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TOPIC HIGHLIGHT

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Primary sclerosing cholangitis - What is the difference between east and west?

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Abstract

Primary sclerosing cholangitis (PSC) is a chronic, progressive, cholestatic liver disease characterized by inflammation and fibrotic obliteration of the hepatic biliary tree. It is commonly associated with inflammatory bowel disease (IBD). A number of complications can occur which require special consideration, the most important of which is the development of cholangiocellular carcinoma (CCC). Unfortunately, no medical therapy is currently available for the underlying liver disease. Liver transplantation is an effective, life-extending option for patients with advanced PSC. Geographical variations between East and West include a second peak for age with a lower association with IBD in a Japanese population and female predominance in a lone study from Turkey. The clinical and biochemical Mayo criteria may not be universally applicable, as different patients show variations regarding the initial presentation and natural course of the disease. Directing research towards explaining these geographical differences and understanding the pathogenesis of PSC is required in order to develop better therapies for this devastating disease.

Key words: Primary sclerosing cholangitis; Endoscopic retrograde cholangiopancreatography; Magnetic resonance cholangiopancreatography; Cholangiocellular carcinoma; Ursodeoxycholic acid

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease characterized by chronic inflammation and fibrotic obliteration of the hepatic biliary tree, resulting in bile stasis and hepatic fibrosis. Ultimately cirrhosis, end-stage liver disease and death ensue. It is commonly associated with inflammatory bowel disease (IBD).

PSC is more commonly a disease of adults, with patients typically presenting during the 4th and 5th decades[1-3], although it has been reported to occur in the pediatric age group[1]. Patients typically present with pruritus and fatigue at the early stages of the disease, although patients with incidental elevated liver enzymes may be diagnosed earlier. As the cholestatic picture progresses with further obliteration of the bile ducts and increased fibrosis, patients develop jaundice and signs of advanced liver disease. Rare presentations include variceal bleeding and cholangiocellular carcinoma (CCC)[4,5]. Due to the diverse clinical picture, PSC patients are generally categorized based on the presence of symptoms, involvement of small *versus* large bile ducts, and its association with IBD or other autoimmune diseases (Table 1).

The cause of PSC is unknown; however, it is not a typical autoimmune disease especially since sex predominance varies with geography. In this review we attempted to establish any differences regarding epidemiology, natural history and management of PSC between different geographical locations, as well as providing insight into recent developments regarding the pathogenesis and treatment of the disease.

EPIDEMIOLOGY AND SYMPTOMATOLOGY

Takikawa *et al*[2] have been pioneers in establishing the

Table 1 Mayo criteria for the diagnosis of PSC[27]

	Mayo criteria
Typical cholangiographic abnormalities involving any part of the biliary tree	Multifocal stricturing and beading, usually involving both the intrahepatic and extrahepatic biliary system
Compatible clinical and biochemical findings (for longer than 6 mo)	Cholestatic symptoms, history of inflammatory bowel disease Twofold to threefold increase in serum alkaline phosphatase levels
Exclusion of identifiable causes of secondary sclerosing cholangitis	AIDS cholangiopathy Bile duct neoplasm (unless diagnosis of PSC previously established) Biliary tract surgery, trauma Choledocholithiasis Congenital abnormalities of biliary tract Caustic sclerosing cholangitis Ischemic stricturing of bile ducts Toxicity or stricturing of bile ducts related to intra-arterial infusion of floxuridine

characteristics of PSC in Japanese patients. In an early analysis of 192 patients[2], they discovered two peaks for age distribution, a characteristic which they reported as "unique", with the disease being associated more often with IBD in the younger age group. In a more recent study[3], the same group performed a nationwide survey, comparing the results with their previous study. They reported on male predominance (59%) with a mean age of 47 years at diagnosis. Although most patients were asymptomatic at the time of diagnosis, jaundice (28%) and pruritus (16%) were the most commonly encountered presenting symptoms.

