outcome and high risk of CCA. In contrast, a serum ALP that is either normal or <1.5 times the upper limit of the normal range after 1 year of follow-up has been shown to be a surrogate marker of a good prognosis.

A simple Child–Pugh classification was found to be a satisfactory alternative to disease-specific models in both research studies and clinical decision-making in patients with advanced disease. Because of the great variability of the disease, in the past models have been of less use in individual cases of PSC than in primary biliary cholangitis. However, three recent prognostic models have been validated in the assessment of short- and long-term prognosis in PSC, although none of these models is able to identify patients at risk of developing CCA.

Hepatic transplantation

Liver transplantation is still the only treatment option for PSC in patients who develop advanced disease. The indications for and timing of transplantation are problematic as the disease course is unpredictable. The presence of CCA is a contraindication to transplantation because of the very high recurrence rates; the 5-year survival after transplant for those with CCA discovered incidentally at operation is only around 35%. A previous diagnosis of CCA is an absolute contradiction to liver transplantation unless the tumour is small (<3 cm) and without evidence of metastases.

Recurrent PSC after liver transplantation is well recognized and occurs in 10–30% of individuals who undergo transplantation within 5 years; it is more common in male patients with an intact colon and in those who require high-dose prednisolone therapy early after transplant. However, adequate immunosuppression should be maintained after orthotopic liver transplantation as rejection is a risk factor for recurrent disease. There are no known therapies to delay the onset or slow the progression of recurrent PSC, but it is rarely responsible for failure of the transplanted organ.

The results of liver transplantation are good, with a 5-year survival after transplant of 75–80%. UC can develop or

worsen in patients with PSC after transplant, and 5–10% of individuals with IBD develop colorectal cancer after liver transplantation, so annual surveillance colonoscopy is recommended. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 30-year-old man presented with a 3-month history of pruritis and weight loss of 5 kg. He had been found to have ulcerative colitis at the age of 18. When aged 25 he developed cholestatic liver function tests but without symptoms. A magnetic resonance cholangiopancreatography revealed stricturing of the whole biliary tree, diagnostic of primary sclerosing cholangitis (PSC). He then remained well for 5 years until the onset of pruritis and 5 kg weight loss. On clinical examination there was slight jaundice but no other abnormality.

Investigations

- Bilirubin at 50 micrograms/litre (1–17)
- Serum CA19-9 at 850 U/mL (<37)

What is the most likely diagnosis?

A. Progressive PSC
B. Hepatocellular carcinoma
C. Cholangiocarcinoma
D. Common bile duct stone
E. Benign dominant stricture

Question 2

A 37-year-old man presented with a 3-month history of intermittent constipation and non-bloody diarrhea. Two years previously he had been found to have total ulcerative colitis and asymptomatic primary sclerosing chlolangitis involving the intrahepatic biliary tree. Clinical examination was normal.

Investigations

- Haemoglobin 139 g/litre (130–180)
- Liver function tests were stable.

What is the most likely diagnosis?

A. Irritable bowel syndrome
B. Coeliac disease
C. Colonic polyps
D. Hypothyroidism
E. Colonic carcinoma

Question 3

A 45-year-old woman presented for review. She was well. She had been found to have Crohn's colitis at the age of 38. Clinical examination was normal.

Investigations

- Albumin 40 g/litre (35–50)
- Bilirubin10 micromol/litre (1–22)
- γ-glutamyltransferase 110 U/litre (4–35)
- Alanine aminotransferase 48 U/litre (5–35)
- Alkaline phosphatase 220 U/litre (45–105)
- Serum autoantibodies and immunoglobulins were normal.

What is the most likely diagnosis?

A. Primary biliary cirrhosis
B. Autoimmune hepatitis
C. Small duct primary sclerosing cholangitis
D. Large duct primary sclerosing cholangitis
E. IgG4-related sclerosing cholangitis