Title

Primary Sclerosing Cholangitis Multiple Phenotypes, Multiple Approaches

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PSC: multiple phenotypes, multiple approaches

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Synopsis

Primary sclerosing cholangitis (PSC) is a heterogeneous, idiopathic, inflammatory disorder of the bile ducts frequently associated with inflammatory bowel diseases (IBD) of the colon resulting in strictures of the intrahepatic and/or extrahepatic bile ducts. In addition to IBD status, several other features of PSC patients allow the classification of several clinical subphenotypes. These include non-IBD PSC as well as small duct PSC. In addition, approximately 10% of PSC patients will have an elevated serum immunoglobulin (Ig) G4 and must be distinguished from the newly defined group of IgG4-related diseases which can involve the bile ducts, so called IgG4-related sclerosing cholangitis. Further investigations of pediatric, non-Caucasian, and female PSC patients have revealed important distinguishing features among these groups. Whether these phenotypes reflect differences in underlying pathology leading to similar clinical features or are simply variations of the same pathway remains unclear. The natural history of PSC is variable in terms of liver disease progression with numerous possible clinical outcomes. In addition to progression to portal hypertension, cirrhosis, and its complications, PSC patients may also suffer from bacterial cholangitis, cholangiocarcinoma, and colorectal adenocarcinoma. Treatment approaches focusing primarily on bile acid therapy and immunosuppression have not yet proven beneficial. Increasing interest in PSC and international collaboration has led to improved understanding of the heterogeneity of the disease and its underlying genetic structure, and opened new opportunities to pursue effective therapeutics.

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Keywords

Primary sclerosing cholangitis; diagnosis; treatment; IgG4-related sclerosing cholangitis; autoimmune hepatitis

Introduction

Sclerosing cholangitis refers to a broad array of diseases that cause fibrosis of the bile ducts, usually of medium and large-size ducts, leading to a segmental pattern of narrowing with proximal dilation. Whereas secondary sclerosing cholangitis may be a complication of a number of different injuries, inflammatory reactions, or malignancies, in primary sclerosing cholangitis (PSC) the underlying insult leading to biliary injury appears in nearly 80% of cases to be an extrahepatic manifestation of inflammatory bowel disease (IBD), either ulcerative colitis (UC) or Crohn's colitis. Although the typical PSC patient is a young male 30 to 40 years of age, approximately one-third are women and onset can occur in childhood or late adulthood (Box 1).

Diagnostic Criteria

Unlike primary biliary cholangitis (formerly primary biliary *cirrhosis*), where there are agreed upon validated, diagnostic criteria, there remains a lack of objective criteria upon which PSC is diagnosed. Current diagnostics for PSC are limited for several reasons. First, the diagnosis of PSC depends upon interpretation of cholangiograms, which are difficult to quantify and limited by technical and inter-observer variability. Although MRCP remains the initial diagnostic imaging tool of choice with a sensitivity 86% and specificity 94% of for the diagnosis of PSC, [1, 2] a negative MRCP does not negate the need for ERCP as MRCP lacks sensitivity in early PSC and cholangiocarcinoma and can lack specificity in cirrhosis [3]. Second, in cases of ambiguous cholangiograms, liver biopsy is neither sensitive nor specific for PSC. Even the classic "onion-skinning" of concentric fibrosis is found in only a minority of PSC cases and may also be present in ischemic cholangitis and other biliary diseases. Third, serum markers such as perinuclear anti-neutrophil cytoplasmic antibody (pANCA) are found in up to 95% of PSC patients but are also present in other liver diseases as well as in IBD, particularly UC, without PSC. Finally, excluding secondary causes of sclerosing cholangitis can be difficult, particularly in patients without IBD who may have undergone cholecystectomy during an evaluation of cholestasis or had a history of cholelithiasis. Thus, the diagnostic certainty of PSC ranges from the highest level in a young man with ulcerative colitis and classic intrahepatic and extrahepatic segmental biliary strictures to the lowest level in, for example, an older woman who present with cholestasis but without any evidence of IBD, a prior history of cholecystectomy, only minor intrahepatic biliary strictures, and a liver biopsy with non-specific portal inflammation and biliary fibrosis.

