Review Article

# Primary Sclerosing Cholangitis and Primary Biliary Cirrhosis Overlap Syndrome: A Review

Sheena Mago* and George Y. Wu

*Department of Medicine, Division of Gastroenterology-Hepatology, University of Connecticut Health Center, Farmington, CT, USA*

## Abstract

Primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) are slow progressive diseases which have been increasing in prevalence. The pathogeneses of PBC and PSC are incompletely understood but the underlying mechanisms appear to be fundamentally autoimmune in origin. Although PBC and PSC appear to be separate entities, overlap has been described. Diagnosis depends on a combination of serological markers, imaging, and pathological criteria. The mainstay of treatment has been ursodeoxycholic acid and in some cases of extrahepatic biliary obstruction and overlap disorder, endoscopic retrograde cholangiopancreatography has been useful.

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## Introduction

Primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) are slow progressive chronic cholestatic diseases which can ultimately cause cirrhosis and liver failure, generally over decades.[1,2] Both are hypothesized to have primarily autoimmune etiologies resulting in cholestasis and progressive biliary ductal destruction due to damage of biliary epithelial cells.[3–5] Although they both cause bile duct damage that can ultimately lead to cirrhosis and liver failure, PSC and PBC have distinct features and are generally considered to be well-defined individual disease states with specific diagnostic criteria based on clinical symptoms, serologic, immunologic, and histologic findings.[4] In the majority of cases, these criteria are sufficient to make the correct diagnosis. However, rarely, cases have been reported in which there are features of more than a single autoimmune entity, including autoimmune hepatitis, PBC or PSC.[3] In particular, primary sclerosing cholangitis-and-primary biliary cirrhosis (PSC-PBC) overlap cases have been reported, albeit rarely. Due to the rarity of these cases presenting with overlapping features, they can pose significant diagnostic and therapeutic questions.[5] The aim of this review is to present the epidemiology, proposed pathogeneses, clinical presentations, diagnostics, and treatments of PSC, PBC, and PSC-PBC overlap syndrome.

## Epidemiology

Data aggregated from 31 case studies between 1972-2007 have estimated that the incidence of PSC ranges from 0-1.3, whereas the incidence for PBC ranges from 0.33-5.8, per 100,000 inhabitants/year.[2] Prevalence rates for PSC and PBC ranged from 0-16.2 per 100,000 and 1.91-40.2 per 100,000 inhabitants, respectively.[2] Over time, the incidence and prevalence rates have been noted to increase, likely due to an improvement in disease awareness, diagnostic tools, and treatments. More cases of PSC are found in men, whereas PBC is seen more often in women, with male:female ratios of 2:1 and 1:9, respectively.[2] Both of these diseases may occur at any age, though the peak age of incidence is approximately 40 years-old.[2] A majority of reported PSC-PBC overlap cases have been in females, ranging from 35-72 years-old. The clinical course of PSC is highly variable, with a median survival rate of 12-18 years from diagnosis or until liver transplantation; whereas, the median survival rate for PBC has been noted to be much shorter, 9.3 years.[2,6] Due to the small sample size of PSC-PBC overlap cases, though, the data cannot be accurately extrapolated to estimate the morbidity and mortality statistics for patients thought to have overlap disease.

## Search strategy and identification of studies

Identification of PBC-PSC overlap cases was achieved by PubMed database search, from its inception until April 01, 2020. A combination of the keywords were used, including "primary biliary cirrhosis," "primary biliary cholangitis," and "overlap". Bibliographies of all identified studies were also searched for any relevant articles. We included all studies published in scientific journals that provided information regarding cases of PSC-PBC overlap. Articles not in the English language were excluded. Overall, eight case reports were found documenting a total of ten cases in the literature.

**Keywords:** Primary sclerosing cholangitis; Primary biliary cirrhosis; Overlap syndrome.

**Abbreviations:** 2-OADC E2, 2-oxo acid dehydrogenase complex; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; AMA-M2, anti-mitochondrial M2 antibody; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; AST, aspartate transaminase; ERCP, endoscopic retrograde cholangiopancreatography; GGT, gamma-glutamyl transferase; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; IgM, immunoglobulin M; MRCP, magnetic resonance cholangiopancreatography; OCA, obeticholic acid; PBC, primary biliary cirrhosis; PDC-E2, pyruvate dehydrogenase complex-E2; PPAR, peroxisome proliferator activator receptor; PSC, primary sclerosing cholangitis; PSC-PBC, primary sclerosing cholangitis and primary biliary cirrhosis; PTC, percutaneous transhepatic cholangiogram; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

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***Correspondence to:** Sheena Mago, Department of Medicine, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030, USA. E-mail: smago@uchc.edu

## Etiology/proposed mechanisms

Both PSC and PBC are slow progressive diseases which occur over decades.[6] The pathogenesis of both PBC and PSC is incompletely understood.

Theories regarding the pathogenesis of PSC include autoimmune, inflammatory, and immunological recurring damage to biliary ducts, likely modulated by genetic and environmental factors. It is thought that PSC occurs in genetically susceptible individuals and involves multifaceted interactions of the immune system, leading to stimulation of innate immunity and proinflammatory cytokines, cholangiocyte damage, and progressive fibrosis.[7]

Bergquist *et al.*[8] found that patients with a first-degree relative diagnosed with PSC had a prevalence of 0.7% for developing PSC, which was 100-times higher than their counterparts without a family history of this cholestatic disease. That study also reported the close association of PSC and inflammatory bowel disease (IBD). Controls for patients with PSC and IBD consisted of patients with IBD but no PSC. Strengths of the study included retention of all participants. However, there is concern for recall bias given that data acquisition was done by questionnaires with no concreate medical data for corroboration.[8] Another weakness of this study is its lack of generalizability, given it was conducted in a single tertiary center in Sweden and only had 145 patients with PSC. As the hospital was also a transplant center, there is concern for selection bias, given that patients admitted may have had more severe disease than average.[8]