Ponsioen *et al*[4] evaluated the natural history of PSC in a Dutch population. Of the 174 patients included in this study, 60% were male, with a mean age of 40.4 years[4]. In a similar study by Broome *et al* on 305 Swedish PSC patients, 64% were male and the median age at the time of diagnosis was 39 years (range 5-80)[5]. Of the symptomatic 171 (56%) patients, abdominal pain (37%), jaundice (30%), pruritus (30%), and fever (17%) were most commonly reported complaints. In a more recent multicenter study on 273 German patients, again male predominance was established at 71.4%, with a mean age at time of diagnosis of 32.4 years (range 9-72 years)[6]. Slightly more than half of these patients were symptomatic initially, with right upper quadrant abdominal pain once being again the most prevalent symptom (34.4%).

On the other side of the Atlantic, in an early study, Weisner *et al*[7] evaluated the natural history of PSC in 174 patients; 37 were asymptomatic and 137/174 (79%) had symptoms related to underlying liver disease. At the time of diagnosis, the mean age was 39.9 years, and 66% of the patients were male. Long-term follow-up (mean: 6.0 years; range: 2.7-15.5 years) was available in all patients. In a more recent population based study in Minnesota by the Mayo clinic, it was projected that approximately 29 000 cases of PSC exist in the white USA population. In this study, the median age at diagnosis was 40 years, and 68% of the patients were men. Although asymptomatic patients with incidental abnormal liver tests was not an infrequent clinical scenario, most patients presented with symptoms of advanced stages of the disease, including jaundice, pruritus, fever, or manifestations of portal hypertension.

Table 2 Comparison of characteristics of PSC patients: European and Japanese studies

Parameter	Takikawa (*n* = 388)	Broome (*n* = 305)	Ponsioen (*n* = 174)	Tischendorf (*n* = 273)
Age (yr)	47	39	40.4	32.4
Male (%)	59	64	60	71
Symptoms				
Jaundice	28	30	NA	NA
Pruritus	16	30	NA	NA
IBD	37	81	66	63
CD	2.4	7	13.2	10.6
UC	29	72	47.7	51.7
Laboratory				
ALP	88	91.5	NA	NA
Bilirubin	39	41	NA	40
pANCA (+)	13	NA	NA	69
Diagnostic procedures				
ERC	80	87.2	76.4	100
MRC	32	NA	NA	NA
Liver biopsy	78	83.2	NA	100
BD involvement				
SD	1.6	0	NA	3.3
Only EHBD	4.8	6	NA	3.7
Only IHBD	27	27	NA	24.9
IHBD+EHBD	68	67	NA	68.1
Treatment				
UDCA	78	NA	NA	NA
Steroid	31	NA	NA	NA
Endoscopy	14	NA	NA	NA
Liver transplantation	10	NA	8	39.6

In an earlier study from Turkey, the "crossroad between east and west", by Bayraktar *et al*[8] evaluating the association between PSC and IBD, the median age of presentation for patients with PSC was 35 years (range 19-48 years). The most intriguing feature was that 15 of the 16 patients with PSC were females, a predominance that had never been previously reported. Although results of two subsequent studies originating from Turkey[9,10] were found to be consistent with those from the West, the reasons behind the findings in the Bayraktar study remain elusive.

It would seem that PSC patients worldwide share the same characteristics regarding sex, age and symptoms on presentation (Table 2). The only differences of note would be the second peak for age of presentation observed in the Japanese population, as well as of course the overwhelming female predominance reported in the Turkish study.

ASSOCIATION WITH IBDS

The intimate relationship between PSC and ulcerative colitis (UC), and to a lesser extent Crohn's disease (CD), is no secret. One of the most attractive hypotheses linking the two entities is that disruption of intestinal mucosa due inflammation results in increased permeability and eventual translocation of bacteria into

the portal system, whose cell products may trigger an immune response in genetically susceptible individuals resulting in peribiliary fibrosis. Indeed, Grant *et al*[11,12] managed to demonstrate the enterohepatic circulation of lymphocytes where memory cells originating from the intestines may actually stimulate hepatic inflammation due to the liver and the intestines sharing the same homing receptors. This may help explain why the course of PSC is usually dependent on the severity and extent of bowel involvement.

