Primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the bile ducts, resulting in end-stage liver disease and reduced life expectancy. PSC primarily affects young and middle-aged men, often in association with underlying inflammatory bowel disease. The etiology of PSC includes immune-mediated components and elements of undefined nature. A cholestatic picture of liver biochemistries with elevations in serum alkaline phosphatase, nonspecific autoantibodies such as perinuclear antineutrophilic antibody, antinuclear antibodies and smooth muscle antibodies, and diffuse multifocal biliary strictures, resulting in a 'beaded' appearance on radiographic studies, are the hallmarks of the disease. No effective medical therapy is currently available, although clinical studies are in progress. Ursodeoxycholic acid at high doses (28 mg/kg/day to 30 mg/kg/day) is the most promising agent but is unproven so far. Liver transplantation is currently the only life-extending therapy for patients with end-stage disease, although recurrent disease can be observed in the transplanted liver. The multiple complications of PSC include pruritus, fatigue, vitamin deficiencies, metabolic bone disease, peristomal varices, bacterial cholangitis, dominant biliary strictures, gallbladder stones and polyps, and malignancy, particularly cholangiocarcinoma, which is the most lethal complication of PSC.

Key Words: *Cholangiocarcinoma; Cholestasis; Diagnosis; Liver transplantation; Sclerosing cholangitis; Therapy*

Cholangite sclérosante primaire

La cholangite sclérosante primaire (CSP) est une maladie hépatique cholestatique chronique caractérisée par une inflammation et une fibrose des canaux biliaires; elle provoque une maladie du foie terminale et abrège l'espérance de vie des patients. La CSP affecte principalement les hommes jeunes et d'âge moyen, souvent en lien avec une maladie inflammatoire de l'intestin sous-jacente. L'étiologie de la CSP inclut des composantes immunitaires et des éléments de nature indéterminée. Le tableau cholestatique des analyses biochimiques hépatiques avec élévation de la phosphatase alcaline sérique, la présence d'auto-anticorps non spécifiques tels qu'anticorps antineutrophiles périnucléaires, anticorps antinucléaires et anticorps anti-muscles lisses, en plus de strictures biliaires multifocales diffuses apparaissant en « collier de perles » à la radiographie, sont caractéristiques de la maladie. On ne dispose, pour l'instant, d'aucun traitement médicamenteux efficace, bien que certaines études cliniques soient en cours. L'acide ursodésoxycholique à forte dose (de 28 mg/kg/jour à 30 mg/kg/jour) est l'agent le plus prometteur, mais son effet n'est pas encore éprouvé. La transplantation hépatique est actuellement le seul traitement qui puisse prolonger la vie des patients atteints de la maladie à un stade terminal, mais une récurrence de la maladie s'observe dans les foies transplantés. Parmi les multiples complications de la CSP, mentionnons le prurit, la fatigue, les carences vitaminiques, la maladie osseuse métabolique, les varices péristomiales, la cholangite bactérienne, les strictures biliaires dominantes, les calculs biliaires et les polypes et la néoplasie, particulièrement le cholangiocarcinome, qui est la complication la plus mortelle de la CSP.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease that primarily affects young and middle-aged men, especially patients with underlying inflammatory bowel disease (IBD) (1,2). The etiology of PSC is undefined, apart from an increasing body of evidence that points to an autoimmune process as a component of the disease. A variety of therapeutic agents with different mechanisms of action have been evaluated in the treatment of this disease, none of which have shown convincing benefit. Among eligible patients, liver transplantation is currently the only life-extending therapy for patients with end-stage PSC. Although PSC is an uncommon disease, it is among the most common indications for liver transplantation in Europe and the United States (3,4). The increased risk for cholangiocarcinoma (CCA) in patients with PSC contributes to the high morbidity and mortality of this disease (3).

