The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Primary sclerosing cholangitis

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1 Introduction

Primary sclerosing cholangitis (PSC) is an idiopathic, chronic, cholestatic liver disease characterised by progressive inflammatory destruction of intra- and extrahepatic bile ducts affecting males more frequently than females (60–80 %). Although the disease may affect children and older adults, the median age of onset is in the fourth decade. In 75–90 % of patients, PSC is associated with an inflammatory bowel disease (IBD), primarily with ulcerative colitis (UC) [1]. The prevalence of PSC in Northern Europe and the US is approximately 1/10 000 while 10–100 fold lower frequencies are reported in Southern Europe and Asia. Cholangiography is the most relevant approach to provide essential diagnostic criteria. The natural course of the disease is quite variable with an average time from diagnosis to death or liver transplant requirement of 12 to 15 years. Approximately 10–15 % of PSC patients will develop cholangiocarcinoma (CCA) during their lifetime. Although PSC is associated with multiple autoantibodies, it cannot be considered as a typical autoimmune disease. In childhood, however, PSC is frequently associated with florid autoimmune features, including elevated titres of autoantibodies (especially antinuclear antibodies and antibodies to smooth muscle antigens), elevated IgG and interface hepatitis resembling autoimmune hepatitis [2]. Overall, no therapy has yet proven effective in PSC, and orthotopic liver transplantation remains the only treatment option increasing patient survival.

2 Diagnostic criteria

PSC is a disease with a variable course, with progressive obliteration of the biliary tree leading to biliary cirrhosis and its complications such as portal hypertension. At presentation, approximately 15–55 % of patients are asymptomatic [1, 3]. Fatigue, pruritus, jaundice or abdominal discomfort develops in 60 % of cases (Table 1).

The diagnosis of PSC is based on characteristic cholangiographic changes in endoscopic retrograde cholangiopancreaticography (ERCP). The imaging hall-

Table 1. Prevalence of symptoms in primary sclerosing cholangitis (according to [1]).

Symptoms	Frequency (%)
Fatigue	50–75
Pruritus	40–70
Jaundice	9–69
Abdominal pain	16–60
Weight loss	10–34
Fevers and chills	5–28
Hyperpigmentation	25
Asymptomatic	15–55

marks are multiple segmental intra- and extrahepatic strictures, diverticular outpouchings, beaded ducts, and a pruned appearance of the biliary tree. The strictures can be as short as 1–2 mm or may be several centimetres.

The biochemical hallmark of PSC is an elevation of alkaline phosphatase (AP) — although some patients may have normal AP levels. Bilirubin can be already increased in early stages due to bile duct strictures. AP and bilirubin can fluctuate during the course, and periods of clinical and cholestatic relapses follow periods of clinical remissions with less cholestasis.

Histologically, PSC is characterised by damage, atrophy and loss of medium- and large-sized bile ducts within or outside the liver.

3 Diagnostic measurements for experts

As mentioned above, cholangiography is considered to be the gold standard for the diagnosis of PSC. It is used for diagnosis but also therapeutically to dilate or stent strictures and screen for cholangiocarcinoma (CCA) by brush cytology and biopsy. However, magnetic resonance cholangiography (MRC) has emerged as a noninvasive, accurate, and rapid alternative method for the examination of the biliary tree achieving sensitivities of 82–88 % and specificities of 92–97 % in distinguishing PSC from other hepatobiliary diseases. Its disadvantage is that it is purely a diagnostic examination although it can be used to identify patients who would benefit from subsequent therapeutic ERC [1].

Although autoantibodies occur quite frequently in PSC (Fig. 1) they do not contribute to its diagnosis (Table 2) [4]. The prevalent autoantibody reactivity is a perinuclear anti-neutrophilic autoantibody (pANCA or xANCA) present in approximately 80 % of patients but lacking diagnostic specificity. Its target antigen is still unknown although there is some evidence that it may be related to human beta-tubulin isotype 5 [5]. The recent finding of antibodies to recombinant sulfite

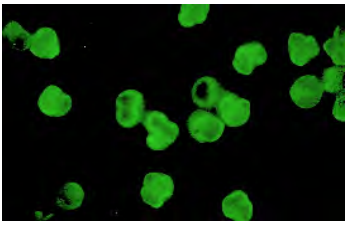

Figure 1. Demonstration of antibodies to neutrophils by immunofluorescence test using human neutrophils in a patient with PSC showing the typical perinuclear staining (pANCA).

Table 2. Autoantibodies in PSC (according to [4]).

