Primary sclerosing cholangitis: Epidemiology and pathogenesis

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease of the liver and bile ducts that is frequently progressive and can lead to end-stage liver disease. The disease is characterized by progressive inflammation, fibrosis, and stricturing of the intrahepatic and extrahepatic bile ducts (picture 1). The diagnosis is best established by contrast cholangiography, which reveals a characteristic picture of diffuse, multifocal strictures and focal dilation of the bile ducts, leading to a beaded appearance [1-3].

The term "primary" is used to distinguish PSC from other conditions that may lead to a similar clinical and cholangiographic syndrome [1]. These include choledocholithiasis, bacterial cholangitis, prior biliary surgery, intra-arterial floxuridine, and acquired immunodeficiency syndrome associated with cholangiopathy [1].

The epidemiology and pathogenesis of PSC will be reviewed here. The clinical manifestations, diagnosis, and treatment of this disorder are discussed separately. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis" and "Primary sclerosing cholangitis in adults: Management".)

EPIDEMIOLOGY

The epidemiology of PSC in the general population has not been well established. A systematic review that focused on eight studies (from North America and Europe) estimated that the overall incidence rate was 0.77 per 100,000 person-years, although there were substantial differences among individual studies [4]. When focusing only on population-based studies, the incidence was estimated to be 1 per 100,000 person-years. The incidence was higher in males, and the median age at diagnosis was 41. All individual studies observed an overall increase in incidence during the time period examined.

As examples:

- In an illustrative, population-based study (from Olmsted County, Minnesota), the age-adjusted incidence in men was 1.25 per 100,000 person-years (95% CI, 0.70-2.06) compared with 0.54 per 100,000 person-years in women (95% CI, 0.22-1.12) [5]. The prevalence in the year 2000 was 20.9 cases per 100,000 men and 6.3 cases per 100,000 women. Inflammatory bowel disease (mostly ulcerative colitis) was present in 73 percent. Overall survival was significantly reduced compared with age and gender-matched population norms.

- In another population-based study (from Calgary, Alberta, Canada), the annual incidence rate adjusted for age was 1.01 per 100,000 men and 0.84 per 100,000 women [6].

- A third population-based study (from a region in southern Sweden) estimated that the annual incidence was 1.22 per 100,000 persons in adults, which represented an increase of more than threefold from 1992 to 2005 [7].

- In a population-based study (from the Netherlands, using data from 50 percent of the population, published after the systematic review), the incidence of PSC was 0.5 per 100,000 person-years, with a point prevalence in 2008 of six per 100,000 persons [8]. Among women, the incidence was 0.4 per 100,000 person-years, and among men it was 0.6 per 100,000 person-years. The authors estimated that based on these data, median survival from diagnosis until liver transplantation or death related to PSC in the entire cohort was 21.3 years. Colorectal carcinoma risk was 10-fold increased as compared to ulcerative colitis controls, and developed at a much younger age (39 years) compared to inflammatory bowel disease (IBD) controls (59 years). Colonoscopic surveillance was associated with improved outcomes.

- A study from Japan reported an increasing prevalence compared with 2007 (1.8 [1.75-1.85] per 100,000 population and an increasing male:female ratio [9].

- In a study from the United Kingdom, the age-standardized incidence of PSC was 0.68 (95% CI 0.45-0.99) per 100,000 person-years and the age-standardized prevalence was 5.58 (95% CI 4.82-7.35) per 100,000 during 1998 to 2014 [10].

The prevalence of PSC appears to be increased among first-degree relatives of patients with PSC. In one report, the prevalence of PSC among first-degree relatives was estimated to be 0.7 percent; among siblings, the prevalence was 1.5 percent [11].

PSC and inflammatory bowel disease — Ulcerative colitis (UC) has been reported in 25 to 90 percent of patients with PSC [1,2,5,12]. A survey of 23 hospitals in Spain, for example, examined the reported cases of PSC from 1984 to 1988; UC was present in 44 percent [12]. It is likely that this figure is an underestimate, since the colonic mucosa may be grossly normal in appearance despite the presence of histologic colitis. The true prevalence of UC in PSC is probably closer to 90 percent when rectal and sigmoid biopsies are routinely obtained [13]. A comprehensive review of 65 papers, which included over 11,000 patients, concluded that the prevalence of IBD in PSC was approximately 70 percent, ranging from 46.5 percent to 98.5 percent depending on the completeness of endoscopic and histologic evaluation; the majority of cases are reported to have UC [14]. However, there is growing evidence that PSC-IBD appears to have a distinct phenotype compared with UC and Crohn colitis with more extensive colitis or pancolitis, milder disease, rectal sparing, and backwash ileitis [15,16].

