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

Ali Shorbagi, Yusuf Bayraktar

Ali Shorbagi, Yusuf Bayraktar, Hacettepe University, School of Medicine, Department of Internal Medicine, Gastroenterology Clinic, Sıhhiye 06100, Ankara, Turkey

Author contributions: Shorbagi A and Bayraktar Y both contributed to this paper; Bayraktar Y is the main physician, responsible for patients with primary sclerosing cholangitis at Hacettepe University; Shorbagi A did the research necessary to make this manuscript possible; and Shorbagi A and Bayraktar Y co-wrote this review.

Correspondence to: Ali Shorbagi, MD, Hacettepe University, School of Medicine, Department of Internal Medicine, Gastroenterology clinic, Sıhhiye 06100, Ankara, Turkey. shorbagi@hacettepe.edu.tr

Telephone: +90-555-2197557 Fax: +90-312-3051480
Received: February 19, 2008 Revised: May 21, 2008 Accepted: May 28, 2008 Published online: July 7, 2008

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.
characteristics of PSC in Japanese patients. In an early analysis of 192 patients[3], 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[4], 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[5]. 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)[5]. Slightly more than half of these patients were symptomatic initially, with right upper quadrant abdominal pain being again the most prevalent symptom (34.4%).

On the other side of the Atlantic, in an early study, Weisner et al[6] 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 29000 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.

In an earlier study from Turkey, the “crossroad between east and west”, by Bayraktar et al[6] 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[6,9] 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

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

| Mayo criteria | Typical cholangiographic abnormalities involving any part of the biliary tree | Compatible clinical and biochemical findings (for longer than 6 mo) | Exclusion of identifiable causes of secondary sclerosing cholangitis |
|---------------|--------------------------------------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------------------|
| Description   | Multifocal stricturing and beading, usually involving both the intrahepatic and extrahepatic biliary system | Cholestatic symptoms, history of inflammatory bowel disease | Bile duct neoplasm (unless diagnosis of PSC previously established) |

### 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 IHBBD         | 27               | 27             | NA               | 24.9                |
| IHBBD+EHBBD        | 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                |
the portal system, whose cell products may trigger an immune response in genetically susceptible individuals resulting in peribiliary fibrosis. Indeed, Grant et al.\[1,2\] 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\[6\].

In Japan, however, a much lower prevalence of IBD has been reported by Takikawa et al.\[8\], 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.\[9\] and Chapman et al.\[10\] 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\[11\]. The most striking result was reported by Prochazka et al.\[10\], 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, DRB30101 positivity, coding for DR52, was associated with reduced survival rate\[18\].

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\[14\]. 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 autoimmune 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\[5\], 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
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 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 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. 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, which later formed the back bone for the updated Mayo Clinic diagnostic criteria of 1984.

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 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 Moffet al, 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 IHBD strictures was good for both modalities, but once again only ERC was good for the presence and the severity of EHBD 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. 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. 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. 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\[^{[49]}\].

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\textsuperscript{55,60}, 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\textsuperscript{47}. 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\textsuperscript{59}. 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\%\textsuperscript{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\textsuperscript{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.

**ACKNOWLEDGMENTS**

A special thank you goes out to Tuna Gul and Nihal Kurtcimen for all their effort and support.