Studies have also shown a distinct geographic distribution of PSC cases in Northern Europe, which supports the argument for the contribution of genetic and environmental factors.[9] Over the years, genomic analysis has shown convincingly strong human leukocyte antigen (HLA) associations with *HLA-B8* and *HLA-DR3* genes, such as the rs9524260 mutation at chromosome 13q31 and including the haplotypes HLA-DRB1*1501-DQB1*0602, HLA-DRB1*1301-DQB1*0603, and HLA-A1-B8-DRB1*0301-DQB1*020.[10–12] A genome-wide association of 285 PSC patients done by Karlsen *et al.*[10] demonstrated strong HLA associations involved with bile homeostasis and inflammation in PSC. This study included PSC patients from different European countries and medical centers. Despite the number of PSC patients in this study ($n$=285), 74% were male, which limits the generalizability of the study's findings.[10]

These *HLA* genes have been shown to be associated with inflammatory pathways, imbalance of killer immunoglobulin-like receptors, and bile homeostasis, all of which are thought to be key features in PSC.[11] A large proportion of patients diagnosed with PSC have an elevated IgM level or positivity for anti-smooth muscle antibodies (ASMA) or antinuclear antibodies (ANA), supporting the theory of immune activation.[13,14] An autoimmune mechanism of PSC is supported by its strong association with IBD, specifically ulcerative colitis (UC).[15] As demonstrated in a systematic review of 65 papers by de Vries *et al.*,[15] the prevalence of IBD in PSC was greater than 70%, of which over 75% of cases were of UC. This review consisted of 65 studies which spanned different time periods and geographical locations. However, unfortunately, this could also account for the large variation of PSC prevalence seen between the studies.[15] Despite the high prevalence of overlap between PSC and UC, genetic commonalities have been found with a very small subset of only 200 shared risk loci between these two diseases.[15] Like PSC, the precise mechanism of PBC is unknown. However, theories regarding its pathogenesis include immunological, autoimmune, genetic, and environmental factors. Tanaka *et al.*[16] noted a genetic predisposition with the increased disease prevalence for first-degree relatives of patients with PBC. This review included five studies conducted in four countries, with over 150 PBC patients each. Collectively, this study consisted of a large number of PBC patients ($n$=1610). However, most of the data regarding PBC familial involvement was collected through questionnaires, which raises concern for recall bias.[16] As the genetics of PBC was not included in the primary data collected in the study, genetics can only be inferred to play a role along with environmental factors.[16]

A meta-analysis encompassing 19 studies amongst different geographical groups, with a total of 6,057 cases and 16,107 controls, demonstrated a predominance of certain *HLA* mutations in patients with PBC, such as those in *HLA-DR 7* and *HLA-DR 8*.[17] However, when assessing the various studies individually, different genotyping methods were used and the sample sizes for subgroup analyses was small.[17] From this data, it was also difficult to separate the contributions of genes versus environmental factors, possibly leading to confounding bias.[17]

Molecular mimicry between the human pyruvate dehydrogenase complex-E2 (PDC-E2) and corresponding bacterial proteins are also thought to play a role in the pathogenesis of PBC. PDC-E2 has been hypothesized to be essential for T cell activity in PBC.[18] That study, however, only assessed 10 microbial proteins which were thought to best mimic human PDC-E2. Studies have also demonstrated a correlation between the epitope of the B and T cells of PBC patients and the 2-oxo acid dehydrogenase complex enzymes (2-OADC E2).[19] Much of the data has not been reproduced, raising concern of its validity.[20,21]

As both PBC and PSC have some evidence of autoimmune, genetic and environmental factors, these diseases may share similar genetic susceptibility. There have been suggestions of progression of PBC to PSC as a continuum of destruction of intrahepatic biliary ducts resulting in ductopenia, and fibrosis followed by extension to extrahepatic biliary ducts seen in PSC. The biochemical and immunological variations of PBC may cause further progression of ductal fibrosis and biliary destruction with time, due to increased inflammatory response and ultimately leading to PSC.[22] Other hypotheses are that overlap syndromes may have atypical manifestations of the classic diseases verses two distinct disease states with their own mechanisms and outcomes.[22] A majority of overlap cases in the literature consist of PBC that gradually acquired PSC characteristics. Most of these cases initially met criteria for PBC based on biochemistry, immunology, and/or histology and later were found to have radiographic evidence of PSC on subsequent imaging. Less commonly, cases had radiological evidence supporting PSC and PBC co-existence at the time of initial diagnosis.[6,23]

## Clinical features and symptomatology

Typical symptoms common to both intrahepatic PSC and PBC include fatigue, pruritis, and jaundice, all of which are due to the cholestatic process.[6] PSC patients may also experience right upper abdominal quadrant pain, fevers and chills, if the cholestasis causes obstruction or infection or bacterial cholangitis.[24,25] However, most patients present as asymptomatic early in their disease course. Studies have shown that

on average only 56% and 61% of patients diagnosed with PSC and PBC, respectively, are symptomatic upon initial presentation.[24,25] Patients were observed for a total of 69 months for the development of symptoms amongst patients with PSC.[24] Given that PSC is a slowly progressive disease, spanning years, this short duration of data acquisition raises concern regarding the number of unaccounted patients who develop symptoms later in the course of their disease.[24] As for PBC, patients were followed for 6-13 years, both by interview and chart review, which decreased the chances of recall bias.[25] Both studies recorded similar symptoms, including pruritus, persistent, abdominal pain, jaundice, variceal bleeding, and ascites.[24,25]