In the Dutch study[4], a total of 114/174 (66%) patients were known to have concurrent IBD, of which 73% had UC while 25% had CD. Tichendorf *et al* reported similar results in a German population, with 172/273 (63%) having concomitant IBD (82% UC, 17% CD, and 1.2% indeterminate colitis). A study in a Swedish population[5] reported a slightly higher association of IBD with PSC of 81% (249/305), of which 88% had UC, and 8% had CD. The situation in the US was no different, with an association of 71% between IBD and PSC, mainly UC[7].

In Japan, however, a much lower prevalence of IBD has been reported by Takikawa *et al*[3], with only 125 of the 388 patients (32%) having an established diagnosis of IBD, 79% of which had UC, while 6.4% were diagnosed with CD. They also discovered that most patients who were afflicted with IBD were mainly adolescents or young adults. The author's went so far as to suggest that this low prevalence deemed some of the Mayo diagnostic criteria to be inapplicable for Japanese patients.

The association with IBD seems to show variability depending on geographical location, with higher rates in the European and American population, and a significantly lower association in Japanese patients (Table 2).

PATHOGENESIS OF PSC

The etiology and pathogenesis of PSC are not yet well understood. However, it is widely believed that immune dysregulation plays a key role in the development of the disease.

Immunogenetics

Most studies on the immunogenetics of PSC were concentrated in the late eighties to the early nineties. Earlier reports by Schrumpf *et al*[13] and Chapman *et al*[14] demonstrated associations of HLA-B8 and -DR3 of up to 60% in patients with PSC associated with ulcerative colitis. In DR3 negative patients, a second association of up to 55% was reported for DR2[15]. The most striking result was reported by Prochazka *et al*[16], where they found HLA-DRw52, encoded by the gene locus DRB3, in 100% PSC patients evaluated for liver transplantation, with a relative risk of 109 when compared to a control group. Subsequent studies failed to demonstrate a similar correlation[17], which raised the suspicion that HLA-DRw52 may perhaps be associated with more severe disease, thus suggesting the need for liver transplantation in such patients. Clinical significance lies in the fact that DR3 positive patients seem to have an earlier age of onset when compared to DR3 negative, DR2 positive patients. Similarly, DRB380101 positivity, coding for DR52, was associated with reduced survival rate[15].

MICA and *MICB* genes, found in the class I region between HLA-B and DRB, express MICA, which is responsible for the activation of T-cells in the gastrointestinal tract. Although initially identified in association with IBD, their contribution to genetic susceptibility to develop PSC has been investigated. PSC was found to be associated to the extended B8-MICA5.1-MICB24-DR3 haplotype[18]. In another study, a previously unreported protective association with the DRB1*0701-DQB1*0303 haplotype was also demonstrated[19]. Other reported associations include significantly increased TNFA2 allele frequency PSC patients, particularly the homozygous genotype in a southern European population[20].

Intercellular adhesion molecule-1 (ICAM-1, CD54) gene polymorphisms have been implicated in the susceptibility to IBD. ICAM-1 is expressed on proliferating and interlobular bile ducts and elevated serum levels of soluble ICAMs have also been detected. Surprisingly, the E469E homozygote status for ICAM-1 was found to be associated with protection against PSC[21].

Studies regarding the immunogenetics of PSC were inconclusive in establishing a difference between East and West, due to a lack of extensive population based research.

Autoantibodies

There is no specific autoantibody for PSC, although ANCA positivity has been known to occur in up to 88% of patients, while ANA positivity has been observed in a substantial portion (53%) of PSC patients[22]. More notably, anticardiolipin positivity, reported in up to two-thirds of patients, was found to be associated with more prominent histological changes and disease severity[23]. In the report by Moritoki *et al*[23], it was concluded that autoimmunity plays a more important role in autoimmune hepatitis and primary biliary cirrhosis rather than PSC, a notion that is supported by the fact that PSC does not respond to immunosuppressive treatment. Some degree of association has also been reported with *H pylori* IgG[24].