**REFERENCES**

1. Batres LA, Russo P, Mathews M, Piccoli DA, Chuang E, Ruchelli E. Primary sclerosing cholangitis in children: a histologic follow-up study. *Pediatr Dev Pathol* 2005; 8: 568-576.
2. Takikawa H, Manabe T. Primary sclerosing cholangitis in Japan—analysis of 192 cases. *J Gastroenterol* 1997; 32: 134-137.
3. Takikawa H, Takamori Y, Tanaka A, Kurihara H, Nakanuma Y. Analysis of 388 cases of primary sclerosing cholangitis in Japan; Presence of a subgroup without pancreatic involvement in older patients. *Hepatol Res* 2004; 29: 153-159.
4. Ponsioen CY, Vrouwenants SM, Prawirodirdjo W, Rajaram R, Rauws EA, Mulder CJ, Reitsma JB, Heisterkamp SH, Tytgat GN. Natural history of primary sclerosing cholangitis and prognostic value of cholangiography in a Dutch population. *Gut* 2002; 51: 562-566.
5. Broome U, Olsson R, Loof L, Bodemar G, Hultcrantz R, Lindberg G. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut* 1996; 38: 610-615.
6. Tischendorf JJ, Hecker H, Kruger M, Manns MP, Meier PN. Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: A single center study. *Am J Gastroenterol* 2007; 102: 107-114.
7. Wiesner RH, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, Fleming TR, Fisher LD, Beaver SJ, LaRusso NF. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. *Hepatology* 1989; 10: 430-436.
8. Bayraktar Y, Arslan S, Saglam F, Uzunalimoglu B, Kayhan B. What is the association of primary sclerosing cholangitis with sex and inflammatory bowel disease in Turkish patients? *Hepatogastroenterology* 1998; 45: 2064-2072.
9. Osmanoglu N, Tekin F, Ozutemiz O, Erosz G, Tekesin O. The prevalence of inflammatory bowel disease in patients with primary sclerosing cholangitis. *Turk J Gastroenterol* 2005; 16: 240-241.
10. Parlak E, Kosar Y, Ulker A, Dagli U, Alikm S, Sahin B. Primary sclerosing cholangitis in patients with inflammatory bowel disease in Turkey. *J Clin Gastroenterol* 2001; 33: 299-301.
11. Grant AJ, Lalor PF, Hubscher SG, Briskin M, Adams DH. MAdCAM-1 expressed in chronic inflammatory liver disease supports mucosal lymphocyte adhesion to hepatic endothelium (MAdCAM-1 in chronic inflammatory liver disease). *Hepatolology* 2001; 33: 1065-1072.
12. Grant AJ, Lalor PF, Salmi M, Jalkanen S, Adams DH. Homing of mucosal lymphocytes to the liver in the pathogenesis of hepatic complications of inflammatory bowel disease. *Lancet* 2002; 359: 150-157.
13. Schrumpl E, Fausa O, Forre O, Dobloog JH, Rtlan S, Thorsby E. HLA antigens and immunoregulatory T cells in ulcerative colitis associated with hepatobiliary disease. *Scand J Gastroenterol* 1982; 17: 187-191.
14. Chapman RW, Varghese Z, Gaul R, Patel G, Kokenin N, Sherlock S. Association of primary sclerosing cholangitis with HLA-B8. *Gut* 1983; 24: 38-41.
15. Farrant JM, Doherty DG, Donaldson PT, Vaughan RW, Hayllar KM, Welsh KI, Eddleston AL, Williams R. Amino acid substitutions at position 36 of the DR beta polypeptide confer susceptibility to and protection from primary sclerosing cholangitis. *Hepatology* 1992; 16: 390-395.
16. Prochazka EJ, Terasaki PI, Park MS, Goldstein LJ, Butsill RW. Association of primary sclerosing cholangitis with HLA-DRw52a. *N Engl J Med* 1990; 322: 1842-1844.
17. Grunnet N, Rasmussen HH, Tage-Jensen U, Norby Rasmussen S. Association of primary sclerosing cholangitis with HLA-DRw52a? *Tissue Antigens* 1991; 38: 133-136.
18. Wienen K, Spirkand A, Schrumpl E, Boberg KM. Primary sclerosing cholangitis is associated to an extended B8-DR3 haplotype including particular MICA and MICB alleles. *Hepatology* 2001; 34: 625-630.
19. Donaldson PT, Norris S. Evaluation of the role of MHC class II alleles, haplotypes and selected amino acid sequences in primary sclerosing cholangitis. *Autoimmunity* 2002; 35: 555-564.
20. Neri TM, Cavestro GM, Seghini P, Zanelli PF, Zanetti A, Savi M, Poddà M, Zuin M, Colombó M, Florenani A, Rosina
Aabakken L, Smith HJ, Aasen S, Boberg KM, de Muckadell OS, Lindgren S, Vleggaar FP, Boland GJ, van Worman HJ. Anti-neutrophil antibodies. Ursodiol for primary sclerosing cholangitis. J Hepatol 2000; 40: 375-379

Terjung B, Worman HJ. Anti-neutrophil antibodies in primary sclerosing cholangitis. Best Pract Res Clin Gastroenterol 2001; 15: 629-642

Terjung B. Anti-neutrophil antibodies in primary sclerosing cholangitis. Best Pract Res Clin Gastroenterol 2001; 15: 629-642

Delbet P. Retirécissement du choledoque cholecysto-duodénostomique. Bull Men Soc Chir Paris 1924; 50: 3

MacCarthy RL, LaRusso NF, Wiesner RH. Ursodiol for primary sclerosing cholangitis: findings on cholangiography and pancreatography. Radiology 1983; 149: 39-44

Kita H, Mackay IR, Van De Water J, Gershwin ME. The lymphoid liver: considerations on pathways to autoimmune injury. Gastroenterology 2001; 120: 1485-1501

Bergasa NV. The pruritus of cholestasis. Saeian K, Geenen JE. Primary sclerosing cholangitis. Retrecissement du choledoque cholecysto-duodénostomique. Bull Men Soc Chir Paris 1924; 50: 3

Borek KM, de Muckadell OS, Lindgren S, Vleggaar FP, Boland GJ, van Worman HJ. Anti-neutrophil antibodies. Ursodiol for primary sclerosing cholangitis. J Hepatol 2000; 40: 375-379

Jones EA, Bergasa NV. The pruritus of cholestasis. Hepatolgy 1999; 29: 1003-1006

Jorgensen RA, Lindor KD, Sartin JS, LaRusso NF, Wiesner RH. Serum lipid and fat-soluble vitamin levels in primary sclerosing cholangitis. J Clin Gastroenterol 1995; 20: 215-219

Hay JE, Lindor KD, Wiesner RH, Dickson ER, Krom RA, LaRusso NF. The metabolic bone disease of primary sclerosing cholangitis. Hepatology 1990; 14: 357-361