Identification of PSC Phenotypes

PSC is a rare disease with an incidence rate in North American and Northern Europe of approximately 1–1.5 cases per 100,000 person-years and a prevalence rate of 6–16 cases per 100,000 inhabitants.[4–6] Estimates of the prevalence of PSC in other parts of the world are

very limited, but suggested to be substantially lower at 0.95 cases per 1000,000 inhabitants in Japan.[7] This has limited to understanding of PSC phenotypes until recently with the accumulation of large cohorts at single centers as well as collaborative efforts such as the International PSC Study Group[8] and the Netherlands EpiPSCPBC Study Group[9] consisting of several thousand patients and analysis of transplant databases[10], all of which have led to a better understanding of the variety of disease patterns within the larger group of patients diagnosed with PSC. The following are the most notable groups of PSC patients (Figure 1).

Large Duct PSC Variants

The classic form of PSC, which accounts for the majority of PSC cases, as originally described has several characteristic features in addition to the classic cholangiographic features of strictures in the large and medium-sized bile ducts. Namely, large duct PSC occurs predominantly in men (male:female ratio 3:2), is co-existent with IBD in 60–80% of cases, and typically presents with cholestasis. The IBD typically is a pan-colitis with frequent ileitis and rectal sparing. In addition, the IBD is commonly mild and asymptomatic. The association between PSC and IBD appears to be greater in Northern latitudes, although even there, the frequency of non-IBD PSC is increasing. The natural history of large duct PSC ranges from rapidly progressive to indolent. The mean transplant-free survival has been reported to be from 12 to more than 20 years, with the latter including more recent population based estimates.[11, 12] This group of PSC is the best described and for which there is the best understanding including the strong association with the human leukocyte antigen (HLA) haplotype defined by HLA-A*01, B*08, DRB1*03.

Special mention should be made regarding the IBD found in PSC, which is commonly asymptomatic and thus, all newly diagnosed PSC patients without a diagnosis of IBD must undergo colonoscopy. Interestingly, the IBD typically is a pan-colitis, which often shares features of both ulcerative colitis and Crohn's colitis with frequent ileitis and rectal sparing [13]. Compared to patient with IBD without PSC, patients with IBD and PSC tend to be younger at presentation, yet have a significantly increased risk of colorectal carcinoma [14]. These patients may also have exacerbation of IBD after liver transplantation for PSC and the risk of pouchitis is significantly increased after proctocolectomy with ileo anal-pouch anastomosis [14]. Of note, PSC is not dependent on active intestinal disease and in fact, can occur after colectomy[13] and immunosuppression, particularly those that are effective for the treatment of IBD, have not been shown to be effective for PSC [15]. Management of IBD remains the same independent of the presence of PSC with the exception that surveillance colonoscopy for dysplasia is recommended to be initiated at the time of PSC diagnosis due to the absence of a lag time in colorectal cancer risk in IBD alone.

With the strong association between PSC and IBD, it is not surprising that they share some common genetic basis. However, only half of the PSC genes that have been identified are also associated with UC, Crohn's disease, or both, with the strongest association with UC compared to Crohn's disease. [16–21]. Notably, most of the genes shared between PSC and IBD are more strongly association with PSC than with UC or Crohn's disease. In addition, network analysis has not identified any common functional pathways to suggest a specific mechanism that predisposes to both IBD and PSC. This lack of a more common genetic

basis between PSC and UC or Crohn's disease supports the clinical notion that PSC-IBD is a unique phenotype.

Stricture Type

Segmental strictures with proximal dilation and sacculation of the bile ducts that create the "beaded" appearance are the classic finding of PSC on cholangiogram. Typically, these findings are present in the intrahepatic and the extrahepatic bile ducts. Strictures limited to the extrahepatic bile ducts alone are rare, whereas isolated changes of the intrahepatic bile ducts have been reported in 20% to 28% of the cases. Dominant strictures, which have been defined as strictures with a diameter of less than 1.5 mm of the common bile duct or less than 1.0 mm of a hepatic duct within 2 cm of the bifurcation, develop in approximately half of PSC patients. The presence of a dominant stricture is of particular concern for cholangiocarcinoma and should be evaluated by brush cytology and/or biopsy. Several studies have shown an association between dominant strictures and poor outcomes even with endoscopic management[22, 23] and more recently this has been suggested to be due to the increased prevalence of cholangiocarcinoma[24].