Antibodies to	Prevalence
neutrophils (pANCA)	26–94
nuclear antigens (ANA)	8–77
smooth muscle antigens (SMA)	0–83
liver-kidney-microsomes	0
soluble liver/liver-pancreas antigen (SLA/LP)	0
mitochondria (AMA)	0–9
biliary epithelial cells (BEC)	63
sulfite oxidase	33
glutathione S transferase theta 1	5
endothelial cells	35
Saccharomyces cereviseae	44
cardiolipin	4–63
immunoglobulin M (rheumatoid factor)	15
thyroid peroxidase (TPO)	16
glomerular basement membrane (GBM)	17
epithelial 40 kDa protein from colon	67

oxidase by Elisa in 56 % of patients with untreated PSC needs to be backed up by larger studies.

The characteristic pathological feature of PSC, i. e. a concentric periductular fibrosis ('onion-skinning'), which progresses to a narrowing and then obliteration of the small bile ducts, leaving a bile duct scar, is found in less than 15 % of PSC patients. Frequently, findings are nonspecific and must be interpreted along with clinical and radiological information [1].

There is more than an 80-fold increased risk of PSC among first-degree relatives suggesting a genetic link. However, it is a 'complex trait' disease, i. e. a

condition not inherited in a Mendelian autosomal dominant, autosomal recessive or sex-linked fashion. Whether there is a primary susceptibility allele is currently controversial, but PSC is probably acquired through inheriting a combination of genetic polymorphisms. An increased frequency of HLA B8 and DR3 (HLA DRB1*0301) in PSC as compared to controls, and also an increase of HLA-DR6 has been observed. The genetics of PSC is still the subject of active research [1, 3].

4 Requirements for family practitioners

The clinical presentation of PSC patients ranges between asymptomatic, symptomatic, advanced liver disease and/or malignancy (CCA), which may occur at any time, and patients will require liver transplantation within a short time. In many cases the diagnostic scenario is that of a patient with inflammatory bowel disease (IBD) presenting with elevated liver enzymes, followed by cholangiography and appropriate supplementary biochemical tests and in some cases liver histology. In some patients the development of benign dominant strictures or cholangiocarcinoma may result in a diagnostic setting with rapidly deteriorating cholestasis and attacks of acute cholangitis, sometimes aggravated by intermittent plugging by biliary sludge.

There is no evidence to support a particular temporal relationship between onset of PSC and onset of IBD. In more than half the patients, the diagnosis of IBD precedes that of PSC, in some patients the diagnosis of PSC precedes that of IBD by several years. IBD may even present after liver transplantation for PSC, but PSC may also present in IBD patients after colectomy.

One of the most important factors influencing the course of PSC and its prognosis is the development of CCA. It is the most feared complication of PSC and occurs in 7–15 % of patients. The survival of patients with PSC and CCA is greatly diminished. Early diagnosis of CCA is, therefore, important. Sudden progressive jaundice, weight loss and abdominal pain are frequently associated with the development of CCA, but the majority of patients with these symptoms have extrahepatic metastases at the initial diagnosis of CCA. Thus, the development of CCA is not reliably heralded by symptomatic or biochemical changes. Elevated AP and bilirubin levels are not specific for CCA, and may simply be a reflection of the patient's underlying liver disease. A new dominant stricture in patients with PSC merits both immediate investigation and close surveillance, especially in patients manifesting progression or deterioration of their clinical condition. Also ultrasonography and computed tomography seldom identify CCA. Cytological acquisition during ERC or percutaneous cholangiogram is an advantage over non-invasive imaging. Despite the increased risk of CCA in PSC compared with the general population, serial cholangiographic or radiological imaging alone are not yet recommended for CCA surveillance in PSC patients. Tumour markers also

play a limited role in early detection of CCA in PSC patients. Thus, the sensitivity of CA19-9 in detecting CCA in PSC is only 63 %, and the sensitivity of CEA is even lower (33 %), although the specificity is rather high (CEA 85 % in contrast to 50 % for CA19-9). Furthermore, benign extrahepatic cholestatic disease has been shown to increase the serum levels of CA19-9, with decreasing levels after the resolution of the cholestatic picture, and in benign cholestasis, a correlation has been demonstrated between CA19-9 and serum alkaline phosphate levels [1, 3].

However, patients with PSC are also at increased risk for cancers of the pancreas, gallbladder and liver. Colon cancer risk is increased particularly if the patient has IBD.

5 Follow up

Clinical observations and expectations

Median survival from time of diagnosis to death or liver transplantation requirement is estimated to be between 9 and 18 years. Asymptomatic patients have a significantly better prognosis than those with symptoms, but up to 17 % of asymptomatic patients present with cirrhosis on liver biopsy at the time of diagnosis. Patients with small-duct PSC seem to have longer survival rates as compared to patients with large-duct disease, and no development of CCA is found in this first group.