Data in the pertinent literature was insufficient to help establish any geographical differences in immunogenetics.

DIAGNOSIS OF PSC-LABORATORY, ENDOSCOPY, HISTOLOGY AND RADIOGRAPHY

In the Japanese study[3], ALP levels were elevated in 65% of patients, while 39% had eosinophilia. ANA were positive in 36% of patients. The majority of the patients (80%) were diagnosed with endoscopic retrograde cholangiography (ERC), while for 32% magnetic

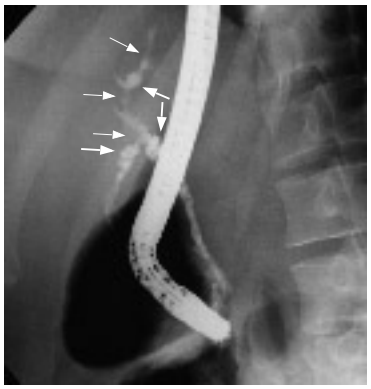

Figure 1 Classical ERCP findings for PSC: Multifocal stricturing (thin arrows) and beading (thick arrows) of the intrahepatic and extrahepatic biliary ducts.

resonance cholangiography (MRC) was utilized, by which more than two-thirds of the patients were observed to have involvement of both intrahepatic bile ducts (IHBD) and extrahepatic bile ducts (EHBD). Isolated involvement of the IHBD and EHBD was encountered in 27% and 4.8% of patients, respectively, while small duct (SD) PSC was observed only in 1.6% of cases. Sixty-nine percent of the patients had histologically proven bile duct damage, with cholestasis apparent in 46% of the 284 patients who underwent a liver biopsy.

Tischendorf *et al*[6] also reported a similar rate of simultaneous involvement of IHBD and EHBD (68%). While 24.9% and 3.7% of patients had either IHBD or EHBD involvement, respectively, SD involvement was encountered in 3.3% of patients. In this study, all patients had undergone ERC evaluation, with no mention of MRC. The Swedish population[5] wasn't far different with 67% dual involvement, 27% IHBD involvement only, and 6% had only extrahepatic PSC. Interestingly, none of the patients in this study had SD PSC.

ERC and liver biopsy are still the most widely used modalities for the diagnosis of PSC, although use of MRC is on the rise.

ERC vs MRC for PSC

PSC was first described by Delbet in 1924[25]. The advent of the widespread use of endoscopic retrograde cholangiopancreatography (ERCP) in the mid-1970s led to further recognition of what was previously thought to be a very rare disease. In an excellent report, MacCarty *et al* described what are now known as the classical ERCP findings (Figure 1) in PSC[26], which later formed the back bone for the updated Mayo Clinic diagnostic criteria of 1984[27].

ERC remains the current standard for imaging of the biliary tract in patients with suspected PSC. However, being less invasive, MRC has gained popularity in recent years. Although promising, many authors have had reservations regarding the sensitivity and specificity of MRC for diagnosing and defining the extent and the severity of PSC. Two recent reports compared these two modalities head-to-head. Berstad *et al*[28] thought that the diagnostic accuracy of ERC and MRC were comparable, despite MRC providing a slightly poorer depiction than ERC of extrahepatic and intrahepatic ducts. They reported independent reader sensitivity and specificity rates of 80% and 87%, with an accuracy of 83% for MRC, compared to 89%, 80% and 85 % for ERC. They concluded that MRC and ERC performed equally well in the diagnosis of PSC when used blinded to clinical information. In a separate study by Moff *et al*[29], EHBD and IHBD visualization was excellent in 64% and 66% of MRCs, and 86% and 74% of ERCs. MRC had sensitivity ranging from 81%-91%, and specificity 85%-96% for diagnosis of PSC. Interobserver agreement for the diagnosis of PSC and for identifying the presence of IHD strictures was good for both modalities, but once again only ERC was good for the presence and the severity of EHD strictures. Similarly, for the assessment of disease severity patients with PSC, interobserver agreement was very poor for both MRC and ERC. They concluded that ERC and MRC were comparable for diagnosing PSC, with very good interobserver agreement for the diagnosis of PSC and IHD strictures. Only ERC had good agreement for EHD strictures. Interobserver agreement was very poor for both MRC and ERC when disease severity of PSC was assessed.