In up to 73% of patients, PBC can co-exist with other autoimmune diseases. Some of the most common co-existing autoimmune processes are Sjogren's syndrome, thyroid dysfunction, and systemic sclerosis. Sjogren's syndrome is the most common condition associated with PBC. The pathophysiology is thought to be similar, with destruction of exocrine glands by chronic autoimmune inflammation.[26] Autoimmune thyroid diseases (Hashimoto's and Grave's disease) have been noted to have an increased incidence in patients with underlying PBC. The hypothesized link between these two entities include the cross-reactivity of epithelial antigens between the liver and the thyroid.[27] Systemic sclerosis shares similarities to the pathogenesis of PBC, with the deposition of extracellular matrix based on immune responses.[26] The literature demonstrates significant variability in the prevalence of these extrahepatic associations, ranging from 3.5% to 73%, and study populations. Each study was restricted to a single geographic region, which may make the data less generalizable.[26]

Most cases of PSC-PBC overlap in the literature demonstrated very variable symptoms. In those cases, patients were evaluated just for abnormal laboratory values.[28,29] In the overlap studies reviewed in this article, up to 50% of patients were asymptomatic at the time of diagnosis and PBC was diagnosed based on the biochemical and immunological studies.[22,28–31] Only one overlap case, described by Floreani *et al.*,[29] had co-existing hypothyroidism. However, there was no documentation of Hashimoto's disease.[27,29]

## Diagnosis

### *Laboratory diagnosis of PSC-PBC*

The diagnosis of PBC requires two of the following three criteria: biochemical, immunological, and/or histological.[6,23] The serum alkaline phosphatase (ALP) should be greater than 1.5 times the upper limits of normal, serum antimitochondrial antibodies (AMA) titers should be greater than or equal to 1:40 (negative: <1:40; low antibody level: 1:40-1:80; elevated antibody level: >1:80; or negative: <0.1 units, positive: ≥1.0 units) or, if AMA-negative, anti-sp100/anti-gp210 is present, and/or the liver histology should demonstrate interlobular biliary destruction.[6,23,32] Typical diagnostic lesions of PBC include florid duct lesions with non-caseating epithelioid granulomas.[33] Biochemical markers that are usually elevated in PBC are ALP and gamma-glutamyl transferase (GGT). Alanine aminotransferase (ALT), aspartate transaminase (AST), and total bilirubin are not diagnostic markers of the disease and can be either normal or elevated; although, these markers are seen to vary as the disease progresses over time.[23] Levels of immunoglobulin M (IgM) are also seen to be elevated in patients with PBC.[34] Positive AMA status is present in over 90% of PBC patients, while some have positive anti-mitochondrial M2 antibody (AMA-M2) (units <1:10). In a meta-analysis done by Hu *et al.*,[35] it was noted that the sensitivity and specificity of AMA for the diagnosis of PBC was 84.5% and 97.8%, respectively, and the sensitivity and specificity of AMA-M2 for the diagnosis of PBC was 84.3% and 94.8%, respectively. This meta-analysis included 24 case-control studies, with 2,992 PBC cases and 18,467 other liver disease/healthy controls.[35] While most studies performed single-center analyses, this paper described a stratified analysis of ethnicities and little difference was found in sensitivity.[35] Each study used different methods of analysis, including enzyme-linked immunosorbent assay, indirect immunofluorescence, and western blot. As a result, the sensitivity and specificity of the source of reagents for each test could not be accurately assessed, causing some limitations in the final analysis.[35]

Besides AMA, other immunological indicators that are now considered diagnostic for PBC include antinuclear antibodies (ANA) directed at anti-Sp100 or anti-gp210 presenting as multiple nuclear dots and perinuclear rims.[23] ANA directed at anti-Sp100 or anti-gp210 are considered to be PBC-specific (specificity of over 95%), but have low sensitivity.[23] In a meta-analysis conducted by Zhang *et al.*,[36] it was noted that for the diagnosis of PBC, anti-gp210 had a sensitivity and specificity of 23% and 99%, along with anti-sp100, which had a sensitivity and specificity of 25% and 97%, respectively. Each of the 11 studies included in the meta-analysis had different inclusion criteria for their control groups, which raises concern regarding its effect on the validity of the study.[36]

### *Histological diagnosis of PSC-PBC*

Although a liver biopsy may not be required for the diagnosis of PBC, in many cases it is very helpful. There are characteristic histological lesions associated with this disease which can confirm the diagnosis but can also assist in assessing the disease progression and severity. PBC can be staged based on 2 different classifications proposed by Ludwig *et al.*[37] and Scheuer.[38] These classifications are based on the amount of inflammation, ductal injury, and fibrosis.[37,38] The Ludwig staging includes (1) portal inflammation, (2) expansion of inflammation surrounding parenchyma, (3) fibrosis parenchyma, and (4) cirrhosis.[37] The Scheuer staging includes (1) presence of florid duct lesions, (2) proliferation of the small bile ducts, (3) fibrosis, and (4) cirrhosis.[38] Typical diagnostic lesions of PBC include florid duct lesions with non-caseating epithelioid granulomas.[33] If biopsies demonstrate histological features correlating to more than one stage, they are classified based on the more severe stage.[34] In a study conducted by You *et al.*,[39] it was demonstrated that PBC patients with granulomas correlated with significantly earlier histological stages. This study assessed liver biopsies from 51 patients with PBC. However, of these 51 patients, there were a significant number with overlap with autoimmune hepatitis and chronic hepatitis B.[39] Histological findings of PSC also seem to be categorized in four stages proposed by Ludwig.[40] The four stages include (1) portal tract and ductal proliferation, (2) periportal fibrosis, (3) septal fibrosis, and (4) cirrhosis.[40] The classical periductal concentric fibrosis is not seen often, though is highly suggestive for PSC.[40]