Non-IBD Large Duct PSC

In contrast to PSC in the presence of IBD, PSC in the absence of IBD tends to be equally distributed among men and women, is diagnosed at a much older age,[25] and may have a better prognosis.[26] Although the rarity of PSC without IBD limits the power of genetic analysis, this group of PSC patients appears to share similar HLA risk alleles compared to PSC with IBD.[27]

High-IgG4 PSC

In addition to several autoantibodies, total serum IgG levels are modestly elevated in approximately 60% of patients and IgM levels can be elevated as well. More recently, it has also been recognized that IgG4 levels are elevated in approximately 10% of PSC patients, but rarely is the level greater than 2.8 g/L or twice the upper limit of normal. [9, 28–33] Notably, elevated IgG4 levels have been associated with decreased transplant-free survival in one cohort,[28] but not another.[33]

PSC-Autoimmune Hepatitis Overlap

Reports of the frequency of PSC with features that overlap with autoimmune hepatitis (AIH) range between 1% and 53.8%. Likely this is because there remains no agreed upon diagnostic criteria for PSC-AIH overlap.[34] Typically, these patients present with significant elevations of liver transaminases and histologic findings consistent with AIH, but they may also initially present as a typical case of AIH that becomes cholestatic with the development of sclerosing cholangitis. In some cases PSC-AIH may respond to immunosuppression. Importantly, autoantibodies including anti-nuclear antibodies and anti-smooth muscle antibodies are frequent in PSC without evidence of AIH. In addition, 10% or more of patients with AIH may have cholangiographic features on magnetic resonance cholangiography consistent with PSC. [35, 36]

Pediatric PSC

PSC in children appears to have many of the same features as PSC in adults, namely a male predominance and strong association with IBD. However, in children PSC appears to be much more responsive to therapies and have a higher frequency of overlap with AIH.[37] Autoimmune sclerosing cholangitis (ASC) is a term used to designate a group of patients with PSC-AIH features with the exceptional reversal of cholangiographic findings with immunosuppression. Recent case series have also reported marked clinical improvement with oral vancomycin in children with PSC. Notably, neither of these therapies has shown similar effects in adults.

Non-Caucasian Large Duct PSC

Most studies of PSC have been performed in Northern European populations or populations which descended from Northern Europe leading some to conclude that PSC is a disease of Caucasians. However, PSC is a "modern" disease and given its association with IBD, it is likely that as the geo-epidemiology of IBD changes, the frequency of PSC in non-Caucasian populations will change with it. To date, there are few data from Asia apart from the IgG4-related sclerosing cholangitis associated with autoimmune pancreatitis (AIP) described in Japan where PSC appears to be extremely rare.

In contrast, studies of a large healthcare organization and US transplant data suggest that the incidence and prevalence rates of PSC among African Americans is at least as great as in Caucasians.[10, 38] In African Americans there is a less striking male predominance and lower IBD rate. Interestingly, HLA-DR3, which is strongly associated with PSC in European populations is rare among African Americans and was not associated with PSC in African American patients. However, the HLA-B8 association is shared between both Caucasian and African American PSC patients.

Small Duct PSC

A small group of PSC patients present with clinical and histologic features compatible with PSC, except for the lack of typical cholangiographic findings and have been defined as small duct PSC.[39] In some series, IBD was required for the diagnosis but not in others. In addition, these patients may have been labeled in the past as anti-mitochondrial antibody (AMA)-negative primary biliary cholangitis (PBC), formerly known as primary biliary *cirrhosis*, or autoimmune cholangiopathy. In most cohorts, small duct PSC comprises approximately 10% of the total PSC population, rarely progresses to large duct PSC, and has a generally favorable outcome. Recent analysis of the HLA region shows that small duct PSC without IBD is genetically distinct from large duct PSC.[40]

IgG4-related sclerosing cholangitis

The recent description of IgG4-related sclerosing cholangitis often found in association with AIP as one of many diseases associated with elevated IgG4 serum levels and tissue infiltration of IgG4-plasma cell has led to the recognition that some previously diagnosed cases of PSC were in fact IgG4-related sclerosing cholangitis.[41] Adding confusion to this issue are findings that serum IgG4 levels are often elevated in PSC and IgG4 plasma cells

are frequent in PSC liver explants, but the two features do not necessarily correlate[29, 42] In addition, IgG4-related diseases are typically responsive to corticosteroids, which is not seen in PSC. For patients with a serum IgG4 level between 1.4 and 2.8 g/L, a ratio of IgG4:IgG1 of less than 0.24 suggests a diagnosis PSC rather than IgG4-sclerosing cholangitis. However, the diagnosis of IgG-4 related sclerosing cholangitis should be based upon histology, imaging, serology, other organ involvement, in addition to response to steroid therapy by the HISORt criteria that were originally developed for the diagnosis of autoimmune pancreatitis.[43]