There are varying reports of the prevalence of PSC in UC. A survey of 1500 patients with UC in Sweden, for example, found that 72 (5 percent) had an elevated serum alkaline phosphatase; endoscopic retrograde cholangiopancreatography (ERCP) was performed in 65, of whom 55 (85 percent) had evidence of PSC [17]. PSC was more prevalent in patients with pancolitis than in those with distal colitis (5.5 versus 0.5 percent). It was also more common in men than women. Another report found that more than 7 percent of patients with UC may have PSC [18]. In a cohort of over 700 patients with IBD conducted magnetic resonance cholangiography (MRC) in over 300 patients and long-term clinical follow-up. MRC showed 24 patients (7.5 percent) had PSC-like lesions; only seven of these patients (2.2 percent) were known to have PSC. Extensive colitis, history of colectomy, and more severe IBD occurred more often in PSC [19]. A single-center study examined IBD patients with and without abnormal liver tests using magnetic resonance cholangiography (MRCP); approximately 10 percent of patients with abnormal liver tests had PSC on MRCP compared to 3 percent with normal liver tests; a historical cohort with abnormal liver tests had PSC in approximately 7 percent [20].

Given these data, estimates of the prevalence of PSC can be made based upon the prevalence of UC. The prevalence of UC in the United States has been estimated to range from 40 to 225 per 100,000 [1]. Thus, if 5 percent of patients with UC have PSC and if apparent UC is present in

50 percent of patients with PSC, the approximate prevalence of PSC is 1 to 6 per 100,000 in the United States [1].

The reported prevalence of PSC in Spain increased from 0.78 cases per million in 1984 to 2.24 cases per million in 1988 [12]. Approximately 16 percent of patients were asymptomatic and were detected by increased screening with serum alkaline phosphatase. This factor plus the use of ERCP to diagnose PSC could account for enhanced detection of the disease without a true rise in prevalence. On the other hand, these data may represent an underestimate of the true prevalence since some patients with PSC have normal serum alkaline phosphatase levels.

In a large Swiss cohort of 2744 patients with IBD (1188 UC; 1556 Crohn disease [CD]), 57 had PSC (48 UC-PSC, 9 CD-PSC). The prevalence of PSC was higher in UC compared with CD (4.04 versus 0.58 percent, P<0.001) [21]. Independent risk factors for PSC in patients with UC included male sex (odds ratio [OR] 2.77), pancolitis (OR 2.86), nonsmoker at diagnosis (OR 9.253), and a history of appendicectomy (OR 4.11).

As noted above, PSC also occurs in patients with CD, predominantly those with CD of the colon [6]. In one earlier report of 262 patients with CD, 38 (15 percent) had long-standing abnormal liver biochemical tests and underwent endoscopic cholangiography and liver biopsy [22]. Nine of these patients (3.4 percent) were diagnosed with PSC.

Gender — Approximately 70 percent of patients with PSC are men, with a mean age at diagnosis of 40 years, even though the sex distribution is equal between men and women in the overall UC population. However, in the small subset of patients without UC, the male:female ratio is lower (0.8:1) and patients are diagnosed at an older age [23]. Women with PSC are generally diagnosed at an older age [17].

PATHOGENESIS

The cause of PSC is unknown, and multiple mechanisms are likely to play a role. The following etiologies have been proposed [1]:

- The tight association between PSC and ulcerative colitis (UC, a known autoimmune disease) suggests an autoimmune process. However, other mechanisms are likely to be important since only a minority of patients with UC have PSC.
- An inflammatory reaction in the liver and bile ducts may be induced by chronic or recurrent entry of bacteria into the portal circulation. Liver damage may also result from

the accumulation of toxic bile acids that are abnormally produced by colonic bacteria or chronic viral infection.