### *Imaging diagnosis of PSC-PBC*

There are no specific features of PBC that can be delineated on ultrasound. For patients who do not have immunological markers, such as AMA or PBC-specific ANA, imaging with magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) is essential to rule out other diagnoses of large duct disease, particularly PSC.[23] Unlike in PBC, ultrasonography can delineate biliary wall thickening and focal ductal dilatations in PSC. However, this is not diagnostic. ERCP or MRCP should be used to demonstrate pathognomonic cholangiographic features of PSC, including mural irregularities and diffuse short, multifocal, annular strictures producing a "beaded" pattern.[41] Longer abnormal stricturing segments may be seen in advanced disease, with most cases involving both intra- and extrahepatic biliary ducts.[41] Approximately 25% of cases have isolated intrahepatic disease, whereas less than 5% of cases have isolated extrahepatic disease.[41] In the past ERCP had been the gold standard for diagnosis. However, now less invasive techniques, such as MRCP, have with less associated risk and comparable diagnostic accuracy, with a sensitivity and specificity of ≥80% and ≥87%, respectively.[42]

### *Diagnosis of PSC-PBC overlap syndrome*

As there are no formal studies on the diagnosis of the overlap syndrome of PSC and PBC, the diagnosis has been made using criteria for both diseases (Table 1). The biochemical and immunological lab findings are consistent with the diagnosis of PBC, i.e. elevated positive AMA, anti-gp210, or anti-sp100, and histologically the diagnosis is consistent with PSC, including evidence of bridging portal fibrosis and small biliary ducts with concentric fibrosis and ductal obliteration.[28] A positive AMA-M2 is seen in over 90% of patients with PBC and a positive anti-gp210 and anti-sp100 has been found to have a specificity of over 95% for the diagnosis of PBC.[23,28] Characteristic PSC-specific histological evidence of 'onion skinning' is not often seen but supports a histological diagnosis of PSC when present.[28,40]

The first case of PSC-PBC overlap was described by Rubel *et al.*[43] The initial diagnosis of PBC was made by AMA positivity, elevated ALP and liver histology demonstrating portal fibrosis, bridging necrosis, and the absence of periductal fibrosis.[43] Many procedures to visualize the extrahepatic biliary ducts were attempted, though unsuccessful until a percutaneous transhepatic cholangiogram (PTC) was done 7 years after the PBC diagnosis. PTC demonstrating multiple regions of structuring and dilations consistent with the 'beaded' pattern diagnostic for PSC.[43]

Jeevagan[44] described a case of PBC based on abnormal liver function tests, a normal ERCP, and liver biopsy suggestive of PBC (Table 2). Eighteen years later, a proposed diagnosis of overlap was made based on MRCP and ERCP which demonstrated a beading appearance of the biliary ducts thought to be consistent with PSC.[45] Despite reported histological findings consistent with subsequent diagnoses of PBC and PSC, this case presented with several weaknesses, including histology of the liver biopsy describing 'deranged liver function tests' not being detailed in the case report and negative AMA titers.[23,44] A repeat biopsy subsequently had findings of lymphoplasmacytic infiltrate and lymphoid aggregate consistent with the diagnosis of PBC, and subsequent imaging 18 years later with MRCP and ERCP demonstrated a beaded appearance of the biliary ducts which was consistent with PSC.[41,44] In that case, the presentation of jaundice, abdominal pain, and fever is consistent with ascending cholangitis. However, this was not reported to be a recurrent event.

Floreani *et al.*[29] described two patients who were ultimately diagnosed with PSC-PBC overlap syndrome. The first patient had a history of PBC suspected due to abnormal cholestasis enzymes and MRCP imaging. She also later had liver histology which was consistent with the diagnosis of PBC. She was initially started on 10 mg/kg/day of ursodeoxycholic acid (UDCA), which was increased to 15 mg/kg/day, though her repeat MRCPs over the years revealed an upstream dilation with sections of marked stenosis consistent with PSC. Shortly prior to that she was also found to have an ANA titer of 1:640 with a speckled pattern, along with positivity of AMA-M2 and anti-gp210. That case showed strong support for the diagnosis of overlap as there were positive PBC-specific immunological markers, such as AMA-M2 and anti-gp210, along with histological evidence of PBC. The imaging supported a diagnosis of PBC initially, and then 2 years later, new findings supported a diagnosis of PSC, despite treatment with

**Table 1. Clinical characteristics of PSC and PBC**

| | PSC | PBC |
|---|---|---|
| Female: male ratio | 1 to 2 | 9 to 1 |
| Biochemical elevations | ALP, GGT (AST, and ALT, later) | ALP, GGT (AST, and ALT, later) |
| Serum Ig elevation | IgG and IgM | IgM |
| Histological/ Imaging features | Multifocal strictures and segmental dilatations in the biliary ducts | Focal duct obliteration with granuloma formation |
| Diagnostic criteria | (1) Elevation of ALP and GGT; (2) ERCP or MRCP demonstrating multifocal strictures and segmental dilatations in the biliary ducts without any other causes | 2 of the 3 criteria: (1) ALP greater than 1.5 times the upper limits of normal; (2) serum AMA titers greater than or equal to 1:40 or anti-sp100/anti-gp210 presence; (3) liver histology demonstrating interlobular biliary destruction |