Multiple Approaches

Diagnosis

Understanding the multiple phenotypes of PSC is important for several reasons. First, recognition that PSC may present in an atypical pattern, for example an older non-Caucasian woman without IBD, is vital to avoid missed opportunities for diagnosis. Second, proper classification can affect management decisions. For example, a patient with undiagnosed quiescent colitis may not receive the appropriate surveillance for colorectal cancer. Third, patients with IgG4-related sclerosing cholangitis respond well to corticosteroids and some evidence suggest that so do some patients with PSC and elevated serum IgG4 levels as well as PSC-AIH overlap patients[30, 34]. Finally, classification can have a tremendous impact on prognosis. Specifically, those with small duct PSC, normal serum alkaline phosphatase levels, and older age at diagnosis appear to have a more benign course[39, 44–47].

Management

Although there are no therapies other than liver transplantation proven to alter the natural history of PSC, the management of these patients is not simple and includes consideration of ursodeoxycholic acid or other therapies, referral to clinical trials, and monitoring of disease progression to cirrhosis and other outcomes including bacterial cholangitis, cholangiocarcinoma, and colorectal cancer (Figure 2). In addition, PSC patients should be tested for associated autoimmune conditions, nutritional deficiencies, and osteoporosis.

Summary/Discussion

PSC is a heterogeneous disorder that varies in clinical presentation, natural history, and, potentially, treatment response. Many studies have documented the specific clinical features that may be used to classify a specific phenotype, but usually these are analyzed in isolation. A rudimentary calculation suggests that there are over 3,000 potential PSC phenotypes (Figure 3)! The actual number is likely to be much smaller, but for a rare disease, fully appreciating the variability in clinical phenotypes and their significance will require the ongoing collaboration of international consortia as well as larger participation from patient advocacy groups and large healthcare systems. In addition, as larger numbers of patients are studied in more detail, a systems-based approach to classifying sub-phenotypes will need to be considered in order to unravel the complexity and heterogeneous nature of PSC. Correlating genetic data with these phenotypes will begin to reveal the mechanisms responsible for this heterogeneity. Ultimately, the goal is to develop a better understanding

of the pathogenic mechanisms underlying each PSC phenotype so that therapies may be individualized for each patient.

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Key Points

- Primary sclerosing cholangitis (PSC) presents as a heterogeneous group characterized by segmental strictures of bile duct, most often in the setting of inflammatory bowel disease involving the proximal colon.
- Several phenotypes of PSC have been recognized based upon the age of diagnosis, presence or absence of inflammatory bowel disease, small duct involvement, IgG4 level, dominant strictures, and race.
- Approximately 10% of PSC patients have an elevated serum IgG4 level, which can lead to misdiagnosis of IgG4-related sclerosing cholangitis, which is a separate disease from PSC.
- Future research is needed to develop systems to classify PSC patients into specific phenotypes based upon the clinical features that have been described so that the pathogenic mechanisms can be better understood and new targets for drug development identified.

Primary Sclerosing Cholangitis Clinical Features

- **Duct Involvement**
  - Large Duct – *classic form*
    - Extra-hepatic *vs* Intra-Hepatic *vs* Both
    - Dominant Stricture – *worse outcomes, especially due to CCA*
  - Small Duct – *Histologic PSC features but normal cholangiogram, better outcomes*
- **Inflammatory Bowel Disease**
  - Ulcerative colitis – *typically mild pancolitis, ileum involvement common*
  - Crohn's disease – *more frequent in small duct PSC, better outcome*
  - Indeterminate colitis
  - No IBD – must be confirmed by colonoscopy, better outcome
- **Serum lgG4**
  - Normal – *typical in 90% of PSC. Elevation of total IgG common*
  - 1-2 x ULN - *~10% of PSC, may predict poor outcome*
  - >2 x ULN - *more likely to be lgG4-related sclerosing cholangitis*
- **Autoimmune Overlap**
  - ALT > 5 x ULN and IgG > 2 x ULN – *no diagnostic consensus, consider AIH treatment, may present concurrent with PSC or following AIH treatment*
- **Race/Ethnicity**
  - European – *most data based upon those of European descent*
  - African – *more advanced disease at younger age, more Crohn's, less male predominance*
  - Asian – appears to be rare
- **Age of Diagnosis**
  - Pediatric – *more overlap with AIH, more responsive to treatment initially*
  - Young adult – *typical presentation, more aggressive*
  - Older adult – *better outcome*

Figure 1.

