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### Review Article

# Primary sclerosing cholangitis associated with inflammatory bowel disease

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### Abstract

Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic liver disease characterized by inflammation of the intra and extrahepatic bile ducts with progression to cirrhosis. To the present, the etiology of PSC is not known. Although it is possible to establish a correlation with a genetic predisposition, it is an autoimmune disease, associated with ulcerative colitis and Crohn's disease. There is no proven medical treatment that prolongs survival in PSC, being liver transplantation the only curative treatment, with recurrence of 20% of cases within the first five years after transplantation.

**Keywords:** autoimmunity, inflammatory bowel disease, primary sclerosing cholangitis, transplantation

### Introduction

Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic liver disease characterized by inflammation of the intra and extrahepatic bile ducts with progression to cirrhosis [1,2]. "Primary" defines a non-recurrent disorder, "sclerosing" is due to tissue hardening and "cholangitis" defines inflammation of the bile ducts [3].

Different from PSC, in secondary sclerosing cholangitis (SSC), biliary lesions occur due to a pathological process, such as cystic fibrosis, mechanical obstruction, or other [1,4]. Approximately 15% to 30% of individuals with PSC may develop cholangiocarcinoma. The association with intestinal diseases is observed in 70% to 100% of the cases [5,6].

The etiology of PSC remains unknown, but several mechanisms point to the involvement of the immune system. Among these mechanisms, is the strong association with HLA-B8, -DR3, -DR2, -Dw2, and especially -DRB1 [7]. It is considered an autoimmune disease since it is associated with ulcerative colitis and Crohn's disease [8].

The involvement of cellular immunity is related to the altered expression of potential autoantigens of the biliary epithelium and the presence of specific anti-cytoplasmic autoantibody of neutrophil with peri-nuclear pattern (pANCA) [9]. Studies indicate that PSC is associated with the targeted response of T lymphocytes, which destroy epithelial cells of the bile ducts. However, this association is not yet proven [8]. Hepatic transplantation is the only curative established treatment, with recurrence of 20% of cases within the first five years after transplantation [2,10].

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Primary sclerosing cholangitis is a challenging and sometimes devastating condition with significant heterogeneity of symptoms and complex genetic associations. However, the pathogenesis of PSC remains unclear, although the strong association with inflammatory bowel diseases (IBD) may be an important clue to the involvement of intestinal tissue in the etiology of the disease. Treatment options remain severely limited so far. The present article aims to describe the association of IBD in patients with PSC.

## Methodology

The methodology used was based on bibliographic research based on relevant articles related to the clinical treatment of PSC. The articles were considered in the context of the European Association for the Study of the Liver (EASL) and the practice guidelines of the American Association for the Study of Liver Diseases (AASLD), published from 2010 to 2017. About 75 articles were selected based on the keywords. We excluded the articles that did not focus primarily on PSC, mentioning other unrelated diseases or basic research articles and clinical cases. Forty articles were selected and included in the present review.

## Development

Although the first PSC report occurred more than a century ago, this disease is still considered rare in the medical community. PSC is a disease whose prevalence rate varies according to geographic location. The prevalence is estimated to be six cases per 100,000 inhabitants in Sweden and 2 to 7 per 100,000 people in the United States. In Brazil, this pathology is extremely rare, with an estimated one per 100,000 inhabitants (Table 1). This disease manifests preferentially in males in individuals from 30 and 40 years of age, but can reach women and children at any age [8].

**Table 1.** Prevalence of PSC

Country	Prevalence (per 100,000 inhabitants)
Brazil	1
Sweden	6
United States	7

Initial studies suggested that the average life expectancy of PSC patients from the diagnosis to death was 10 to 12 years. However, a more recent study in the Dutch population indicates an average life expectancy of 21 years [3]. The causes of death are varied, with hepatocarcinoma being the main cause (40-50%), followed by hepatic insufficiency (30-40%) [11].

Symptoms and histological characteristics of PSC (Table 2) are similar to those of autoimmune hepatitis, which may lead to a false diagnosis. The presence of biliary calculus, previously considered an exclusion criterion for the diagnosis of PSC, is now considered an important component of the disease. Portal hypertension is present in the advanced stage of the disease [1,12].

**Table 2.** Symptoms of PSC [1,12-14]

Main symptoms	Mean percentage of patients
Fatigue	69%
Pruritus or itch	59%
Jaundice	69%
Hepatosplenomegaly	69%
Asymptomatic patients	44%

## Diagnosis and Prognosis

The diagnosis of PSC is performed by cholangiography (endoscopic or transperietal), magnetic resonance imaging, liver biopsy and laboratory tests such as glutamic oxaloacetic transaminase and glutamic pyruvic transaminase, alkaline phosphatase, gamma-glutamyl transpeptidase, bilirubin, albumin, coagulation factors and lactate dehydrogenase among others [6,15-18].

## Treatment of PSC

There is no proven medical treatment that prolongs the survival of PSC patients [10]. Many immunosuppressant agents such as corticosteroids, methotrexate, thiopurine and tumor necrosis factor (TNF) have been tested with little success and with some cases of

induction of accelerated osteoporosis. Since 1990, ursodeoxycholic acid has been used, with beneficial effects on PSC patients. This drug reduces cholestatic liver enzymes, bilirubin and albumin, but do not prevent transplantation or disease progression [19]. However, higher doses of this drug have been associated with increased mortality, mainly related to colorectal cancer [20].