- Ischemic damage to the bile ducts may occur.
- Novel genetic associations have been reported with increasing frequencies in the last several years, as noted below.
- Associations with mutations in cystic fibrosis transmembrane receptor have suggested that decreased biliary chloride transport leading to inspissated bile may be a cause in some patients. Similarly, mutations in genes regulating cholangiocyte bicarbonate transport (TGR5, FUT2) have been postulated to result in disruption of the "bicarbonate umbrella," protecting cholangiocytes from toxic effects of bile acids.
- The increasing recognition of a "gut-liver-axis" has been important in greater examination of the microbiome in liver disease in general, and PSC in particular. Identification of differences in microbiome profiles in PSC patients has suggested that this relationship may be more complex than just increased bacterial translocation into the portal circulation. It has been proposed that exposure to microbial antigens may affect immune response in PSC and may also be affected by the intestinal microbiome. In addition, there may be a contribution from antigens derived from microbes in the liver and biliary tract. Since the IBD associated with PSC is now being recognized as a distinct type from Crohn disease, it is more likely that a unique microbiome in PSC may be a factor in the disease [24].

Although the relationship between PSC and UC suggests a possible common pathogenesis, the two disorders may occur at different times. PSC may develop years after colectomy for UC, and UC may first present after liver transplantation has been performed for PSC [2].

It is likely that immunologically-mediated bile duct injury is a major mechanism leading to PSC. However, the putative antigen which elicits the aberrant immune response and the mechanism by which autoantibodies or abnormally activated T cells lead to clinical expression of the disease are unknown. The most plausible explanations are that PSC is a multifactorial disorder, possibly developing in individuals with a genetic predisposition when exposed to the appropriate environmental stimulus, or that PSC represents multiple diseases with a similar clinical presentation [15].

Immune activation — There are multiple lines of evidence supporting an immunopathogenic cause for PSC. A number of abnormalities in humoral immunity have been described in these patients:

- Up to 50 percent have an elevated IgM level, and some may also have an increased IgG fraction [25].

- Autoantibodies are frequently present in patients with PSC, with titers in the range associated with autoimmune hepatitis. The most common are antismooth muscle antibodies and antinuclear antibodies, which are found in approximately 75 percent of patients [26].

- Antibodies directed against cytoplasmic and nuclear antigens of neutrophils with a characteristic perinuclear staining pattern (P-ANCA) are found in up to 80 percent of adults with PSC [25]. The antibodies appear to be directed against a myeloid 50 kilodalton nuclear envelope protein, not myeloperoxidase as in typical P-ANCA antibodies [27]. In one report, P-ANCA had a 100 percent specificity for PSC compared with controls with other liver diseases; P-ANCA is also found in 25 to 30 percent of unaffected first-degree family members of patients with PSC [25]. P-ANCA has also been identified in children with PSC but not in those with UC alone [28]. These antibodies are not related to the presence or absence of UC.

Abnormalities of the cellular immune response have also been described in patients with PSC:

- There are conflicting data reporting either an increase or decrease in the total number of circulating T cells; however, the number of CD4-positive T cells in the liver is increased [29].

- Bile duct epithelial cells in PSC may be targets for immune-mediated attack by T cells [26].

- The bile duct cells in PSC express antigens which cross-react with colonic epithelial cells [30].

- Bile duct cells aberrantly express HLA class II antigens, and intercellular adhesion molecule (ICAM)-1 is expressed by ductular epithelial cells [31].

Genetic factors — First-degree relatives of patients with PSC have an increased risk of PSC and ulcerative colitis, supporting a genetic predisposition to these conditions [32]. The basis for the genetic predisposition is not well understood. Patients have an increased prevalence of HLA-B8, -DR3, and -DRw52a [25]. One study, for example, found that HLA DRw52a was present in 100 percent of patients with PSC [33]. Subsequent reports, however, have only found a 50 percent prevalence of this haplotype [34]. Both HLA-DRw52a and -DR4, which occurs less frequently, appear to increase the risk for severe or progressive disease [25]. Overall, HLA association appears to be the strongest of the genetic factors in PSC [24].