Multiple clinical features have been identified which can be used to describe a variety of PSC phenotypes. In isolation, each has been shown to segregate groups of PSC patients with differences in outcomes or response to treatment.

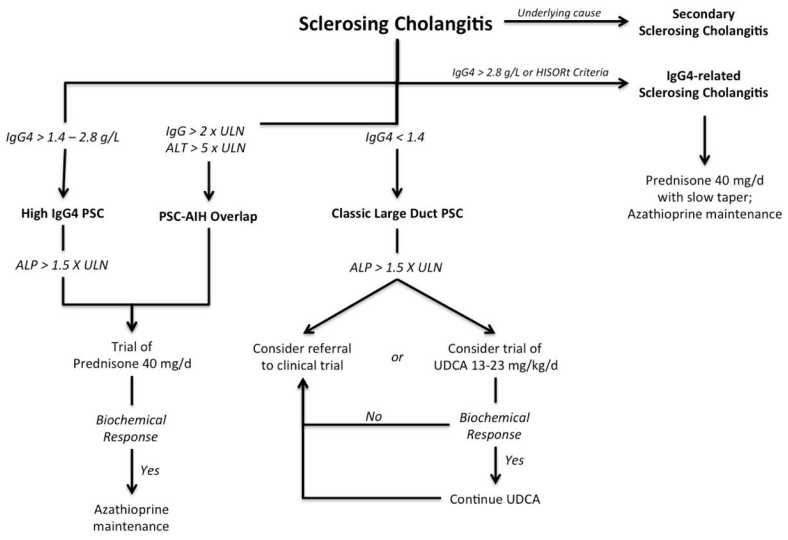

Figure 2.

A proposed management algorithm for PSC patients presenting with sclerosing cholangitis. Data is limited to case series for PSC patient with elevated IgG4 levels or PSC-AIH Overlap and response-guided treatment with ursodeoxycholic acid (UDCA) has not been prospectively validated. [30, 48, 49] A biochemical response is defined by a reduction in alkaline phosphatase to lower than 1.5 X ULN. In addition to treatment, monitoring and surveillance studies should include those to investigate liver disease progression (laboratories, transient elastography or MR elastography); malignancy (annual colonoscopy if inflammatory bowel disease is present; annual abdominal imaging and serum CA19-9); and co-morbid conditions (bone density scan; fat soluble vitamins; celiac disease serologies).

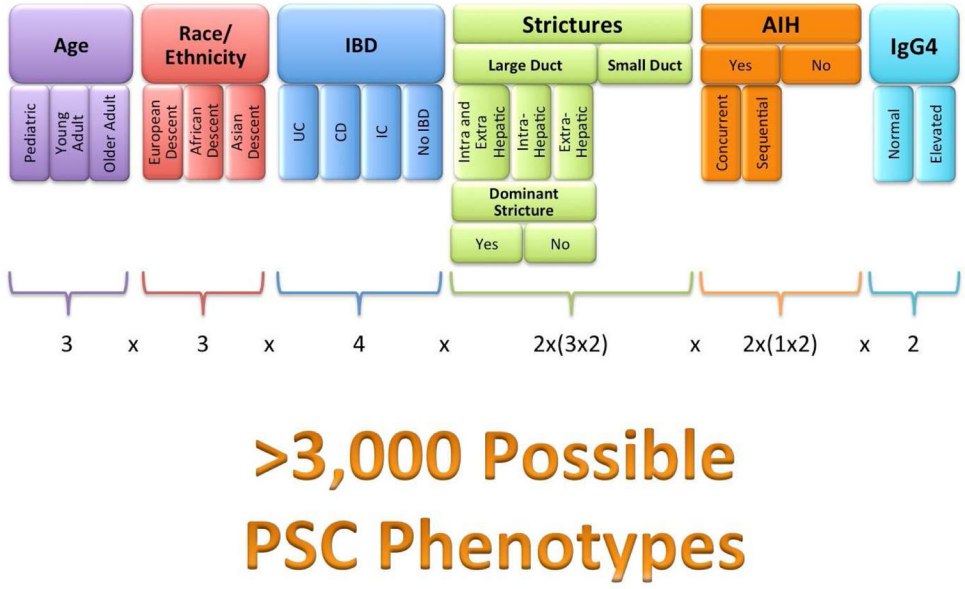

Figure 3.

Graphical representation of the possible combinations of clinical features associated with PSC phenotypes. Not included is sex/gender.