EPIDEMIOLOGY

Approximately two of three PSC patients are male, and affected individuals are young (mean age at diagnosis is approximately 40 years). A large proportion of patients with PSC have associated IBD (1,5); the association is higher in patients of Northern European descent (6). The only population-based estimates of incidence and prevalence of PSC conducted in the United States revealed rates of 0.90 per 100,000 person-years and 13.6 per 100,000 persons,

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TABLE 1
Prevalence of primary sclerosing cholangitis symptoms

Symptom	Frequency, %
None	15–55
Fatigue	50–75
Pruritus	40–70
Jaundice	9–69
Abdominal pain	16–60
Weight loss	10–34
Fevers and chills	5–28
Hyperpigmentation	25

Data from references 2,10-14,98,106,145

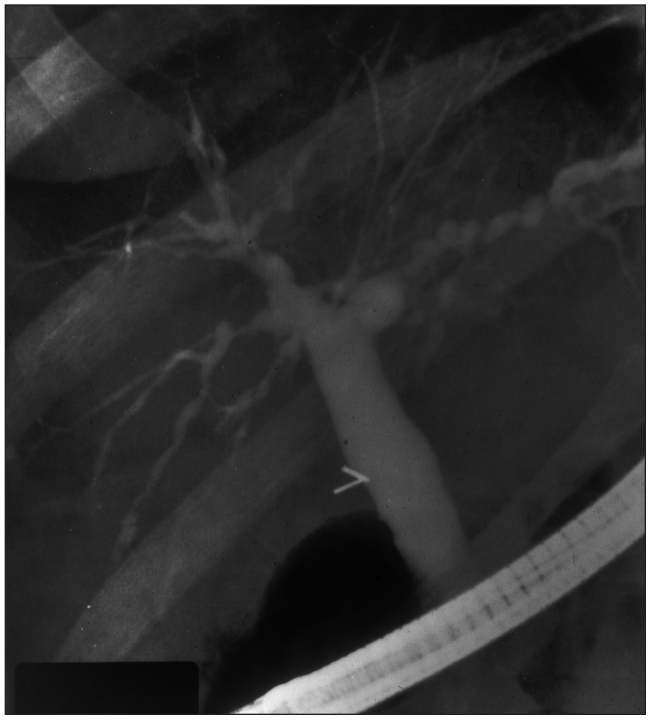

Figure 1) *Cholangiographic findings. Endoscopic retrograde cholangiogram demonstrating multifocal strictures with intervening saccular dilation of both intrahepatic and extrahepatic bile ducts, which is characteristic of primary sclerosing cholangitis*

respectively (7). Population-based studies of disease frequency are also available from Sweden (8), Norway (9), Great Britain (10) and Canada (11), and indicate comparable incidence and prevalence.

DIAGNOSIS

Clinical features

At presentation, approximately 15% to 55% of PSC patients are asymptomatic (11-14). Patients are at increased risk for developing symptoms over time (2). Table 1 illustrates the described prevalence of symptoms in several PSC studies. Fatigue, pruritus, jaundice or abdominal discomfort develops in 60% of cases. Symptoms such as pruritus and right upper abdominal pain are the most common intermittent symptoms, occurring with considerable individual variation and resolving spontaneously, in most cases (15).

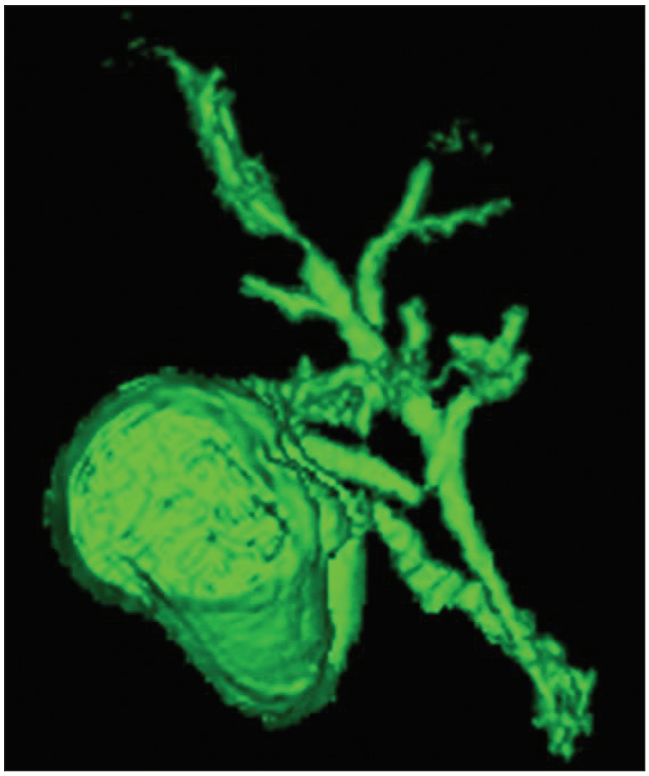

Figure 2) *Cholangiographic findings. Magnetic resonance cholangiogram with three-dimensional reprocessing demonstrating characteristic findings of primary sclerosing cholangitis*

