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Clinically oriented look into diagnostics and therapy of primary sclerosing cholangitis. Review of literature

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ABSTRACT

Introduction: Primary sclerosing cholangitis (PSC) is a complex liver disorder marked by multifocal bile duct strictures and dilatations, leading to cholestasis and liver fibrosis. Although the exact cause is unknown, autoimmune mechanisms are strongly suspected.

Aim of the Study: This paper reviews current knowledge on PSC, covering its etiology, prevalence, treatment options, and practical management strategies.

Current State of Knowledge: PSC management focuses on symptom relief and liver transplantation, with limited success in pharmacological treatments. New therapies, including immune modulators and anti-fibrotic agents, show promise but require further research. Liver transplantation remains the most effective treatment, though recurrence risks necessitate ongoing monitoring.

Materials and Methods: This article reviews the current understanding of PSC, including its pathophysiology, diagnostic approaches, clinical features, and management strategies. A comprehensive literature search was conducted using PubMed and Google Scholar, with articles selected based on relevant keywords and evaluated for inclusion in this review.

Conclusions: Effective management of PSC necessitates a multidisciplinary approach involving hepatologists, gastroenterologists, radiologists, and transplant surgeons. Ongoing

efforts to better understand PSC's pathogenesis, refine diagnostic methods, and develop more effective therapies are crucial for improving patient outcomes.

KEYWORDS: Primary Sclerosing Cholangitis; Bile Duct Disease; Pharmacotherapy; Hepatic Failure

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a hepatobiliary disease marked by the presence of multifocal strictures and dilatations, resulting in cholestasis affecting both extra- and intrahepatic bile ducts [1] . In the majority of cases, the disease's distinctive clinical presentation obviates the necessity for biopsy in its diagnosis. However, biopsies become crucial when identifying specific PSC variants, influencing the overall prognosis [2] . The natural course of PSC unfolds with the progression of biliary liver fibrosis, culminating in end-stage cirrhosis, ultimately necessitating liver transplantation (LT). Notably, the median transplantation-free survival period for adults post-diagnosis is documented at 14.5 years. In contrast, a noteworthy 30% of children require transplantation within a decade of the initial diagnosis [3] . Despite extensive research, the etiology of PSC remains unknown [1] . Current understanding leans towards a connection with autoimmune reactions in its pathogenesis. Notably, immunosuppressive therapy has not demonstrated efficacy, leading to the absence of a standardized medical treatment for PSC. Consequently, the long-term outlook for individuals with PSC remains unfavorable, characterized by a notably high mortality rate. For individuals at an advanced stage of PSC, liver transplantation emerges as the sole viable option for recovery[4].

EPIDEMIOLOGY, PREVALENCE AND COEXISTENCE

Primary sclerosing cholangitis (PSC) presents itself as a rare disease, with prevalence rates ranging from 0 to 16 per 100,000 adults and 1.5 per 100,000 children [3] . The exact prevalence varies among adult populations, notably demonstrating dissimilarities such as 16.2

per 100,000 in Northern Europe and North America, in contrast to 0.95 per 100,000 in Japan. While an apparent surge in prevalence has been noted in European countries, discerning whether this reflects an actual increase or stems from enhanced diagnostic capabilities remains an ongoing challenge. In Western nations, a notable trend of male dominance persists[4], with over 60% of PSC patients globally being males. The median age at diagnosis typically spans from 30 to 40 years[2]. Strikingly, an intriguing correlation emerges between PSC and inflammatory bowel disease (IBD), where approximately 70% of PSC patients also receive an IBD diagnosis. This association is markedly asymmetrical, as only 5% of IBD patients concurrently grapple with PSC. Among IBD cases, ulcerative colitis (UC) tends to exhibit a more prevalent connection with PSC compared to Crohn's disease (CD) [5] . The coexistence of PSC within the IBD population serves as a singular predictor of premature mortality. PSC carries a substantial burden of associated risks, including a 20%-30% lifetime likelihood of colorectal malignancy, a risk four times higher than colitis itself without PSC. Additionally, PSC is intricately linked with hepatobiliary malignancies, particularly cholangiocarcinoma, boasting a lifetime risk of 20% and an unfavorable prognosis. The increased risk of cancer-related mortality extends even to the pediatric population grappling with PSC[3].

PATHOGENESIS

The picture of PSC consists of a multifocally occurring inflammatory process and fibrosis within intra- and extrahepatic bile ducts, leading to secondary dilation of segments unaffected by inflammation[6]. However, the exact pathogenesis, as is often the case with autoimmune diseases, remains not fully understood. Nevertheless, it is certainly a disease in which autoantibodies play an important role in causing cholangiocyte damage, especially in individuals with genetic predispositions[7].