For defining a strategy of therapy and timing of liver transplantation, several prognostic models and risk scores have been constructed on the basis of clinical variables proven to correlate independently with prognosis. A high concordance index has been obtained with a novel prognostic model ('PSC score') including cholangiographic changes (distribution of PSC manifestation, presence of dominant bile duct stenosis) together with other clinical parameters [3]. This score has been shown to be superior to other scores, e. g. the Model for End-Stage Liver Disease score, revised Mayo score, and Child-Pugh score. Nevertheless, the major limitation of all prognostic models is the inability to predict CCA development.

Blood tests

Blood tests should be regularly performed. An increase of bilirubin and cholestatic enzymes may be indicative for the development of strictures or even CCA. As already mentioned, the determination of autoantibodies plays no major role in the diagnosis of PSC, but may unmask overlap syndromes with other autoimmune conditions especially with autoimmune hepatitis. Tumour markers are not sensitive and specific enough to be recommended for the diagnosis of CCA.

6 Management

So far, no treatment for PSC has been proven to be effective in randomised, controlled studies. Medical therapeutic approaches currently in use attempt to target the cholestatic and hepatitic features of PSC. Treatment of cholestatic features includes ursodeoxycholic acid (UDCA) and various means of relieving pruritus. UDCA has been the drug most widely evaluated in the treatment of PSC. Several controlled and uncontrolled studies have consistently demonstrated that UDCA, in a wide dose range from 10 mg/kg/day to 30 mg/kg/day, has beneficial effects on liver biochemistries. However, the relationship between improvement in liver biochemistries and clinically relevant findings such as the development of cirrhosis and its complications, the need for liver transplantation and survival is unknown, and it has not yet been proven to prolong survival or improve the outcome of PSC [1, 3].

Prednisone or immunsuppressive therapy has no beneficial effect in PSC, but may be useful in patients with features of AIH [1–3]. However, progression to cirrhosis occurs in a majority of these patients despite such treatment indicating that some of the pathological processes may be unaffected by immunosuppression.

Strictures of the extrahepatic bile ducts may be amendable to endoscopic or radiological dilation with or without a biliary drainage procedure such as sphincterotomy or stenting.

For disease-associated complications of PSC such as pruritus, fatigue, steatorrhoea and vitamin deficiencies, metabolic bone disease, bleeding peristomal varices, bacterial cholangitis, biliary strictures, gall bladder stones and polyps, and CCA symptomatic treatment is required (Table 3). The medical treatment of IBD in PSC follows the same guidelines as for IBD without PSC.

For patients with end-stage disease, liver transplantation is the treatment of choice. It should be considered before the disease becomes too advanced to enhance the long-term survival rates after OLT. Timing of liver transplantation in PSC does not differ from that of other indications for liver transplantation (consideration of MELD score and local waiting time). Additional circumstances that require evaluation for possible liver transplantation include recurrent bacterial cholangitis, severe extrahepatic biliary obstruction, uncontrolled peristomal variceal bleeding, intractable pruritus, and findings of biliary dysplasia in brush cytology specimens. PSC is among the indications for liver transplantation with the best patient survival with survival rates of 90 % to 97 % at one year, and 83–88 % at five years. However, a major complexity in the pre-transplant evaluation of PSC patients is related to the increased risk of malignancy.

Recurrence of PSC in the liver graft occurs in 2–40 % of the transplanted grafts [1, 3]. This wide range depends upon the rather vague diagnostic criteria. Proposed risk factors for recurrent PSC include recipient age, male sex, sex mismatch, coexistent IBD, cytomegalovirus infections, biologically related living donor liver transplantation, and recurrent and steroid-resistant acute cellular rejection.

Table 3. Disease-associated complications of primary sclerosing cholangitis and their treatments [1].

Complication	Treatment
Pruritus	cholestyramine
	rifampicin
	opioid antagonists
	sertraline
	ondansetron
	liver transplantation (for refractory pruritus)
fatigue	no specific treatment available
vitamin deficiencies	vitamin supplementation
metabolic bone disease	calcium and vitamin D supplementation
	bisphosphonates?
bleeding peristomal varices	local control
	liver transplantation
	transjugular intrahepatic portosystemic shunt
bacterial cholangitis	antibiotics
	prophylactic antibiotics before ERCP
dominant biliary strictures	endoscopic treatment
	surgical treatment
gallbladder stones	cholecystectomy for symptomatic stones
gallbladder polyps	consideration for cholecystectomy due to malignant potential
cholangiocarcinoma	surgical resection
	liver transplantation protocols with neoadjuvant chemoradiation
	palliation with endoscopy and photodynamic therapy

7 Diagnostic test and testing methods

As stated above, there is no single test for the diagnosis of PSC. The demonstration of pANCA may be taken as an additional parameter but is neither sensitive nor specific enough to serve as diagnostic marker. The gold standard for the diagnosis is endoscopic cholangiography.

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