Biochemical features

A cholestatic picture of liver function with an elevation in serum alkaline phosphatase level is the biochemical hallmark of PSC (1), although some patients may have normal alkaline phosphatase levels (16). Increases in serum aspartate and alanine aminotransferase levels are usually only mild to moderate. Patients with PSC often have fluctuations in bilirubin and alkaline phosphatase levels during the course of the disease. Periods of clinical and cholestatic relapses follow periods of clinical remission with less cholestasis (17).

Serological features

Currently, testing for specific autoimmune antibodies does not contribute to the diagnosis of PSC. Multiple autoantibodies can be detected in PSC. Antinuclear antibodies and smooth muscle antibodies can be found in 20% to 60% of patients, usually in lower titres than those observed in autoimmune hepatitis (18). In contrast, antimitochondrial antibodies are seldom seen in patients with PSC (1). The prevalent autoantibody reactivity is a perinuclear antineutrophilic autoantibody (perinuclear antineutrophil cytoplasmic antibody), present in approximately 80% of patients, but lacking in diagnostic specificity (19-22).

Radiographic features

Diagnostic features include diffuse multifocal strictures, usually involving both the intrahepatic and extrahepatic ducts (Figures 1 and 2). Strictures are typically short and annular, alternating with normal or minimally dilated segments to produce a characteristic 'beaded' appearance (23).

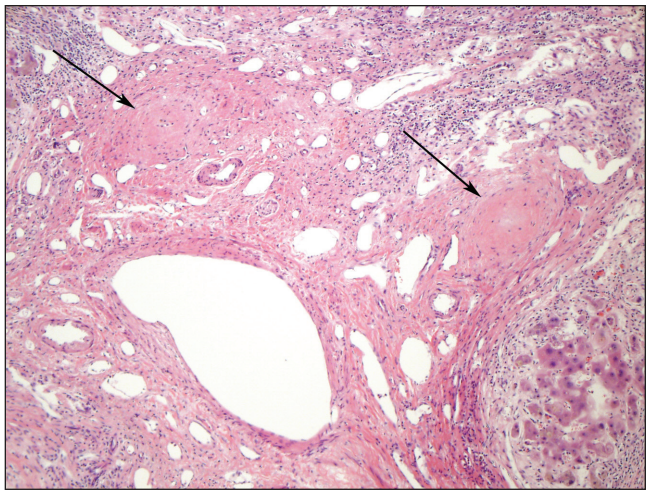

Figure 3) *Histological findings. Expanded portal area with two distinct fibro-obliterative lesions (arrows) in end-stage primary sclerosing cholangitis. There is no intact bile duct present in this portal area; only cross-sections of portal vein and hepatic artery branches (hematoxylin and eosin stain; original magnification, ×100). Photograph courtesy of Dr Schuyler Sanderson*

Cholangiography is considered to be the gold standard for the diagnosis of PSC (5) and is still commonly used, not only for diagnosis, but also therapeutically to dilate or stent the dominant stricture and screen for CCA by way of brush cytology and biopsy. Endoscopic retrograde cholangiography (ERC) in patients with PSC is associated with a risk for complications such as cholangitis, pancreatitis, bile duct perforation and stent migration. Repeated ERC in patients with PSC may increase the likelihood of seeding the biliary system with bacteria, possibly causing disease progression. Multiple studies (24-26) have described highly variable rates of endoscopy-related complications in PSC patients, ranging from 3% to 18%. A recent study (27) comparing therapeutic ERC in patients with PSC and those with other biliary strictures, showed that the complication rates were similar, but PSC patients with acute symptoms had a higher rate of complications than those whose procedures were performed electively.

Magnetic resonance cholangiography (MRC) for detecting PSC has emerged as an accurate, rapid, noninvasive alternative examination of the biliary tract, and is commonly used in multiple centres. Other advantages of MRC over ERC include cost savings (26) and the lack of radiation exposure (28). The major disadvantage of MRC is that it is a purely diagnostic examination, although it can be used to identify patients who would benefit from subsequent therapeutic ERC (29).