**Table 2. Summary of reported cases PSC and PBC overlap**

| Author | Age/ Sex | Past medical history | Surgical/Family history | Presentation | Laboratory values | Liver biopsy/ERCP/ MRCP/US | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|
| Oliveira *et al.*[28] | 48/F | Hypertension | None | Elevated liver enzymes | ANA: titer >1/640 with speckled pattern<br>AST: 98 U/L<br>ALT: 125 U/L<br>GGT: 227 U/L<br>Total bilirubin: 0.41 mg/dL<br>Direct bilirubin: 0.06 mg/dL<br>ASMA: negative<br>AMA M2: positive<br>Anti-Sp100: positive<br>Anti-gp210: positive | Liver biopsy: bridging portal fibrosis, lymphomononuclear infiltrate with lymphocytic interface hepatitis and marginal ductular reaction; with some small biliary ducts with concentric fibrosis ("onion skin" type) with ductal obliteration | UDCA (dose unknown) | Normalization of liver enzymes in 4 months |
| Jeevagan[44] | 64/F | PBC diagnosed via liver biopsy and was treated with UDCA | None | 2-week history of jaundice, abdominal pain, decreased appetite, nausea, vomiting, weight loss, fever, pale stools, dark urine, right upper quadrant tenderness | 18 years after diagnosis<br>LFTs: 'deranged'<br>AMA: negative<br>Bilirubin: 377 μmol/L<br>ALP: 2627 U/L<br>AMA-M2: negative<br>ASMA: negative | ERCP: low benign-looking stricture with intrahepatic dilation suggestive of PSC<br>MRCP: dilatation of CBD distally tapering at the ampulla; significant beading appearance along the ducts | IV fluids, antibiotics, UDCA (dose unknown) | Unknown |
| Sundaram *et al.*[22] | 35/F | None | None | 4 years of generalized weakness, easy fatigability, and generalized pruritus; 4 months of ascites, jaundice, pedal edema | AST: 117 U/L<br>ALT: 41 U/L<br>GGT: 353 U/L<br>Total bilirubin: 4.0 mg/dL<br>Direct bilirubin: 3.1 mg/dL<br>ALP: 1047 U/L<br>ANA: titer >1/640<br>AMA-M2: positive | Liver biopsy: portal tracts with fibrosis and bile ductular proliferation with mild portal tract inflammation; no onion-skin fibrosis or granulomas MRCP: smooth, short-segment narrowing in the CBD at the porta and irregularity of left-sided intrahepatic biliary radicles with subtle beading | Diuretics, UDCA 750 mg daily | Ascites resolved in 4 weeks; total bilirubin and ALP improved to 2 mg/dL and 510 U/L respectively. No episodes of decompensation occurred over the 3 months follow-up period |
| Floreani *et al.*[29] | 51/F | Psoriasis, arthritis, PBC suspected due to elevated liver enzymes and MRCP (treated with 10 mg/kg/ day) | Laparoscopic cholecystectomy (25 years prior) | Elevated liver enzymes | Abnormal liver enzymes for 3 years<br>ALP: 201 IU/mL<br>GGT: 229 IU/mL<br>AMA: positive (1:160 titer)<br>AMA-M2: positive<br>anti-gp210: positive<br>ANA: titer >1/40 with speckled pattern | Liver biopsy: marked fibrosis in the portal tracts extending to the parenchyma and interface hepatitis<br>MRCP: marked reduction of the right segmental duct with upstream dilatation and marked stenosis of the biliary tree | UDCA increased to 15 mg/kg/ day and adalimumab 40 mg every 2 weeks | Normalization of ALP, decrease of GGT to 124 IU/L |

(*continued*)

**Table 2.** (*continued*)

| Author | Age/ Sex | Past medical history | Surgical/Family history | Presentation | Laboratory values | Liver biopsy/ERCP/ MRCP/US | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|
| Floreani *et al.* [29] | 60/F | Hypertension, diabetes type 1, subclinical hypothyroidism, PBC based on liver biopsy, AMA negative, and ANA titer 1:80 (12 years prior) | Malignant melanoma excision (35 years prior), left ovariectomy (19 years prior), excision of frontal meningioma (10 years prior), laparoscopic cholecystectomy (17 years prior) | Elevated cholestasis enzymes for 24 years and 3 years of pruritus | AST: 77 IU/L<br>ALT: 85 IU/L<br>GGT: 534 IU/L<br>ALP: 621 IU/L<br>Total bilirubin: 4.0 mg/dL<br>Direct bilirubin: 3.5 mg/ dL<br>ASMA: negative<br>AMA: positive<br>anti-gp210: positive<br>anti-SP100: positive | MRCP: bile duct changes with multifocal strictures and segmental dilatation in the left liver and no dilations in the primary biliary ducts | Not listed | Not listed |
| Kingham *et al.*[31] | 72/F | Coronary artery disease and gastroesophageal reflux disease | Laparoscopic cholecystectomy due to symptomatic gallstones (2 years prior) | 2 years of abnormal liver function labs, xanthelasma, and modest hepatomegaly | Bilirubin: 37 μmol/L<br>ALP: 945 U/L<br>AST: 97 U/L<br>GGT: 752 U/L<br>AMA: titer 1:320<br>ANA: negative<br>ASMA: negative | Ultrasound: abnormal liver texture and mild intrahepatic and extrahepatic biliary dilation; ERCP 2 years after: extrahepatic biliary strictures, diffuse dilation and stricturing of intrahepatic ducts | UDCA 750 mg/daily started after abnormal ultrasound and labs | Improvement of liver enzymes with UDCA, but had recurring episodes of hepatic encephalopathy due to biliary sepsis requiring multiple endoscopic balloon dilation of extrahepatic biliary strictures. Died of liver failure 1.5 years post 1st ERCP |
| Kingham *et al.* [31] | 49/F | PBC diagnosed via liver biopsy and AMA titer 1:640, negative ANA and SMA (11 years prior) | CBD stone extraction via endoscopic sphincterotomy/ daughter with autoimmune hepatitis | Hepatomegaly and biliary pain recurrence | AMA: positive (1:640 titer)<br>ASMA: negative<br>ANA: negative | ERCP: irregularities in the intrahepatic duct suggestive of PSC | Not listed | 5 years after diagnosis patient had clinical, biochemical, and autoantibody profile suggestive of autoimmune hepatitis; ERCP demonstrated diffuse stricturing and dilatation of intrahepatic bile ducts; remission with prednisolone 5 mg and azathioprine 100 mg per day |