HLA-B8 is present in 60 to 80 percent of patients with PSC, compared with only 25 percent of control subjects [25]. Furthermore, the HLA-B8/DR3 haplotype is infrequent in patients with UC who do not have PSC. This haplotype is also associated with a number of other autoimmune diseases such as celiac disease, myasthenia gravis, and diabetes mellitus.

A specific polymorphism of MICA (an MHC class I-related molecule located between tumor necrosis factor-alpha and HLA-B) may also be strongly associated with PSC. In one study, the homozygous MICA008 allele was present significantly more often in 112 patients with PSC compared with 118 controls (58 versus 22 percent) [35]. Other reports have identified additional loci that confer susceptibility to ulcerative colitis and PSC [36-38].

A genome-wide association study in patients with PSC and UC demonstrated the presence of risk loci at GPR35 and TCF4 [39]. A large multicenter study of over 80,000 individuals with several autoimmune diseases concluded that biological pleiotropy rather than heterogeneity of disease was the explanation for different diseases sharing a genetic profile. In particular, the authors found that "strong comorbidity" between PSC and IBD was due to a genetically distinct disease from other IBD phenotypes [40].

Bacterial infection — The strong association between PSC and UC has led to speculation that increased permeability of bacteria into the portal circulation across an inflamed colonic wall may lead to chronic or recurrent cholangitis, or that bacterial products may cause liver and biliary tract inflammation, leading to the characteristic pathologic and cholangiographic appearance [1,41]. The evidence in support of these hypotheses has been contradictory. Early studies, for example, found that patients with PSC had an increased risk of portal venous bacteremia; subsequent reviews, however, did not confirm portal vein phlebitis in these patients [42,43]. On the other hand, an animal model of small intestinal bacterial overgrowth noted changes in the appearance of the bile ducts similar to those seen in patients with PSC [44]. Changes in the microbiome of PSC patients have also been recently described, characterized by reduced diversity of bacterial species and altered taxonomy [45,46].

Ischemic ductal injury — Ischemic injury to the bile ducts results in a clinical, biochemical, and cholangiographic picture similar to PSC. Intra-arterial infusion of floxuridine also results in a comparable appearance [26]. Thus, it is possible that ischemic injury to peribiliary arterioles and capillaries may be involved in the pathogenesis of PSC. However, there are no data to support this hypothesis, or to demonstrate that hepatic or biliary blood flow is deficient in patients with this disorder.

Cystic fibrosis transmembrane conductance regulator mutations — Because of the radiologic and histologic similarities between PSC and cystic fibrosis, mutations in the cystic

fibrosis transmembrane conductance regulator (CFTR) have been sought in patients with PSC. One preliminary study suggested that a subset of patients with PSC had evidence of CFTR-mediated ion transport dysfunction; affected patients had a chloride secretory response intermediate between patients with cystic fibrosis and controls [47].

A subsequent report from the same authors compared the genotypic and phenotypic expression of CFTR mutation in 18 patients with PSC with 35 disease controls (inflammatory bowel disease without PSC or primary biliary cirrhosis) [48]. CFTR mutations were present significantly more often in patients with PSC (33 versus 6 percent). All mutations were on one allele, thus representing a carrier state. A reduced chloride response on nasal potential testing was also more common in patients with PSC (50 versus 9 percent). Combining genotype and phenotype data, significantly more patients with PSC had abnormalities in CFTR (67 versus 17 percent).

Environmental exposures — Possible environmental exposures have been associated with PSC. A study of over 1000 patients from North America identified dietary patterns, relationship to smoking, history of urinary tract infections, and method of food preparation in patients with PSC [49]. Smoking was associated with PSC only when IBD was present (OR 0.5; 95% CI 0.4-0.7) but not among those PSC patients without IBD (OR 0.9; 95% CI 0.7-1.2). Women with PSC (independent of the presence of IBD) were less likely to have received hormone replacement therapy (HRT; OR 0.5; 95% CI 0.4-0.7) but more likely to have recurrent urinary tract infections (OR 1.6; 95% CI 1.2-2.3). Interestingly, PSC patients regardless of sex or IBD status were less likely to eat fish (OR 0.4; 95% CI 0.3-0.6) and grilled or barbecued meat (OR 0.8; 95% CI 0.7-0.9). By contrast, PSC patients with and without IBD were more likely to consume steak/burgers that were more well done (OR 1.3; 95% CI 1.2-1.5).