Histological features

PSC is histologically characterized by damage, atrophy and, ultimately, loss of medium- and large-sized bile ducts, within or outside the liver (30,31). These are not typically captured in a percutaneous liver biopsy. The smaller ducts are affected by the resultant obstruction and gradually disappear (ductopenia). The characteristic pathological feature of PSC is concentric periductal fibrosis ('onion-skinning'), which progresses to a narrowing and then obliteration of the small bile ducts, leaving a bile duct scar (Figure 3). However, this is found in less than 15% of patients with PSC (32). Frequently, findings are nonspecific and must be interpreted along with clinical and radiological information.

One main staging system for PSC has been devised. Ludwig et al (33) described four stages of PSC: cholangitis or portal hepatitis (stage 1); periportal fibrosis or periportal hepatitis (stage 2); septal fibrosis, bridging necrosis or both (stage 3); and biliary cirrhosis (stage 4).

The role of liver biopsy in the evaluation of PSC appears to be of limited value (32). Despite its potential usefulness for disease diagnosis, exclusion of alternative diagnoses and estimation of prognosis in PSC, caution must be exercised because the histological lesions may be spotty and findings that are consistent with different stages may be present in a single liver simultaneously (34). Diagnosis is usually established by cholangiography and cholestatic liver profile, and in the vast majority of cases, liver biopsy does not reveal atypical findings and does not have any impact on the management of the patient (32). A validated mathematical model for predicting survival in patients with PSC independent of histological findings is available (34). Liver biopsy can be helpful in selected cases, such as in patients with cholestasis and IBD with normal cholangiogram findings, and when small-duct PSC may be diagnosed. It can also be helpful in patients with chronic cholestatic diseases who present with unusually high transaminase levels and hypergammaglobulinemia, when an overlap syndrome of autoimmune hepatitis might be diagnosed and the patients are treated with corticosteroids and immunomodulators.

TABLE 2
Differential diagnoses and variant syndromes of primary sclerosing cholangitis

Secondary sclerosing cholangitis
Portal hypertensive biliopathy
Ischemic-like cholangiopathy in critically ill patients
Overlap syndrome of primary sclerosing cholangitis and autoimmune hepatitis
Immunoglobulin G subclass 4-associated cholangitis

Data from references 146-150

Differential diagnosis and variant syndromes

Table 2 highlights differential diagnoses and variant syndromes of PSC.

MANAGEMENT

Medical treatment

Different forms of medical treatment have been tried, but no treatment for PSC has been proven to be effective in randomized, controlled studies. Drugs evaluated to date have included budesonide (35), colchicine (36), cladribine (37), cyclosporine (38), etanercept (39), infliximab (40), methotrexate (41), mycophenolate mofetil (42,43), oral and transdermal nicotine (44,45), penicillamine (46), pentoxifylline (47), pirfenidone (48), silymarin (49) and tacrolimus (50,51). Table 3 summarizes the current status of many clinical studies. Despite encouraging results from a few studies, none have demonstrated convincing evidence of benefit and some are associated with significant side effects

TABLE 3
Medications evaluated in the treatment of primary sclerosing cholangitis

No benefit	Possible benefit	Under consideration
Azathioprine	Metronidazole	UDCA (28 mg/kg/day to 30 mg/kg/day)*
Budesonide	Minocycline*	DHA*
Cladribine	Silymarin	Thalidomide*
Colchicine	Tacrolimus	Nor-UDCA*
Cyclosporine		6-EDCA*
Etanercept		Losartan*
Infliximab		
Methotrexate		
Mycophenolate mofetil		
Nicotine		
Penicillamine		
Pentoxifylline		
Pirfenidone		

*Please refer to text for references. *Unpublished or ongoing studies. 6-EDCA 6-alpha-ethyl-chenodeoxycholic acid; DHA Docosahexaenoic acid; UDCA Ursodeoxycholic acid*

(35,42,51). Similarly, studies evaluating the combination of low-dose prednisolone and colchicine (52); ursodeoxycholic acid (UDCA) and methotrexate (53); prednisone or budesonide combined with UDCA (54); UDCA, prednisolone and azathioprine (55); and metronidazole and UDCA (56) have not yet shown evidence supporting the long-term use of any particular drug combination. Most of these drugs were evaluated in pilot studies, including a small number of patients treated for a short period of time. The end points used in these studies have been primarily changes in biochemical measurements and Mayo risk score, and little is known about the effects of those drugs on survival free of liver transplantation and overall survival.

