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Small duct primary sclerosing cholangitis: A discrete variant or a bridge to large duct disease, a practical review

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Abstract

The natural history, associations with IBD, and long-term outcomes of large duct primary sclerosing cholangitis (ldPSC) have been well documented. Small duct primary sclerosing cholangitis (sdPSC) is a much less common and relatively more benign variant. The natural history of sdPSC has been difficult to characterize given the limited number of studies in the literature especially with regards to the subset of patients who progress to large duct involvement. It has been unclear whether sdPSC represented a subset of ldPSC, an earlier staging of ldPSC, or a completely separate and distinct entity of its own. Strong associations between sdPSC and inflammatory bowel disease (IBD) have been established with suspicion that concurrent sdPSC-IBD may be a key prognostic factor in determining which patients are at risk of progression to ldPSC. Little is known regarding the discrete circumstances that predisposes some patients with sdPSC to progress to ldPSC. It has been suspected that progression to large biliary duct involvement subjects this subset of patients to potentially developing life-threatening complications. Here the authors conducted a thorough review of the published sdPSC literature using Pubmed searches and cross-referencing to compile all

accessible studies regarding cohorts of sdPSC patients in order better characterize the subset of sdPSC patients who progress to ldPSC and the associated outcomes.

Key Words: Small duct primary sclerosing cholangitis; Inflammatory bowel disease; Progression; Primary sclerosing cholangitis; Outcomes

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Core Tip: Strong associations between small duct primary sclerosing cholangitis (sdPSC) and inflammatory bowel disease (IBD) have been established with suspicion that concurrent sdPSC-IBD may be a key prognostic factor in determining which patients are at risk of progression to ldPSC.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic liver disease with the potential of progression to cirrhosis that is characterized by multi-focal cholestatic inflammation and fibrosis[1-3]. PSC has an incidence of 0.9 to 1.3 cases per 100,000 in the United States[2, 4]. PSC has a close association with inflammatory bowel disease (IBD) and has a risk of developing various hepatobiliary malignancies including cholangiocarcinoma (CCA)[1-3]. Classic or large-duct primary sclerosing cholangitis (ldPSC) has very distinct clinical, cholangiographic, and histologic features with cholangiography typically establishing a diagnosis[1, 3-5]. In 1985, Ludwig *et al* brought into question the possibility of small intra-hepatic biliary duct involvement which led to pathologic studies in 1991 confirming the diagnosis of small duct primary sclerosing cholangitis (sdPSC), also referred to as pericholangitis[6].

The natural history, associations with IBD, and long-term outcomes of ldPSC have been well documented. Small duct primary sclerosing cholangitis is a much less

common and relatively more benign variant[7-9]. In recent years, it has been discovered that this variant can rarely progress to having large biliary duct involvement[7-14]. Several studies have attempted to characterize this unique subset of patients, with the rate of progression to ldPSC ranging from 7.1-22.9%[7-9, 11-14]. Little is known regarding the etiology or discrete circumstances that predisposes some patients with sdPSC to progress to ldPSC. It is known, however, that progression to large biliary duct involvement subjects this subset of patients to potentially developing life-threatening complications[8,9].

The natural history of sdPSC has been difficult to characterize given the limited number of studies in the literature. Describing the subset of patients who have progressed to ldPSC is even more challenging. The authors conducted a thorough evaluation of the published literature to compile all accessible studies regarding cohorts of sdPSC patients using PubMed searches and cross-referencing. Table 1 summarizes the individual studies, the baseline characteristics, and outcomes of each cohort of sdPSC patients.

GENETIC PATHOGENESIS

The etiology of PSC is not well understood however it is believed to be predominantly autoimmune due to its association with elevated levels of antineutrophilic cytoplasmic, antinuclear, and anticardiolipin antibodies in addition to the HLA DR3 and HLA B8 genes[2,4,15]. A strong association between PSC and IBD has also been well established with studies showing a significantly increased risk of developing PSC and UC in first-degree relatives of patients who have PSC with or without UC[3,4,16,17].