Lindor KD, Jorgensen RA, Teges RD, Khosla S, Dickson ER. Etoradone for osteoporosis in primary biliary cirrhosis: a randomized trial. J Hepatol 2000; 33: 878-882

Guanaibus N, Parés A, Ros I, Alvarez L, Pons F, Caballera L, Monegal A, Martínez de Osaba MJ, Roca M, Peris P, Rodés J. Alendronate is more effective than etoradone for increasing bone mass in osteopoenic patients with primary biliary cirrhosis. Am J Gastroenterol 2003; 98: 2268-2274

Pus T, Beuers U. Ursodeoxycholic acid treatment of vanishing bile duct syndromes. World J Gastroenterol 2006; 12: 3487-3495

Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. N Engl J Med 1997; 336: 691-695

Okolicsanyi L, Groppo M, Flourea A, Morselli-Labate AM, Rusticali AG, Battocchia A, Colombo M, Galatola G, Gasbarrini G, Podda M, Ricci G, Rosina F, Zuin M. Treatment of primary sclerosing cholangitis with low-dose ursodeoxycholic acid: results of a retrospective Italian multicentre survey. Dig Liver Dis 2003; 35: 325-331

Olsson R, Borek KM, de Muckadell OS, Lindgren S, Hultcrantz R, Folvik G, Bell H, Gangsøy-Kristiansen M, Måte J, Rydning A, Wikman O, Danielsson A, Sandberg-Gertzén H, Ung KA, Eriksson A, Löf L, Prytz H, Marschall HU, Broomé U. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. Gastroenterology 2005;129: 1464-1472

Chen W, Glaud C. Bile acids for primary sclerosing cholangitis. Cochrane Database Syst Rev 2003; CD003626

Sekhon JS, Chung RT, Epstein M, Kaplan MM. Steroid-responsive (autoimmune?) sclerosing cholangitis. Dig Dis Sci 2005; 50: 1839-1843

Lindor KD, Wiesner RH, Colwell LJ, Steiner B, Beaver S, Kamel IR, Eustace J, Lawler LP, Kantsevoy S, Mackay IR, Van De Water J, Gershwin ME. The metabolic bone disease of primary sclerosing cholangitis. A multicentre survey. Dig Liver Dis 2003; 35: 571-576

van Hoogstraten HJ, Vleggaar FP, Boland GJ, van Steenbergen W, Griffioen P, Hop WC, van Hattum J, van Berge Henegouwen GP, Schalm SW, van Buuren HR. Budesonide or prednisone in combination with ursodeoxycholic acid in primary sclerosing cholangitis: a randomized double-blind pilot study. Belgian-Dutch PSC Study Group. Am J Gastroenterol 2000; 95: 2015-2022

Allison MC, Burrowks AK, Noone P, Summerfield JA. Biliary lavage with corticosteroids in primary sclerosing cholangitis. A clinical, cholangiographic and bacteriological study. J Hepatol 1986; 3: 118-122

Tjandra K, Le T, Swart A, et al. Glucocorticoid receptors are downregulated in hepatic T lymphocytes in rats with experimental cholangitis. Gut 2003; 52: 1363-1370

Lee YM, Kaplan MM, Gheorge L. [Guidelines for the diagnosis and therapy of primary sclerosing cholangitis. Guidelines of the American College of Gastroenterology 2002] Rom J Gastroenterol 2002; 11: 346-350

Kaplan MM. Toward better treatment of primary sclerosing cholangitis. N Engl J Med 1997; 336: 719-721

Brandsaeter B, Isoniemi H, Broomé U, Olausson M, Bäckman L, Hansen B, Schumpf E, Oksanen A, Ericzon BG, Harewood GC, Rumalla A, Pochron NL, Harmsen S, Nagorney DM, Sebo TJ, Therneau TM, Gores GJ, de Groen PC, Baron TH, Levy MJ, Halling KC, Roberts LR. A comparison of routine cytology and fluorescence in situ hybridization for the detection of malignant bile duct strictures. Am J Gastroenterol 2004; 99: 1675-1681
Höckerstedt K, Mäkisalo H, Kirkegaard P, Friman S, Bjørk K. Liver transplantation for primary sclerosing cholangitis; predictors and consequences of hepatobiliary malignancy. J Hepatol 2004; 40: 815-822

58 Cullen SN, Chapman RW. Review article: current management of primary sclerosing cholangitis. Aliment Pharmacol Ther 2005; 21: 933-948

59 Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005; 5: 307-313

60 Ricci P, Therneau TM, Malinchoc M, Benson JT, Petz JL, Klintmalm GB, Crippin JS, Wiesner RH, Steers JL, Rakela J, Starzl TE, Dickson ER. A prognostic model for the outcome of liver transplantation in patients with cholestatic liver disease. Hepatology 1997; 25: 672-677

61 Neuberger J. Recurrence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. Liver Transpl Surg 1995; 1: 109-115

62 Neuberger J, Gunson B, Komolmit P, Davies MH, Christensen E. Pretransplant prediction of prognosis after liver transplantation in primary sclerosing cholangitis using a Cox regression model. Hepatology 1999; 29: 1375-1379

S- Editor Li DL  L- Editor Rippe RA  E- Editor Yin DH