UDCA has been the drug most widely evaluated in the treatment of PSC and is the most promising one to date. Several controlled and uncontrolled studies (38-46) 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. To date, the relationship among 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 (57).

Studies evaluating lower doses of UDCA (13 mg/kg/day to 20 mg/kg/day) have demonstrated beneficial effects on serum hepatic biochemistries (58), cholangiographic appearance and liver histology after two years of therapy (59), but no difference in predicted survival. Similarly, one study (60) evaluated intermediate doses of UDCA (17 mg/kg/day to 23 mg/kg/day) and did not observe any significant decrease in serum alkaline phosphatase level in UDCA-treated patients, significant benefit from UDCA on survival without liver transplantation or prevention of CCA. However, the study was too small to exclude a significant beneficial effect on survival. In contrast, higher doses of UDCA (25 mg/kg/day to 30 mg/kg/day) were associated with substantial reductions, not only in serum hepatic biochemistries but also in Mayo risk score after therapy (61,62). Most of the trials performed to date have been limited by a small number of patients and relatively short follow-up periods, and have not allowed conclusions with regard to effects on survival free of liver transplantation and overall survival. UDCA has not yet been proven to prolong survival or improve the outcome of PSC. A large multicentre, randomized trial sponsored by the National Institutes of Health (63) to evaluate the use of high-dose UDCA (28 mg/kg/day to 30 mg/kg/day) is currently underway, but results will not be available for at least three years.

Innovative approaches to therapy

Trials evaluating antibiotics such as metronidazole and minocycline have been promising but inconclusive. A small study (64) of docosahexaenoic acid, which improves cystic fibrosis transmembrane conductance regulator gene function, is currently underway. Most promising for the near future are antifibrotic agents (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and sirolimus/rapamycin), inhibitors of formation of toxic bile (such as 24-norursodeoxycholic acid) (65) and bile acid derivatives (such as 6-alpha-ethyl-chenodeoxycholic acid) (66-69).

Disease-associated complications

Disease-associated complications of PSC include pruritus, fatigue, steatorrhea and vitamin deficiencies, metabolic bone disease, bleeding peristomal varices, bacterial cholangitis, dominant biliary strictures, gallbladder stones and polyps, and CCA. Table 4 summarizes the proposed treatments for these conditions.

Endoscopic treatment

Some patients present with clinical and biochemical deterioration, and exhibit a dominant stricture that involves the larger extrahepatic biliary ducts (Figure 4). The incidence of dominant strictures in patients with PSC has been estimated to be as high as 45% to 58% (17), whereas others have found a much lower frequency (70). Such lesions may be amenable to endoscopic or radiological dilation with or without a biliary drainage procedure, such as sphincterotomy and stenting (71). This leads to symptomatic, biochemical and radiographic improvement. The use of endobiliary stents in PSC has been associated with greater frequency of intervention-related complications including acute cholangitis; balloon dilation alone is preferred in this population (70,72). Repeated balloon dilations of dominant biliary strictures resulted in improved actual survival rates compared with survival rates predicted by Mayo risk score in two studies (73,74), although the clinical relevance of these results is controversial. No randomized studies have been published demonstrating the benefits of endoscopic treatment in PSC.

Surgical treatment

Before the widespread use of liver transplantation and endoscopic balloon dilation to manage PSC, surgical resection was used as the predominant method of treatment. Operative management of PSC entails resection of the extrahepatic biliary tree including hepatic duct bifurcation and postoperative transhepatic stenting (75). In carefully selected patients without cirrhosis and with predominantly extrahepatic biliary strictures, resection of the extrahepatic biliary tree may prolong the interval to liver transplantation and provide relief of jaundice (75). Presently, biliary surgery in patients with PSC, other than simple cholecystectomy, should be minimized and

TABLE 4
Disease-associated complications of primary sclerosing cholangitis and their treatments

Complication	Treatment
Pruritus	Cholestyramine
	Rifampin
	Other agents: opioid antagonists, sertraline, ondansetron
	Refractory pruritus: liver transplantation
Fatigue	No specific treatment available
Vitamin deficiencies	Vitamin supplementation
Metabolic bone disease	Calcium and vitamin D supplementation
	Bisphosphonates?
Bleeding peristomal varices	Local control (usually ineffective over the long term)
	Liver transplantation
	TIPS
Bacterial cholangitis	Antibiotic therapy
	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