The etiology of sdPSC is even less understood, though it carries a more favorable prognosis than its large-duct counterpart[8]. It has been unclear whether sdPSC represented a subset of ldPSC, an earlier staging of ldPSC, or a completely separate and distinct entity of its own[8,10]. A study evaluating the components of sdPSC within the subset of patients with and without concomitant IBD suggested the strongest association existed between HLD-DRB1*13:01 and sdPSC[15]. In contrast to the strong

association of HLA-B*08 with ldPSC, HLA-B*08 was found to be more prevalent in sdPSC when compared to healthy controls, but not to the extent found in ldPSC[15]. Additionally, patients that have the DRB1*13:01 haplotype are at an increased risk of developing IBD[15]. A noteworthy hypothesis drawn from this study is the notion that patients with sdPSC and concomitant IBD could represent precursors to classic PSC while those sdPSC patients without IBD may actually represent a different biliary disease process, such as primary biliary cholangitis, or a secondary cause of sclerosing cholangitis, such as those related to the ABCB4 gene[15].

ENVIRONMENTAL PATHOGENESIS

It has been speculated that in addition to genetic factors, environmental factors contribute to the pathogenesis of PSC in part due to persistent insult to the cholangiocytes[2-4]. More recent studies suggest the involvement of the gastrointestinal microbiome and its metabolites as an important and modifiable component of the pathogenesis of PSC[3,4]. The relationship of PSC with the enteric microbiome, known as the "leaky gut" hypothesis, describes the passive translocation of bacterial products from an inflamed gut to the portal venous system triggering an inflammatory cascade that leads to the characteristic "onion skinning" intrahepatic biliary duct fibrosis that is seen in all variants of PSC[2,4,18,19]. The development of the laminar concentric fibrosis interrupts the arterial and biliary interface causing ischemia to the cells lining the biliary system[4]. Injured cholangiocytes facilitate the pathogenic strictures and fibrosis through the secretion of inflammatory cytokines and chemokines[2,4]. Other theories exist focused on defects in the protective mechanisms against toxicity from bile acids, gut-derived T cell recruitment to the liver, and even disruptions in bile homeostasis as potential key factors in PSC pathogenesis[2,4].

Based on initial investigation of the pathophysiologic association of hepatobiliary disorders and colonic inflammation, the role of bacterial chemotactic peptides in the development of sdPSC has been evaluated[20,21]. Colitis was induced in the specimens using intrarectal infusions of acetic acid and saline, followed by intrarectal infusion of

N-formyl L-methionine L-leucine L-tyrosine (fMLT), a bacterial chemotactic peptide produced by *Escherichia coli*. The experimentally induced colitis and rectal fMLT induction resulted in an eight-fold increase in biliary excretion of fMLT. Liver specimens showed evidence of pericholangitis affecting the small biliary ducts suggesting bacterial chemotactic peptides could play a pathogenic role in the development of sdPSC[20].

EPIDEMIOLOGY AND NATURAL HISTORY

Approximately 75% of patients with PSC have both small and large duct involvement, while 15% have only small duct and 10% with only large duct involvement[3,8]. PSC often insidiously progresses to advanced liver disease with an estimated 10-year survival of 65%[2,3]. LdPSC affects men twice as frequently as women and typically presents within the fourth decade of life with the mean age of diagnosis being 41 years[3]. However, a study in Norway suggested that PSC may occur as commonly in females as in males but with a more clinically subtle course[5]. The incidence per year is estimated to be 0.9-1.3 per 100,000 and the prevalence is approximately 0.5-16.2 per 100,000 patients in the United States[4, 5]. Studies in Asia and Spain have reported a lower prevalence of up to 10-fold when compared to the US and EU[22-24]. Some studies suggest an increase in the incidence of PSC in recent decades though this trend has also been associated with other autoimmune and idiopathic inflammatory disorders and could be related to increased use of magnetic resonance cholangiography[3]. Approximately 70% of patients with PSC have concurrent IBD with UC accounting for 80% of PSC-IBD patients, while CD and intermediate colitis affects 10% each[2,3,5]. Hepatobiliary malignancies affect up to 10.9% of PSC patients with a five-fold increased risk of colorectal cancer when compared to IBD patients without PSC[3,25].

