**Supplemental Digital Content (SDC)**

**Methods**

This was a retrospective cohort study of patients diagnosed with PSC between 1984 and 2014 at Boston Children’s Hospital. Patient ascertainment was accomplished mainly by search for PSC/ASC of our Hepatology clinic database. To ensure that all PSC patients were captured, medical records were queried for both “PSC” in patient problem lists as well as for patients with both ICD-9 codes for cholangitis (576.1) and colonoscopy (45.23) as this would have identified PSC patients who underwent IBD surveillance. This methodology was employed as there are no ICD-9 codes specific to PSC or ASC. This study was approved by the institutional review board.

Inclusion and exclusion criteria

 Males and females less than 20 y of age were included based on diagnostic imaging or histopathology reports with findings consistent with PSC. The presence of “large” (macroscopic) duct abnormalities was based on magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) reports, with findings that included bile duct stenosis or dilation, or attenuation of intraparenchymal arborization.8 The identification of “small” (microscopic) duct abnormalities was based on histology reports, which included acute or chronic cholangitis associated with portal tract fibrosis, portal hepatitis, or cirrhosis, as well as concentric periductal fibrosis known as “onion skinning”.3 The term “small duct PSC” was reserved for those cases where the abnormalities defining PSC were present only on histology (normal cholangiography) within 6 months of diagnosis. “ASC” was defined as findings consistent with both PSC and AIH. The investigators reviewed liver histology reports as well as clinic records to determine if patients were appropriately assigned a diagnosis of ASC. The diagnosis of ASC was made when, in addition to meeting diagnostic criteria for PSC, patients had lymphoplasmacytic infiltrates and parenchymal necroinflammatory activity in excess of what would be expected with PSC alone, with or without the appropriate autoantibodies in serum (anti-nuclear antibodies [ANA] or anti-smooth muscle antibodies [SMA]).9 Patients with “isolated PSC” were those with PSC but without AIH overlap, regardless of other diagnoses, such as IBD. Cases were excluded if they had any co-existing liver disease apart from AIH or if the PSC diagnosis could not be confirmed retrospectively by review of cholangiography or histology reports.

Data collection

Data was collected from the time of baseline PSC diagnosis as well as in follow-up. The PSC diagnosis date was defined as the first abnormal study, either the liver biopsy or the cholangiogram. Baseline data was defined as that ascertained 6 months before or after the date of PSC diagnosis. This included demographic data, symptoms or signs (including pruritus, jaundice, abdominal pain, diarrhea, hepatomegaly, splenomegaly), anthropometric data, prescribed medication, biochemical test results, liver histology, and diagnostic imaging (ultrasound and cholangiography). Large duct PSC was defined as involvement of macroscopic intrahepatic or extrahepatic biliary duct abnormalities on cholangiography. Longitudinal data collected at 1 y (±3 months), 2 y (±6 months), 5 y (±9 months), and 10 y (±12 months) post-PSC diagnosis included information listed as well as pertinent liver-related outcomes: episodes of bacterial cholangitis, documentation of cirrhosis, portal hypertension, esophageal varices (EV +/- bleeding), interventions via ERCP, hepatobiliary malignancy, LT, and death.

IBD phenotypic data included: ulcerative colitis (UC) vs. Crohn disease (CD) vs. IBD-unclassified (IBD-U), location of disease,10 and IBD severity, as defined by the Pediatric Ulcerative Colitis Activity Index (PUCAI) and the Pediatric Crohn's Disease Activity Index (PCDAI).11-13 The IBD-U subset was a small group of patients with colonic disease, as well as upper intestinal or small bowel abnormalities that were ambiguous. Due to the frequent pancolitis seen in IBD-U associated with PSC, and the low numbers of patients with IBD-U, the UC and IBD-U subsets were combined for the purposes of analysis.14 Other autoimmune diseases in the index cases and family members were recorded when available.

Statistical analyses

Statistical analysis included descriptive methods and standard tests of association. Percentages and means (or medians in non-normally distributed data) were used to describe the clinical data. Tests of association included Student’s t-tests for continuous data, and chi-square or Fisher exact tests for categorical data. The distribution of large duct disease was assessed by examining the intrahepatic and extrahepatic cholangiographic changes over time using the Bowker’s test for multi-level, symmetrical, non-linear, categorical data. A time to event analysis (Kaplan-Meier curve) was calculated to describe the liver transplant-free survival of the cohort; patients were censored after the last encounter at Boston Children’s Hospital (clinic visit or diagnostic tests). Statistical analyses were completed using SAS/STAT® software, version 9.4 (SAS Institute, Cary, North Carolina, USA).

Outcome analyses

Outcomes, including fibrosis or LT rate, were compared between patients with isolated small duct PSC and those with large duct disease. Patients diagnosed with IBD prior to PSC were compared to patients who either were later found to have IBD or never developed IBD, as this group had regular surveillance with liver biochemistry prior to the PSC diagnosis.