COMPLICATIONS OF PSC

Cholelithiasis, choledocholithiasis, and biliary strictures

Chronic cholestasis predisposes to the formation of cholesterol gallstones and bile stasis with bacterial cholangitis leads to the formation of pigment stones of the bile ducts, which are known to occur in a third of PSC patients. Continuing inflammation eventually results in the development of benign biliary strictures, usually of the EHBD, and they have been reported in up to 7% of patients within 10 years[30-32]. Patients usually present increased jaundice, pruritus or relapsing bacterial cholangitis. Progression of these symptoms warrants cholangiographic examination. Endoscopic intervention, with balloon dilatation for biliary strictures, remains the preferred treatment modality. Some authors have advocated the use of short-term biliary stenting to help improve prognosis[33]. Surgical intervention should be avoided where possible, as it may predispose to recurrent bacterial cholangitis, while at the same time making future attempts at liver transplantation more challenging.

CCC

CCC is the most feared complication among patients with PSC, occurring in 7% to 15% of patients with PSC[34,35]. Chronic inflammation of the bile ducts and cholestasis predispose the development of CCC in PSC patients, although a correlation between severity of disease and incidence of CCC has yet to be established. The difficulty in establishing a diagnosis of CCC lies in the fact that they may not be easily distinguished from benign biliary strictures. The usual serum marker CA 19-9 is not useful in this setting, as PSC itself may result in marked elevations, and secondary bacterial cholangitis

has also been reported to result in increases in CA 19-9 levels[36,37]. Nevertheless, in a patient with PSC, sudden and unexpected clinical deterioration, which is associated with progressive elevation of alkaline phosphatase and serum CA 19-9 (> 100 U/mL), in the absence of bacterial cholangitis indicates probable development of CCC.

Novel diagnostic methods include digital image analysis (DIA) and fluorescence *in situ* hybridization (FISH) performed on bile duct brushings collected at the time of ERC. DIA allows deoxyribonucleic acid (DNA) content quantification, assessment of chromatin distribution and nuclear morphology, while FISH offers promise to evaluate bile duct lesions for cellular aneuploidy and chromosomal aberrations[37]. A number of studies have demonstrated higher sensitivity of both modalities when compared to standard cytological examination, with comparable specificities[36,38,39].

The diagnosis of CCC requires a meticulous and careful combination of a clinical exam, biochemical results, and imaging procedures (ERC, MRC), especially in patients who present with sudden clinical deterioration. Early diagnosis of CCC in PSC can be treated by liver transplantation in selected medical centers.

SPECIAL CONSIDERATIONS

Pruritus

Pruritus in PSC is a rather disabling symptom, resulting in a diminished quality of life. The mechanism behind pruritus associated with cholestasis is unknown. Ursodeoxycholic acid (UDCA), cholestyramine, and antihistaminics opiate receptor antagonists have been used to treat patients with cholestatic pruritus[40].

Fat-soluble vitamin deficiency

Fat-soluble, A, D and E, vitamin deficiencies have been recorded to occur in 2%-40% of patients with PSC, especially in those with advanced disease[41]. Recommended treatment doses for established or suspected deficiencies are 25-50 000 units two to three times per week orally for Vitamins A and D and 100 U/d for Vitamin E. Vitamin E deficiency is the most difficult to correct, with poor responses to replacement therapy. Vitamin K deficiency, although rare, is treatable with intravenous replacement.

Metabolic bone disease

Metabolic bone disease, usually caused by osteoporosis, rather than osteomalacia, is relatively common and an important complication among patients with PSC[42]. It is a rather unfortunate complication, with no proven therapy. Calcitonin and bisphosphonates have been tested on patients with primary biliary cirrhosis with mixed results[43,44], but data on their benefit on PSC is still lacking.