SdPSC is more benign when compared to ldPSC with most mortality limited to the small subset that progress to large-duct involvement or who develop liver failure[8]. Studies have shown a median survival of 29.5 years in sdPSC *vs* only 17 years in ldPSC without liver transplantation[8,10,23,26]. SdPSC seems to have a similar predilection for

male gender however percentages vary across individual studies. Evaluating the data in Table 1 yielded a 60.9% male predominance of sdPSC across all studies of adult and pediatric populations. The annual incidence of sdPSC is estimated to be 0.15 per 100,000 patients and the median age of diagnosis is 35 and 9.5 years in adults and children respectively[8,10,27]. IBD affects approximately 80% of sdPSC patients with the large majority being diagnosed at initial presentation[8,27]. Of the patients with sdPSC and concomitant IBD, approximately 78% have UC, 21% CD, and 1% an intermediate colitis[8,15]. A study describing differences between sdPSC patients with and without IBD reported a mortality of 9% and 7% respectively and transplantation in 6% and 14% respectively[15]. Hepatobiliary malignancies are extremely rare in sdPSC with very few reported cases. One long-term retrospective, multi-institutional study reported approximately one-fourth of patients with sdPSC may show evidence of progression to ldPSC[8].

CLINICAL PRESENTATION

PSC has a highly variable initial presentation with approximately 50% of patients being asymptomatic at presentation and up to 40% of cases being incidentally diagnosed after routine blood work revealing cholestatic elevation of liver enzymes[3, 4]. Those who go without early incidental detection can present with the sequelae of advanced liver disease[4]. Patients who develop symptoms at the time of diagnosis typically present with weight loss, jaundice, pruritis, abdominal pain, diarrhea, fever, and fatigue[1]. Patients with sdPSC present with generally similar symptoms though weight loss and jaundice at diagnosis is more significantly seen in ldPSC than in sdPSC[8,10].

DIAGNOSIS

Several factors contribute to the clinical diagnosis of PSC. The first includes a cholestatic elevation in liver biochemical testing, specifically with a significantly higher elevation in serum alkaline phosphatase compared to milder elevations in the serum aminotransferases[1]. Concomitant autoimmune hepatitis may cause more substantial

elevations in the serum aminotransferases[1,28]. Second, cholangiographic findings of multifocal intrahepatic, extrahepatic, or a combination of both are typically seen[1]. Lastly, a liver biopsy may be warranted in the appropriate context to exclude other diseases, establish stage of disease, or to diagnose sdPSC[1]. Not all patients will present with a significant elevation in serum alkaline phosphatase so a strong clinical suspicion should warrant further investigation with magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), or percutaneous transhepatic cholangiography (PTC)[1,5]. Cholangiography is negative in sdPSC due to the involvement of biliary ducts that are less than 100 micro millimeters making liver biopsy necessary to confirm the diagnosis of sdPSC[10]. The subset of sdPSC patients who progress to large-duct involvement will develop the characteristic cholangiographic findings in classic PSC[10, 14].

HISTOPATHOLOGIC FEATURES OF SDPSC

Most studies have reported that sdPSC has similar histopathologic features as PSC, albeit with normal imaging findings[10]. As mentioned above, several studies have reported that sdPSC may just be an earlier form of well-developed PSC[8]. Therefore, the histopathologic features may be subtle and easily missed[10]. At our institution, we recently encountered a 35-year-old female that reported intermittent pruritis with previous episodes of jaundice and persistently elevated alkaline phosphatase. An MRCP showed no abnormalities within the biliary tract, sdPSC was suspected, and a liver biopsy was performed. The liver biopsy was evaluated by a board-certified hepatopathologist and showed several portal tracts containing atrophic bile ducts (i.e., evidence of biliary senescence changes). These were subtle by hematoxylin and eosin (H&E) evaluation (Figure 1A); however, additional stains were able to highlight peribiliary sclerosis with focal areas of fibrous bile duct obliteration (Figure 1B). Cytokeratin 7 (Figure 1C) and copper stains (Figure 1D) were helpful to confirm the presence of chronic biliary injury and suboptimal bile flow[29].