ERCP Endoscopic retrograde cholangiopancreatography; TIPS Transjugular intrahepatic portosystemic shunt. Data from references 2,29,41,73-75,135, 137,151-158

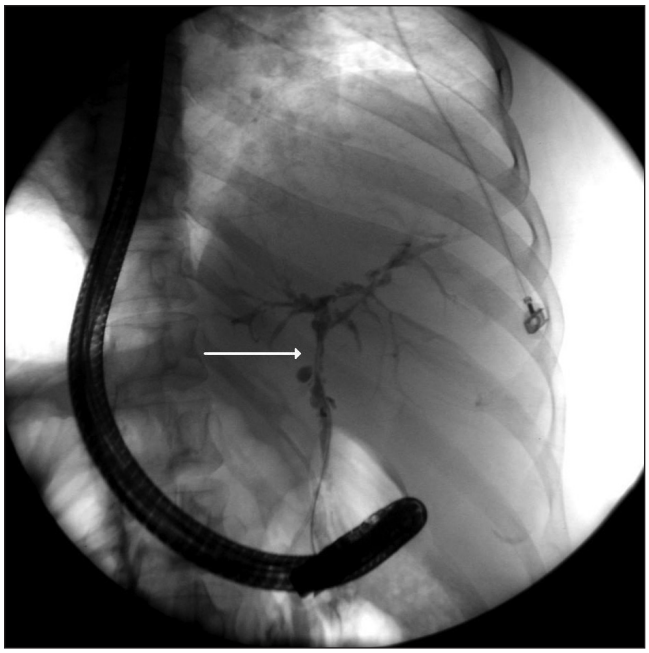

Figure 4) *Dominant stricture. Endoscopic retrograde cholangiogram demonstrating characteristic findings of primary sclerosing cholangitis and dominant common hepatic bile duct stricture (arrow)*

reserved for selected rare noncirrhotic patients who have marked cholestasis or recurrent cholangitis caused by a dominant extrahepatic or hilar stricture not amenable to endoscopic or percutaneous dilation (71). In patients who may undergo liver transplantation, previous biliary surgery has been associated with a significantly longer operation time, greater intraoperative blood loss and a higher incidence of biliary complications following liver transplantation compared with those patients with no history of biliary surgery (76-80).

Liver transplantation

Liver transplantation is the treatment of choice for patients with end-stage disease due to PSC. Liver transplantation should be considered before the disease becomes too advanced, to enhance the long-term survival rates after liver transplantation (81). Prognostic models can aid in the timing of liver transplantation. Unique circumstances that require evaluation for possible liver transplantation include recurrent bacterial cholangitis despite intensive medical and endoscopic therapy, severe extrahepatic biliary obstruction that precludes operative repair and uncontrolled peristomal variceal bleeding. Intractable pruritus may also be an indication for liver transplantation. Over a 12-year period, among patients with PSC, no statistically significant change in the number of patients receiving or listed for transplantation occurred in the United States (82). PSC is among the indications for liver transplantation with the best patient survival (83). Reports from single centres performing liver transplantation in PSC patients have demonstrated excellent survival rates of 90% to 97% at one year, and 83% to 88% at five years (83,84). However, retransplantation rates seem to be higher for patients with PSC than for those with other diagnoses (85).

Recurrence of PSC in the liver graft occurs in 2% to 40% of the transplanted grafts (86). The different diagnostic criteria used for recurrent PSC and variable length of follow-up account for part of the variation observed. Diagnosis of recurrent PSC can be challenging, because nonspecific bile duct injuries and strictures caused by allograft reperfusion injury, ischemia, rejection and recurrent biliary sepsis can mimic the findings of PSC following transplantation, and need to be carefully excluded before the diagnosis of recurrence can be established (87,88). A set of criteria has been proposed by a group of investigators at the Mayo Clinic (89). These criteria have been increasingly used as the standard tool for diagnosis of recurrent PSC (90). The diagnostic criteria consist of a confirmed diagnosis of PSC before transplantation, cholangiogram showing nonanastomotic biliary strictures occurring more than three months after liver transplantation, exclusion of other conditions associated with biliary strictures, and/or liver biopsy showing fibrous cholangitis and/or fibro-obliterative lesions (89).

