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Review

Diagnosis and classification of primary sclerosing cholangitis

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ABSTRACT

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease of the liver and that is characterized by progressive inflammation, fibrosis, and stricturing of the intrahepatic and extrahepatic bile ducts. It is progressive in most patients and leads to cirrhosis. It is a rare disease, mostly affecting people of northern European descent, males greater than females. 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. Inflammatory bowel disease (IBD) is present in ~75% of the patients with PSC, mostly ulcerative colitis (~85% of the cases). In addition to biliary cirrhosis, complications of PSC include dominant strictures of the bile ducts, cholangitis, cholangiocarcinoma, colon dysplasia and cancer in patients with IBD, gallbladder polyps and cancer, and hepatic osteodystrophy. The etiology of PSC is not clear, but studies are ongoing. The median survival without liver transplantation is 12 to 15 years after diagnosis. Currently there are no effective treatments except liver transplantation. Immunosuppressive medications have not been shown to be effective but antibiotics and anti-fibrotic agents seem promising.

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1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestasis disease of the liver and bile ducts of unknown cause characterized by progressive inflammation, fibrosis, and stricturing of the intrahepatic and extrahepatic bile ducts [1]. The disease progresses slowly in most patients over a 10 to 15 year period and usually leads to cirrhosis complicated by portal hypertension and premature death from liver failure [1]. The first description of sclerosing cholangitis is credited to Delbet in 1924 [2]. Although considered for many years to be an extremely rare disorder, the advent of endoscopic retrograde cholangiography (ERC) in the 1970s and magnetic resonance cholangiography (MRC) in the 1990s has allowed an improved understanding of the true prevalence of this disorder and facilitated careful study of its natural history. Nevertheless, many aspects of PSC remain poorly understood; most notably lacking is a detailed knowledge of its etiology and proven effective medical therapy.

2. Epidemiology

PSC is more common in men than woman, and the majority of patients are diagnosed in the third to fourth decades [1]. However, cases are seen in all age groups, and studies in Japan have suggested a bimodal age distribution with a second peak in the seventh decade [3]. In addition to liver disease, PSC is closely associated with inflammatory bowel disease (IBD). Approximately 75% of patients with PSC have IBD, and of these, nearly 80–90% are diagnosed with ulcerative colitis (UC) [4–6]. This association with IBD has been noted to be greater in the Northern European and American populations than Southern European (50%) and Asian (35%) populations with IBD [3,7–9].

The true incidence of PSC is unknown, though studies from Oslo, Norway, Sweden, Wales, and Olmstead County, Minnesota estimate it to be between 0.9 and 1.3 cases per 100,000 person-years [4,10–14]. However, a recent study in the UK noted an incidence of 0.41 cases per 100,000 person-years [15]. Our own analysis in a population of over three million members enrolled in a large health care system in Northern California found a similar annual incidence of 0.41 cases per 100,000 person-years [16]. This discrepancy may be explained by the ethnic diversity of the populations in these latter analyses. We also evaluated the population-stratified demographic, clinical, and HLA data from 6767 liver transplant (LT) registrants of the United Network for Organ Sharing who had a diagnosis of PSC (4.7% of the registrants) and found that European Americans and African Americans were more frequently listed with a diagnosis of PSC relative to Hispanics and other ethnic groups. PSC accounted for 5.4% and 6.4% of all LT listings in European Americans and African Americans, respectively, compared to less than 2% in any other group [17]. Overall, there appears to be a higher prevalence of PSC in the Northern Europeans and Caucasians. Regardless, the true incidence of this disease may be underestimated, as it is a relatively rare condition with an insidious course that requires specialized expertise and invasive procedures for diagnosis.

3. Clinical manifestations of PSC

3.1. Symptoms and signs

The clinical presentation of PSC can vary greatly. Asymptomatic patients represent about 15% to 40% of the patients at time of diagnosis in early studies [18,19]. More recently, more patients are identified at an earlier stage of the disease with fewer symptoms. Due to its close association to IBD, many cases come to medical attention when patients with IBD are screened for liver disease. The most common symptoms in patients with PSC are fatigue, jaundice, pruritus and abdominal pain, whereas ascites, bleeding from esophageal varices and acute cholangitis are much less frequent (Table 1) [19,20].

Table 1
Signs and symptoms of PSC at diagnosis.
Adopted from references [19,20].

Symptoms	Prevalence
Asymptomatic	15–44%
Fatigue	43–75%
Pruritus	25–59%
Jaundice	30–69%
Hepatomegaly	34–62%
Abdominal pain	16–37%
Splenomegaly	14–30%
Hyperpigmentation	25%
Weight loss	10–34%
Variceal bleeding	2–14%
Ascites	2–10%

Physical examination is abnormal in approximately half of symptomatic patients at the time of diagnosis; jaundice, hepatomegaly, and splenomegaly are the most frequent abnormal findings [19–21].

3.2. Biochemical features

Elevations in serum alkaline phosphatase values are the biochemical hallmark of PSC. Increases between 3 and 10 times the upper limit of normal occur in 95% of cases. Serum alanine and aspartate aminotransferase levels are usually 2–3 fold higher than normal levels [20,21]. The serum total bilirubin level is normal in 60% of individuals at diagnosis [22]. IgG serum levels are modestly elevated in approximately 60% of patients (1.5 times the upper limit of normal). The liver tests can be normal and can fluctuate during the course of the disease [23,24].

3.3. Serological features

Several autoantibodies have been detected in the serum of PSC patients, indicating an altered state of immune responsiveness or immune regulation (Table 2) [21]. However, none have been found to have sufficient specificity or sensitivity to be used for screening or diagnosis. The most prevalent autoantibody, perinuclear antineutrophil cytoplasmic autoantibodies, is seen in 65–95% of patients with PSC, 50–80% of those with UC, and 10–20% of patients with CD [20,21,25–27]. IgG4 levels are often elevated in patients with autoimmune pancreatitis, as well as IgG4-related sclerosing cholangitis, which should be distinguished from typical PSC [28,29]. Notably, an elevated level of IgG4 in PSC patients is associated with a worse clinical outcome [29].

3.4. Radiological features

Cholangiography remains the gold standard for the diagnosis of PSC. Findings of segmental strictures with proximal dilation and sacculation of the bile ducts create the “beaded” appearance that is classic for PSC (Fig. 1). Intrahepatic duct involvement is nearly universal with most

Table 2
Prevalence of autoantibodies in patients with PSC.
Adopted from reference [19].

Autoantibody	Prevalence
Anti-neutrophil cytoplasmic antibody	50–80%
Anti-nuclear antibody	7–77%
Anti-smooth muscle antibody	13–20%
Anti-endothelial cell antibody	35%
Anti-cardiolipin antibody	4–66%
Thyroperoxidase	7–16%
Thyroglobulin	4%
Rheumatoid factor	15%