(*continued*)

**Table 2.** (*continued*)

| Author | Age/ Sex | Past medical history | Surgical/Family history | Presentation | Laboratory values | Liver biopsy/ERCP/ MRCP/US | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|
| Mandolesi *et al.*[30] | 66/F | None | None | Fatigue, pruritus, and abnormal hepatic enzymes for 1 year | AST: 181 IU/L<br>ALT: 171 IU/L<br>GGT: 91 IU/L<br>ALP: 440 IU/L<br>Bilirubin: 0.43 mg/dL<br>ANA: titer 1/640 with speckled and multiple nuclear dots pattern<br>AMA titer: 1:80 positive<br>anti-Sp-100: positive<br>ASMA: slight positivity | Liver biopsy: no significant fibrosis, there was evidence of ductular proliferations, no evidence of portal and lobular granulomas<br>MRCP: intrahepatic bile ducts with irregular profiles and slight concentric wall thickening without a dominant stricture<br>MRCP (2 years after): development of a dominant stricture on the bile duct in the 4th liver segment MRCP (5 years after): unchanged | UDCA 20 mg/kg/day | Improvement of LFTs after 1 year of UDCA treatment with decrease of AST, ALT, GGT, and ALP; 5-year follow-up demonstrated stability of disease and no signs of decompensated liver disease |
| Burak *et al.*[3] | 40/F | Not listed | Laparoscopic cholecystectomy due to symptomatic gallstones (2 years prior) and normal ERCP | Fevers and right upper quadrant pain and elevated liver enzymes | ANA: titer 1:1280<br>ASMA: negative<br>+ antibodies to PDC-E2 and OGDC-E2 | ERCP (3 months after): irregular narrowing and dilatation of the central intrahepatic and proximal extrahepatic ducts liver biopsy (6 months after): portal tracts expanded by fibrosis and an inflammatory infiltrate; Bile duct destruction and cholestasis without "onion-skinning" fibrosis or granulomata | UDCA 750 mg/day | Repeat liver biopsy and ERCP due to recurrent bouts of ascending cholangitis and elevated liver enzymes 2 years after showed features consistent with PSC including a dominant stricture; consideration for liver transplantation |
| Rubel *et al.*[43] | 52/M | Peptic ulcer disease, chronic cholestatic hepatic disease, rheumatic heart disease, congestive heart failure, hypertension, coronary heart disease | None | Pruritis, skin pigmentation, 8 years of intermittent episodes of right upper quadrant pain | AST: 177 mU/mL<br>ALT: 95 mU/mL<br>GGT: 1.9 g/dL<br>ALP: 1164 mU/mL<br>Bilirubin: 2.1 mg/dL<br>ANA: negative<br>AMA titer: 1:1280 | Percutaneous hepatic cholangiogram (7 years after): multiple strictures and dilations of intrahepatic biliary system creating a "beaded" appearance<br>liver biopsy (7 years after): absent interlobular bile ducts and basement membrane damage without evidence of periductal fibrosis | Not listed | Continued to have intermittent episodes of abdominal pain and pruritus and eventually died from cardiovascular disease 8 years after being diagnosed with PBC |

UDCA.[29] Mandolesia *et al.*[30] discussed a similar case of overlap, in which the patient was noted to fit the diagnostic criteria for PBC based on the immunologic, biochemical, and histological data. MRCP demonstrated slight irregularities; thus, the patient was treated with 20 mg/kg/day of UDCA for presumed PBC. Despite treatment, a repeat MRCP 2 years later demonstrated findings consistent with PSC. Burak *et al.*[3] also demonstrated a similar case, where repeat liver biopsy and ERCP demonstrated evolving evidence of PSC in a patient previously presumed to have PBC based on immunological, biochemical, histological, and ERCP findings. However, the case presented by Burak *et al.*[3] did not have positive PBC-specific markers, unlike the cases presented by Floreni *et al.*[29] and Mandolesia *et al.*[30] The second patient described by Floreni *et al.*[29] also had immunological and biochemical evidence of PBC. However, MRCP features, including multifocal strictures and segmental dilation, were more consistent with PSC.[29] The cases described by Sundaram[22] and Kingham *et al.*[31] also demonstrated patients with immunological, biochemical, and/or histological evidence meeting the diagnostic criteria of PBC. However, their MRCP findings were consistent with PSC.

## Treatment/prognosis

The first-line therapy for PBC treatment is the anticholestatic medication, UDCA.[6] This medication has a variety of beneficial effects, including anti-cholestatic, cytoprotective, anti-inflammatory and immunomodulatory effects which reduce the immune injury to biliary epithelial cells and ultimately slows disease progression.[6,23] Treatment of PBC with UDCA has been shown to have a beneficial effect on the histologic and biochemical disease progression. However, it has not been shown to improve survival outcomes.[45] Despite data collected over 16 randomized trials, with a total of 1,447 patients, the majority of trials were only conducted for an average of 2 years, which poses the concern of long-term effectiveness and side-effects of UDCA for PBC patients.[45] Each separate trial had a relatively small sample size, thus making the possibility of bias and random errors a concern.[45] This specific review, however, took these biases into account when analyzing data.[45]

With regards to dosing of UDCA in PBC patients, 14-16 mg/kg/day of UDCA for at least 2 years has demonstrated significant biochemical and histological improvements.[46] A randomized double-blinded study by Pares *et al.*[46] analyzed both biochemical and histological data with blood-work and liver biopsies, and to reduce bias, patients that were not compliant with 70% of the therapy were discontinued from the trial. Like many prior studies, that trial was only conducted for an average of 3.6 years, raising concern of the medication effectiveness after this short time span.[46] Angulo *et al.*[47] conducted another randomized trial demonstrating that UDCA doses of 13-15 mg/kg/day demonstrated the highest rates of biochemical improvement when compared to higher (23-25 mg/kg/day) and lower (5-7 mg/kg/day) doses.[47] One major drawback of the study was that it only followed patients at each dose for 2 years. It did not, however, include patients who were on UDCA 3 months prior to the initiation of the trial, which makes the observed effects more likely due to the assigned UDCA dose.[47] Despite this analysis, treatment with UDCA did not alter the time to death or transplantation.[46]