For patients who are on steroid therapy for PSC associated with IBD or AIH, recommendations include close monitoring of bone mineral density with initiation of vitamin D and calcium supplementation at the first signs of osteopenia.

MEDICAL TREATMENT OF PSC

UDCA

A hydrophilic dihydroxy bile acid, UDCA has its roots in ancient Chinese medicine. Its ability to dissolve gallstones contributed to its newly found worldwide fame in the eighties. It was then that its benefit for the cholestatic syndromes was established. Described mechanisms of action include stimulation of hepatobiliary secretion, inhibition of apoptosis and the protection of bile epithelial cells from the toxic effects of hydrophobic bile acids[45].

The use of UDCA was first explored after the earlier success with primary biliary cirrhosis. Although the three major studies all showed decreases in liver enzyme levels with UDCA, they failed to demonstrate any improvement in symptoms or liver histology[46-48]. In a meta-analysis by Chen[49], no difference was observed between UDCA and placebo regarding overall survival and disease progression with the development of complications, requiring transplantation. UDCA also did not prevent deterioration of histological or cholangiographic findings. However, patients included in these studies had advanced disease, making them less responsive.

The general belief is that although UDCA is widely recommended in the treatment of PSC, there is a desperate need for new therapies which may hopefully prevent disease progression.

Immuno modulators/suppressants

Steroid therapy has been the mainstay for the treatment of autoimmune liver diseases; however, its role in the treatment remains controversial. Good response rates have been observed on patients showing histologic signs of both PSC and AIH, otherwise known as autoimmune cholangitis, an overlap syndrome[50]. This group of patients show more characteristic signs of autoimmune disease, such as female predominance, which may account for this response.

In classical PSC, however, the situation is rather bleak. No study has conclusively demonstrated the benefit of systemic steroids in preventing disease progression[51,52]. Endoscopic application of topical corticosteroid failed to impress, but in fact resulted in more frequent episodes of bacterial cholangitis[53]. The results of these studies have left many clinicians baffled, but an interesting study by Tjandra *et al*[54] offered an explanation. They demonstrated a reduction in steroid receptors on hepatic T lymphocytes in a rat model of cholangitis, making them less responsive to steroid treatment. Many authors firmly believe that corticosteroids only help to augment the risks commonly associated with classical PSC, such as metabolic bone disease (osteoporosis) and increased susceptibility to infections.

Several studies on other agents like methotrexate, colchicine, D-penicillamine, pentoxifylline and

tacrolimus[55,56], failed to show any added benefit in the treatment of PSC.

LIVER TRANSPLANTATION FOR PSC

Liver transplantation is the only option that can reverse or correct end-stage liver disease seen in advanced PSC. Controversy lies in the most appropriate timing for surgery, since transplantation after the development of CCC is associated with a poorer outcome[57]. The classical indications still apply, including complicated cirrhosis, intractable itch and fatigue, jaundice refractory to endoscopic or medical treatment or the development of hepatocellular or CCC[58]. The MELD system is used in the United States for all patients with end stage liver diseases, regardless of etiology.

Survival rates after transplantation for PSC have improved throughout the years, rates as high as 84%[59]. Post-transplantation survival has been found to be dependent on a number of pretransplantation factors, such as compromised renal function and the presence of hepatobiliary malignancy at the time of surgery, with recurrence of the original disease being a particular problem[60-62].

CONCLUSION

PSC is a chronic slowly progressive cholestatic liver disease of unknown etiology. A number of complications can occur, which require special consideration, the most important of which is the development of CCC. Unfortunately, no medical therapy is currently available for the underlying liver disease. Liver transplantation is an effective, life-extending option for patients with advanced PSC.

Geographical variations include a second peak for age with a lower association with IBD in a Japanese population, female predominance in a lone study from Turkey. The clinical and biochemical Mayo criteria may not be universally applicable, as different patients have shown variations regarding the initial presentation and natural course of the disease.

Directing research towards explaining these geographical differences and understanding the pathogenesis of PSC is required in order to develop better therapies for this devastating disease.

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