The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) do not support the use of ursodeoxycholic acid, although moderate doses are widely prescribed by hepatologists' worldwide. There is some evidence that ursodeoxycholic acid has a chemopreventive effect on the gut, although there are few retrospective studies [20]. Clinical trials with children have indicated an amelioration of patients using oral vancomycin and metronidazole, although these drugs are not indicated due to the association of microbiota with the etiology of the disease, raising the risk of gut syndrome [21].

For the treatment of specific symptoms such as pruritus, bile sequestrants such as cholestyramine or colesevelam may be used. Pruritus resolves instantly after transplantation due to decreased bilirubin levels. There is no effective treatment for fatigue [22].

Although it can have improved symptoms in some patients, surgery of the bile duct can lead to sepsis and become liver transplantation inadequate. Previous surgeries augment the risk during transplantation, increasing operative time and prognostic complications [23]. However, in some cases of choledochal stenosis, the use of bile prostheses or removal of stones, since dilatations may alleviate the symptoms [24,25].

Endoscopy with cytological analysis is mandatory to exclude the risk of cholangiocarcinoma. Hepatic transplantation is established as the only curative treatment, with recurrence of 20% of cases within the first five years after transplantation [10].

### Pathogenesis

The pathogenesis of PSC is not fully understood. However, several mechanisms have been proposed, including deregulation of immunological signaling, an increase of toxins in the liver, damage caused by bile acids, among others [26]. All of these mechanisms are associated with the genome and gene loci associated with the risk, in particular with genes of the human leukocyte antigen (HLA), located on chromosome 6, especially HLA-DRB1 and HLA -B8 [27].

People with a first degree relative with PSC have an increased risk by 9-39 times of developing the disease [26]. More than 15 gene loci were identified, including the gene encoding the enzyme  $\alpha$  (1,2) fucosyltransferase (alpha glucosyltransferase genes (1,2) - fucosyltransferase, FUT2), interleukin (IL) -2 and its receptor (IL-2RA) as well as macrophage stimulating genes (MST-1) [10].

Research suggests an accumulation of C-C9 chemokine receptor (CC chemokine receptor type 9, CCR9) in liver tissue of patients with PSC but not in healthy patients or in patients with other liver diseases. Also, it is reported the involvement of chemokine (CC motif) ligand 25 (CCL25), which is a chemokine receptor expressed in the intestinal epithelium, in non-inflammatory conditions, associated to T and B lymphocyte recruitment [17,18].

Other etiological models have been studied, such as the toxic effect of bile acid on the damaged biliary epithelium and the "leaky gut" theory where pre-existing inflammatory bowel disease predisposes to increased intestinal wall permeability and, therefore, increased exposure bile ducts for bacteria and other pathogenic agents and toxins [2].

### Associations with Intestinal Inflammatory Diseases

The association of PSC with ulcerative colitis (RCU) is also debated. This association was studied by some authors, with several reports of cases associating RCU to liver diseases [28,29]. However, the PSC association with colitis was only accepted after the publication of a series of 42 cases of PSC, where 12 patients had ulcerative colitis [30]. The histological nomenclature was standardized and Chapman and colleagues [15] and Wiesner and colleagues [31] detailed the clinical and pathological characteristics of the PSC, such as predominance in male, variable clinical course and elevated IgM production and also the identification of asymptomatic patients.

It is known that the immune system in the gut and liver is intimately connected and the drainage of the intestine flows through the hepatic tissue. This close relationship can explain the extra-intestinal tissue effects over the liver [32]. A hypothesis to explain the association between PSC and IBD is that intestinal mucosa effector cells are recruited into the liver in response to augmented endothelial expression of adhesion molecules, generally restricted to the intestine. It was reported a high expression of CCL25 and of mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in the inflamed liver of PSC patients [2].

Also, it is known that PSC associated with Crohn's disease has been less severe than PSC coexisting with ulcerative colitis. Recent studies suggest that colectomy is associated with a decreased risk of recurrent PSC following liver transplantation, challenging the traditional idea that PSC and IBD evolve independently. However, further research is necessary to characterize the protective role of colectomy in post-transplant PSC. Although much on the intestinal liver axis in PSC-IBD remains poorly understood, IBD associated with PSC has a unique phenotype, with subclinical inflammation [13,14].

## Malignity Associated with PSC

Malignancy is common in patients with PSC, occurring in 25% of patients. The main type of malignant tumor is colorectal cancer [33], an occurrence that supports the annual colonoscopy for PSC patients. Cholangiocarcinoma is also a major concern since most transplant centers consider this diagnosis a contraindication for transplantation. The survival rate in these cases is reduced [11]. Also, gallbladder cancer can be present between 2% and 3% of patients with PSC, indicating the annual screening with ultrasound [1,7,34].

## Final Considerations

PSC is a chronic cholestatic liver disease, progressive and that can lead to the development of biliary cirrhosis and its complications. Although PSC has been documented in the literature for more than a century, there are only sparse details about the genetic factors associated with pathogenesis. The strong link between RCU and PSC suggests that the pathogenesis of PSC involves intestinal tissue, including altered intestinal microbiota and aberrant activation of mucosal lymphocytes.

Little is known about the successful approach to treatment. Despite the supposed autoimmune etiology of the disease, a clear benefit of immunosuppressive agents has not yet been demonstrated and its use may be limited by side effects. Currently, liver transplantation is the only therapy that prolongs the life of patients with a terminal disease, but relapse of the disease can occur.

More studies are needed to develop an optimal therapeutic strategy to reduce the incidence of complications of the disease as well as to evaluate the real need for transplantation and to extend the patients' life expectancy. Although the knowledge about this pathology has advanced in the last decades, there is still much to be researched about the disease, its mechanisms and especially the therapies for its treatment.

## Conflict of interest

The authors declare no conflict of interest.

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