Until recently, studies have not been able to demonstrate a survival benefit from the treatment of PBC with UDCA. A study published by Harms *et al.*[48] analyzed 3,902 patients and demonstrated that patients treated with UDCA with complete biochemical resolution had a prolonged time to liver transplant in comparison to those not treated. The strength of that study lies in the number of patients studied. However, it was not a randomized control trial and most patients were assigned to the treatment group. That study also was not free of time-dependent bias as the initiation of disease cannot clearly be delineated. However, sub-group analysis based on the histological stage of disease at the time of initiation of the study showed that only 33% of patients were noted to have stage III and IV disease.[48]

The use of steroids for treatment of PBC has also been widely studied. In a trial conducted by Leuschner *et al.*,[49] 30 PBC patients received UDCA 10 mg/kg/day monotherapy verses the UDCA and 10 mg prednisolone for 9 months. Biochemical remission was achieved in both groups, though the time to histological and biochemical improvement was superior with dual therapy.[49] That study, however, did not have balanced arms and the patients with more progressive disease (higher stages) were assigned to the UDCA/prednisolone group, which decreased the reliability of the analysis.[49] Rautiainen *et al.*[50] demonstrated histological improvement with dual therapy of 6 mg/day budesonide and 15 mg/kg/day of UDCA over 3 years in comparison to monotherapy with UDCA. However, there was no statistically significant difference between the results in the arms.[50] Patients did not have a washout period prior to starting the medications studied in the trial, which could have impacted the results, specifically if a higher dose of UDCA was used. That study also included patients early in their disease course. Thus, extrapolation of data to patients at a later stage of the disease course is uncertain.[50] However, follow-up studies have shown a greater decrease in bone mineral density amongst these patients, which poses concern of the risk verses benefits of this treatment.[51] Longer term follow-up is needed to adequately study the effect of chronic steroids on patients with PBC.

Obeticholic acid (OCA) is another novel treatment used for PBC. It is a farnesoid X receptor agonist which alters the cycle of bile acid production, transportation, secretion, and metabolism.[52] Nevens *et al.*[53] conducted a phase III study of the use of OCA in 216 PBC patients, demonstrating a decrease in ALP and total bilirubin levels in comparison to levels detected in those who did not receive therapy. Despite these positive outcomes, data were only obtained after 2 years of treatment. There was also an increased dose-dependent incidence of pruritis noted among patients treated with OCA in comparison to those not treated.[53] Research regarding the use of fibrates, which affects bile acid homeostasis due to the activation of peroxisome proliferator activator receptor (PPAR), has yielded promising data.[54] In a 100 patient double-blinded study conducted by Corpechot *et al.*,[54] treatment with bezafibrate in addition UDCA demonstrated higher rates of decreased alkaline phosphatase and total bilirubin in comparison to those treated with only UDCA. Similar to the OCA study, that phase III trial was only conducted for 2 years and only a total of 50 patients received UDCA and fibrate therapy, which again raises concern about the long-term effectiveness of the drug.[54]

Despite the supporting evidence of the benefit of UDCA in the treatment of PBC, studies have not yet proven the effectiveness of UDCA for the treatment of PSC. Lindor *et al.*[55] studied 105 patients diagnosed with PSC in a

randomized double-blind study which compared the effectiveness of ursodiol 13-15 mg/kg/day in comparison to placebo. The authors demonstrated improvement in biochemical test results but no significant improvement in histology or symptoms.[38] That study spanned over three USA-based institutions. However, only bloodwork and patient surveys were used to assess the effectiveness of the drug. Endoscopy and ERCP was only conducted if clinically warranted.[55] Lindor *et al.*[56] conducted a similar study using a higher-dose of UDCA, 28–30 mg/kg/day, in a randomized double-blinded placebo-controlled trial conducted in seven sites across the USA and over 5 years. They showed a biochemical improvement, but the study was terminated due to disease progression. A daily dose of 20 mg/kg of UDCA for the treatment of PSC over a 2 year period was also studied and showed a significant improvement in biochemical and histological progression but did not show significant improvement in symptoms.[57] That study was double-blind and acquired a large amount of data, including biochemical, clinical, and histologic analysis.[57] Despite these strengths, it was a single center study, with only 26 patients who were followed for only 2 years, which raises concerns about the applicability to long-term progression of PSC, and the generalizability of the study.[57] A small 18-patient randomized double blinded study was performed by Van Hoogstraten *et al.*[58] to assess the effect of corticosteroid therapy (budesonide vs. prednisone) for the treatment of PSC.[54] That study, however, was only conducted for 8 weeks and in patients that were previously treated with UDCA; no significant biochemical changes were noted among the limited number of patients with short duration of follow-up.[58]

OCA and fibrates were studied in patients with PSC.[59,60] In a phase II 76-patient study conducted by Kowdley *et al.*,[59] 5-10 mg of OCA were reported to decrease ALP levels among PSC patients, similar to the results of Nevens *et al.*[53] from PBC patients. This study demonstrated the similar side-effect of dose-dependent pruritis. However, the total bilirubin levels were comparable to those of the placebo group.[59] That study consisted of 76 patients, containing three arms of 25-26 patients each, treated with varying doses of OCA.[59] Bezafibrate in combination with UDCA has also demonstrated significant biochemical improvement with decrease in ALP and GGT in comparison to those treated with only UDCA.[60] That study, however, consisted of a small cohort of 31 Japanese patients, of which the majority were female. That study also included only patients with early-stage PBC (Scheuer's classification I or II), which limits the generalizability of the data.[60]