ASSOCIATED DISORDERS

Similar to ldPSC, sdPSC has a strong association with IBD. The large majority of sdPSC patients present with concurrent UC[8,15]. A key difference from ldPSC is a higher prevalence of Crohn's disease with a study showing a prevalence of 21% in sdPSC *vs* 5-10% in ldPSC populations[8]. Studies have not shown any significant differences in outcomes when comparing sdPSC-UC and sdPSC-CD populations[8,10,15,30]. Hepatobiliary cancers in sdPSC are quite rare with only 1 documented case of hepatocellular carcinoma in all of the evaluated studies[11]. In contrast, cholangiocarcinoma (CCA) is seen in approximately 15% of ldPSC patients while cases seen in sdPSC are exceedingly rare[31]. Additionally, ldPSC patients have five times increased risk of developing colorectal cancer when presenting with concurrent IBD when compared to ldPSC patients without IBD[4,25]. This association with malignancies is the thought behind routine colorectal screening in those with PSC-IBD and may warrant evaluation for the need of routine surveillance in the sdPSC-IBD population. An overlap syndrome exists between PSC and autoimmune hepatitis (AIH) which is more commonly seen in the pediatric population though adult PSC patients can develop superimposed AIH years after the initial PSC diagnosis[27,28]. A similar trend is seen in sdPSC as the majority of sdPSC-AIH patients were seen in the pediatric populations[27,28,32]. Other disorders associated with PSC include type I diabetes mellitus, membranoproliferative glomerulonephritis, hypothyroidism, and autoimmune hemolytic anemia though the prevalence of these conditions in sdPSC have not been as well established[8,10].

TREATMENT

No widely accepted method of therapy has been established for patients with ldPSC or sdPSC in part, due to ambiguity regarding the pathogenesis of the disease. Ursodeoxycholic acid (UDCA) at lower doses improved serum liver biochemical tests however there was little symptomatic improvement and no significant improvement in overall outcomes[33, 34]. A study using moderate doses of UDCA failed to produce a

statistically significant outcome[35]. Most recently a multi-center study examining high doses of UDCA was aborted due to increased morbidity and mortality despite improvement in serum biochemical profiles[1]. The major gastroenterology societies within the United States recommend against the use of UDCA in patients with PSC[1]. Additionally, the role of immunosuppressive agents and corticosteroids in the treatment of PSC has been explored[1,37,38]. However, no studies demonstrated significant improvement in morbidity and mortality with these agents.

Ultimately, the only definitive therapy for PSC is liver transplantation which has a five-year survival rate of nearly 85%[1,39]. A possibility of recurrence has been seen in 20-25% of cases, 5-10 years post-transplant[39]. Patients with sdPSC have a significantly longer median survival without liver transplantation compared to those with ldPSC[8]. However, studies have shown that among the cohort of patients who progress from small to large-duct involvement, up to half will develop outcomes of death or liver transplantation[8].

CONCLUSION

SdPSC is a rare disorder with the potential of progressing to ldPSC. The definitive etiology and pathogenesis of sdPSC and the circumstances that lead to progression to large-duct involvement are not well understood. Strong associations between sdPSC and IBD have been established with suspicion that concurrent sdPSC-IBD may be a key prognostic factor in determining which patients are at risk of progression to ldPSC. Additionally, this association may warrant future studies regarding the need for routine colorectal cancer screening in sdPSC patients with concomitant IBD. Evaluation using the current available literature is limited due to small cohorts and limited data regarding this specific subset of patients. It is therefore crucial for clinicians to continue reporting readily accessible data in hopes that future studies can further characterize which patients are at most risk of progression as large-duct involvement carries a more grim prognosis and requires more diligent surveillance.

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