SUMMARY

- Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease of the liver and bile ducts that is frequently progressive and can lead to end-stage liver disease. The disease is characterized by progressive inflammation, fibrosis, and stricturing of the intrahepatic and extrahepatic bile ducts (picture 1). (See 'Introduction' above.)

- PSC has an incidence of approximately 1 case per 100,000 person years. Approximately 70 percent of patients with PSC are men, with a mean age at diagnosis of 40 years. (See 'Epidemiology' above.)

- First-degree relatives of patients with PSC have an increased risk of PSC and ulcerative colitis (UC), supporting a genetic predisposition to these conditions.

- Up to 90 percent of patients with PSC also have UC, but less than 10 percent of patients with UC have PSC. Although the relationship between PSC and UC suggests a possible common pathogenesis, the two disorders may occur at different times (see 'PSC and inflammatory bowel disease' above). It is increasingly thought that the IBD of PSC may be distinct from UC and Crohn disease with different endoscopic and histological features.

- The cause of PSC is unknown, and multiple mechanisms are likely to play a role. The following etiologies have been proposed (see 'Pathogenesis' above):

  - The tight association between PSC and UC (a known autoimmune disease) suggests an autoimmune process. However, other mechanisms are likely to be important since only a minority of patients with UC have PSC.

  - An inflammatory reaction in the liver and bile ducts may be induced by chronic or recurrent entry of bacteria into the portal circulation. Liver damage may also result from the accumulation of toxic bile acids that are abnormally produced by colonic bacteria or chronic viral infection.

  - Ischemic damage to the bile ducts may occur.

- It is likely that immunologically-mediated bile duct injury is a major mechanism leading to PSC. However, the putative antigen which elicits the aberrant immune response and the mechanism by which autoantibodies or abnormally activated T cells lead to clinical expression of the disease are unknown. The most plausible explanations are that PSC is a multifactorial disorder, possibly developing in individuals with a genetic predisposition when exposed to the appropriate environmental stimulus, or that PSC represents multiple diseases with a similar clinical presentation. (See 'Pathogenesis' above.)

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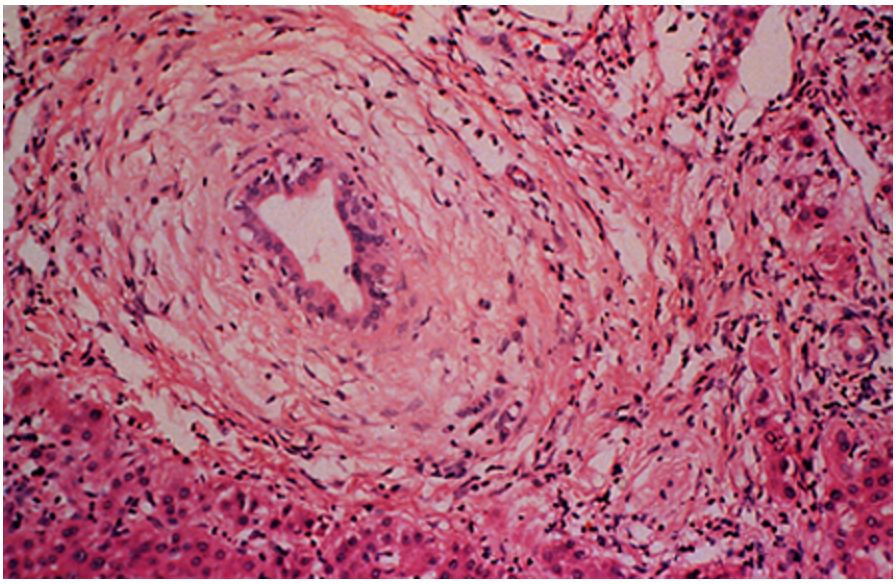
GRAPHICS

Primary sclerosing cholangitis



Medium power view of a liver biopsy from a patient with primary sclerosing cholangitis shows a portal bile duct with periductal sclerosis associated with degeneration of the bile duct epithelium.

Courtesy of Robert Odze, MD.

Graphic 70795 Version 1.0

Contributor Disclosures

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