PSC patients with symptoms of biliary obstruction, including jaundice, pruritus, abdominal pain, and rapid progression of liver enzymes, have a higher morbidity/mortality and benefit from endoscopic treatment. Studies have shown that ERCPs are potentially safe, with a complication rate of 2%; although, they do pose a higher rate of complications (14%) when dilation and stent placement were performed.[61] In a retrospective study of 286 PSC patients over a span of 9.9 years, it was shown that patients with dominant strictures who had regularly undergone endoscopic balloon dilations showed a significant benefit as fewer patients required liver transplants and patients required them after a longer period of time.[62]

For both PSC and PBC, liver transplantation is performed in patients with end-stage complications, including decompensated cirrhosis, liver failure, severe intractable pruritus, recurrent variceal bleeding, recurrent encephalopathy, or recurrent cholangitis.[63,64] Various studies have reported different rates of PSC and PBC recurrence post-liver transplant. These discrepancies may have been due to the fact that the diagnosis of recurrence was heavily based on liver biopsy interpretations.[64] In a retrospective study conducted by MacQuillan *et al.*[64] on 400 PBC patients who underwent liver transplantation, histological recurrence of PBC was found in 17% of the transplant patients, at a mean time of 36 months. Likewise, a study conducted by Graziadei *et al.*[65] followed 120 patients with PSC post-liver transplant for an average of 55 months and found that 20% had either cholangiographic or histologic evidence of recurrent PSC. Unfortunately, both studies only followed patients for an average of 56 months, which could underestimate the number of recurrences that may take a longer time to develop.

Studies have been conducted to determine the treatment of PSC and PBC as solitary disease states. However, due to the limited number of cases of overlap with no definitive diagnostic criteria, studies have not been conducted to determine adequate therapy. As most reports have addressed treatment of both disease states with UDCA, this was the medication predominantly used in the reviewed literature of PSC-PBC overlap.[23] Seven of the ten cases reviewed in the literature used UDCA in varying doses as a first-line treatment.[3,22,29,31,44] Of the seven patients treated with UDCA, three were treated with 750 mg/day, one was treated with 15 mg/kg/day (standard dose), one was treated with 20 mg/kg/day (high dose), and two did not have details on the dose used to treat. Patients treated with 750 mg/day did not have their weights detailed. However, if each female was approximately 50 kg, they were treated with a standard low dose of UDCA. Of these cases, five had improvement of liver enzymes, though the post-treatment follow-up time was limited and, thus, long-term benefits from treatment could not be deduced. Of the patients treated with UDCA, two of them were already being treated for PBC with UDCA prior to endoscopic evidence of PSC, suggesting that UDCA was not effective against the progression of PSC.[29,44] The patient treated with a high dose of UDCA did have biochemical remission with UDCA treatment but had recurring episodes of biliary stenosis requiring multiple endoscopic balloon dilation of extrahepatic biliary strictures; the patient ultimately died 1.5 years after diagnosis. This case poses the concern that higher doses of UDCA have more risk of long-term mortality, as postulated in the study by Lindor *et al.*[56] However, as this is only one case, there seems to be insufficient evidence in support of this. Though there have not been studies specifically on the use of biologics for PBC or PSC, Floreani *et al.*[29] used adalimumab and UDCA for treatment due to concurrent arthritis and showed positive results. However, it cannot be determined which medication was responsible. Despite the study demonstrating no benefit of corticosteroids for the treatment of PSC, the case reported by Kingham *et al.*[31] attained remission with prednisolone and azathioprine in a case of autoimmune hepatitis, PBC, and PSC overlap.[31] Due to the limited number of cases present in the literature, long-term follow-up of these patients has not been reported in the literature. The longest follow-ups have been reported as 5 years. Therefore, the long-term complication rates cannot be adequately assessed.[30,31] This raises uncertainty regarding the clinical progression of these overlap syndromes and their long-term prognosis.

## Discussion

PSC had been noted to appear in patients with previously diagnosed PBC. The timeline between the diagnosis of these two disease states was variable and in some instances was noted to range from as little as 3 months to as long as 18 years. Some cases were also concurrently diagnosed, as their biochemical and immunological characteristics were consistent with PBC, but histological characteristics were noted to be compatible with PSC. While the literature demonstrates a higher predominance of PSC in men and PBC in females, most overlap syndromes were found in females, ranging from 49-72 years-old. The cases demonstrated in the literature varied greatly in the clinical setting and time range between the diagnosis of the two disease states, from as little as 3 months to 18 years.

These overlap syndromes often present with similar symptoms and at times are even asymptomatic and incidentally found. Ultimately, MRCP remains the best non-invasive approach to determine if PSC overlap exists. Most cases were diagnosed as PBC based on biochemical and immunological characteristics. However, if imaging with ERCP/MRCP had not been done, most of these cases of overlap would have gone undiagnosed. As no standardized diagnostic work-up and management has been formulated, it is unclear if this is more prevalent than previously thought. It is possible that histologic data from biopsy could detect the presence of PSC before imaging characteristics appear. As the overlap syndrome of PSC and PBC is uncommon, this poses challenges as to the diagnostic guidelines, treatment regimens, and understanding the complications. It is important to be aware that development of a PSC overlap with extrahepatic ductal disease may be responsible for the sudden worsening in cholestasis in PBC patients previously responsive to UCDA, and that dominant strictures may be present that are amenable to endoscopic management.

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## Conflict of interest

The authors have no conflict of interests related to this publication.

## Author contributions

Wrote and revised the review article (SM), edited the review article (GYW).

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