Proposed risk factors for recurrent PSC include recipient age (91), male sex (92), sex mismatch (87), coexistent IBD, presence of intact colon after liver transplantation (92), cytomegalovirus infections (91), biologically related living donor liver transplantation (93), recurrent and steroid-resistant acute cellular rejection (91,94,95), muromonab-CD3 for acute cellular rejection (91,96) and maintenance corticosteroids after liver transplantation (96,97). As more liver transplant recipients survive longer, the recurrence of disease may become the primary cause of morbidity and mortality in PSC (86).

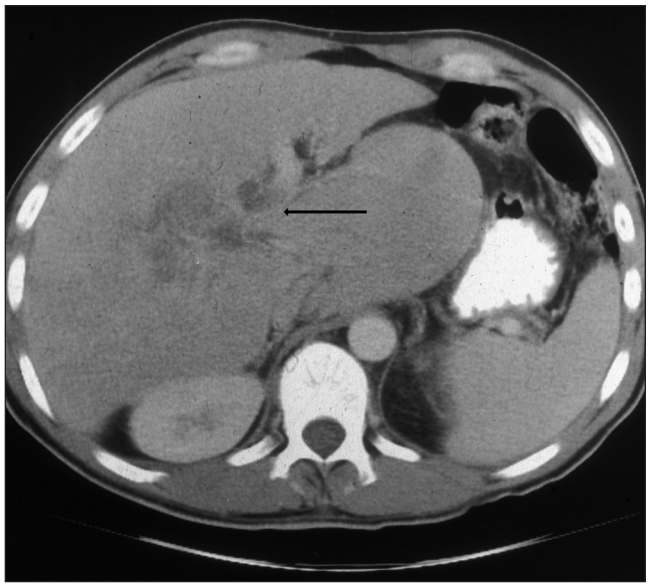

Figure 5) *Computed tomography demonstrating cholangiocarcinoma (arrow)*

PROGNOSIS

Although its course is variable from one patient to another, PSC is generally progressive, and usually leads to the development of primary biliary cirrhosis along with its complications. In early cohorts, a median transplantation-free survival of approximately 12 years was observed (12,13,98). More recent reports suggest a median transplantation-free survival of 18 years (99). CCA and liver failure are the two major complications that affect survival in patients with PSC. Over the past 25 years, mortality from PSC in the United States has remained largely unchanged, highlighting the need for effective therapeutic strategies (100).

In PSC, disease progression and prognosis can be established over time by tracking serum bilirubin, alkaline phosphatase and/or the composite Mayo risk score, which is calculated based on measurements of serum bilirubin, aspartate aminotransferase and albumin levels, patient age and the presence of variceal bleeding (34). The use of surrogate end points of disease progression and survival in PSC has been well described (34,101-105). Less is known about the reliability of these biochemical parameters and PSC-Mayo risk score in predicting response to therapy in PSC (57). Other mathematical models have been developed to predict the natural history of the disease in an individual patient in the absence of effective therapy (12,13,98,99,101,106).

Strictures

A dominant stricture is a frequent finding and occurs in up to 45% of patients during follow-up (17,107). Stenotic lesions in PSC are thus more often benign than malignant in nature. High-grade intrahepatic but not extrahepatic strictures have been shown to predict poor prognosis in two independent studies (108,109). Recently, however, a combination of intrahepatic and extrahepatic scoring proved to be predictive of survival (99). Further studies are needed to confirm these findings.

CCA

Patients with PSC are at high risk for developing CCA (Figure 5). CCA is the most feared complication of PSC and occurs in 7% to 15% of patients (13,110-112), with an annual incidence of 0.5% to 1.5% (110,112). The survival of patients with PSC and CCA is greatly diminished (112). Most cases (37% to 50%) are diagnosed within one year of diagnosis of PSC (111,112). However, CCA can also be a later complication of PSC (106). Although there is no clear association between the duration of PSC and the development of CCA, the presence of cirrhosis may be associated with an increased risk for CCA (98,106,110). Long-term UDCA therapy may reduce the risk of CCA in PSC (113,114).

The diagnosis of CCA can be challenging because its cholangiographic characteristics can imitate the stricturing lesions of PSC (115). The development of CCA is not reliably heralded by symptomatic or biochemical changes. Sudden progressive jaundice, weight loss and abdominal pain are frequently associated with the development of CCA in patients with PSC, but the majority of patients with these symptoms have extrahepatic metastases at the initial diagnosis of CCA (116). Anatomic location of the tumour influences the ease of diagnosis. Hilar tumours are easier to diagnose, with earlier onset of signs and symptoms of biliary obstruction, whereas small or peripheral intrahepatic lesions can be quite challenging, because obstructive symptoms may only be a late finding (117). Elevated alkaline phosphatase and bilirubin levels are not specific for CCA, and may simply be a reflection of progression 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.

There are no specific tumour markers for the diagnosis of CCA in patients with PSC. In patients with PSC, ultrasonography and computed tomography seldom identify CCA (118), but can detect duct dilation as a sign of a tumour. Magnetic resonance imaging studies are considered by some to be the optimal noninvasive investigation for suspected CCA (119), particularly with the administration of ferumoxides (Feridex; AMAG Pharmaceuticals Inc, USA) (120). Positron emission tomography using F-fluoro-2-deoxy-D-glucose to assess human tissue metabolism, has a high sensitivity and specificity for tumour detection in patients with CCA (118,121). However, its clinical application has been limited so far (122,123). Multislice three-dimensional spiral computed tomography cholangiography without a biliary contrast agent but with minimum-intensity projection may become an alternative technique (124). Diagnosis can be performed by direct cholangiography. However, typical cholangiographic features of PSC make it difficult to accurately detect new, malignant strictures. An asymmetric appearance or irregular stricture margins on ERC may be particularly suggestive of malignancy (125). Cytological acquisition during ERC or percutaneous cholangiogram is an advantage over noninvasive imaging. Brush cytology studies have shown a specificity close to 100% for malignancy, but a sensitivity of only 17% to 73% (107,126-129). New diagnostic methods, such as digital image analysis and fluorescence in situ hybridization, have been developed to increase the diagnostic yield of cytology in bile duct strictures (126,130).

Despite the increased risk of CCA in PSC compared with the general population, there are currently no data to support serial cholangiographic or radiological imaging alone for CCA surveillance in patients with PSC. Serum tumour markers such as carbohydrate antigen 19-9 and carcinoembryonic antigen

lack sensitivity and specificity for the diagnosis of early stage CCA (131). Tumours often present at an advanced stage and have a poor prognosis (132,133). In contrast, early-stage CCA in the setting of PSC can be amenable to successful liver transplantation in highly selected individuals, especially at centres employing neoadjuvant protocols such as radiotherapy, chemosensitizing 5-fluorouracil and subsequent capecitabine at the Mayo Clinic, and brachytherapy and continuous 5-fluoracil infusion in Nebraska (134-137). Curative resection among individuals with early-stage CCA may also be of benefit in PSC, although transplantation with neoadjuvant chemoradiation with localized, node-negative hilar CCA may achieve better survival than conventional resection, with less recurrence.

Other malignancies

Patients with PSC are at increased risk for cancers of the pancreas, gallbladder and liver (112,138,139). Colon cancer risk is increased particularly if the patient has IBD (112,140,141). UDCA may reduce the risk of colon dysplasia and/or cancer with long-term use (142,143); however, not all studies have shown similar benefit (144).

CONCLUSION

PSC is a chronic cholestatic liver disease that is generally progressive, and usually leads to the development of primary biliary cirrhosis along with its complications. Other disease-specific complications of PSC include pruritus, fatigue, vitamin deficiencies, metabolic bone disease, peristomal varices, bacterial cholangitis, dominant biliary strictures, gallbladder stones and polyps, and malignancy, particularly CCA. There is no proven medical treatment available for PSC. Despite the presumed autoimmune etiology of PSC, a clear benefit from immunosuppressive agents has not been demonstrated to date and their use can be limited by side effects. Patients with PSC should be considered for therapeutic trials. Liver transplantation is currently the only life-extending therapy for patients with end-stage disease, but disease recurrence can be a source of morbidity and mortality as transplanted patients survive longer. Further studies are needed to develop an optimal therapeutic strategy for patients with PSC to decrease the incidence of complications of the disease and the need for transplantation, and to extend the life expectancy of patients with PSC.

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