Although the MRI image of the bile ducts in PSC is characteristic, the histopathological image - fibrosis of the bile ducts in a concentric pattern, the so-called "onion skin" pattern, is a common final image of epithelial damage of the bile ducts caused by various factors, including toxic damage or chronic mechanical injuries.

Currently, several models of PSC pathogenesis coexist. This does not mean that they exclude each other, but rather that they may complement each other. It is worth mentioning that patients with a history of *ulcerative colitis* are particularly prone to developing PSC.

One of the previously mentioned models of PSC pathogenesis suggests the process of migration of T lymphocytes from the damaged intestinal mucosa in patients with *ulcerative colitis* to the liver, where cross-reaction with bile duct antigens occurs.

The influence of HLA polymorphisms would also be significant here, and consequently, the adaptive immune response in terms of antigen presentation to the T lymphocytes through TCR. Some studies also indicate the presence of different clones of TCR receptors in the liver of patients with PSC, but their specificity for this disease has not been confirmed.

Another proposition seems to be the process of passive leakage of pro-inflammatory microbial components (e.g. LPS) into the portal circulation, overlapping with the toxicity of bile acids, which together initiates an autoimmune response.

Also worth mentioning is the observed change in gut microbiota in patients with PSC compared to the healthy population. Although it is not entirely clear whether this is a primary phenomenon or secondary to the development of the disease, its primary nature is postulated, which would complement the set of PSC pathogenesis models[8].

SIGNS, SYMPTOMS AND DIAGNOSTICS

PSC (Primary Sclerosing Cholangitis) most commonly affects men aged 30-40, but anyone can develop it [9] . Half of the individuals are diagnosed incidentally when a cholestatic pattern of liver function tests is observed. Among symptomatic patients, the most common symptoms include hepatomegaly (44%), and splenomegaly (39%). Right upper quadrant abdominal pain (20%) and itching (10%) are also prevalent. Weight loss, recurrent inflammations of the bile ducts, jaundice (6%) and fatigue (6%) are also common[10].

It has been observed that certain symptoms are more pronounced when accompanied by another autoimmune disease. Fatigue is more severe and more frequently seen in patients with Inflammatory Bowel Disease (IBD) compared to patients without this condition. Symptoms of autonomic dysfunction, such as orthostatic hypotension, vasomotor functions, secretomotor functions, gastrointestinal functions, bladder functions, and pupillomotor functions, are more commonly present than in the control population. The level of fatigue experienced by PSC patients correlates directly with the severity of autonomic dysfunction symptoms.

In patients with Primary Sclerosing Cholangitis (PSC) after liver transplantation, it has been noted that the median fatigue score improves; however, fatigue persists in one-third of the patients. Improvement in perceived fatigue is more significant in men than in women[11].

It should be noted that laboratory test results may be normal, especially in the early stages of the disease; however, certain deviations may raise suspicion of Primary Sclerosing Cholangitis (PSC). In laboratory tests, an increase in serum alkaline phosphatase activity,

which is a characteristic feature, may be noted. Elevated levels of aspartate transaminase and alanine transaminase can be up to 2-3 times the upper limit of normal. Bilirubin and albumin levels may initially be within the normal range but become increasingly abnormal as the disease progresses. Elevated serum bilirubin levels suggests the possibility of advanced disease, liver cirrhosis, or dominant biliary strictures.

Atypical perinuclear antineutrophil cytoplasmic antibodies are positive in about 26% to 94% of patients with Primary Sclerosing Cholangitis (PSC), although they are not specific to this disease. Elevated concentrations of total immunoglobulins (IgM in 50%) may be observed. Positive antinuclear antibodies and smooth muscle antibodies should alert clinicians to the possibility of autoimmune hepatitis-related PSC or overlap syndromes. Elevation of immunoglobulin subsets (IgG4 in 10%) may also occur. Elevated serum IgG4 levels are not specific to IgG4-related diseases. Serum IgG4 levels exceeding four times the upper limit of normal and/or an IgG4:IgG1 ratio greater than 0.24 strongly suggest IgG4-associated Primary Sclerosing Cholangitis[12].

70% of patients with Primary Sclerosing Cholangitis (PSC) also suffer from inflammatory bowel disease (IBD), most typically ulcerative colitis, which may serve as a negative prognostic factor for the risk of carcinogenesis and liver diseases [5] . Only about 5% of patients with IBD suffer also from PSC. The mean age of diagnosis of PSC in the PSC-IBD group was 37 years compared with 48 years in the PSC-only group[13].

The epidemiology may vary depending on the region, but in Europe, North America, and Australia, the results are consistent. In the Korean population, it has been observed that over time, there is a cumulatively increased likelihood of developing PSC after the diagnosis of IBD. In the first 5 years, the probability of PSC-UC was around 0.71% (significantly lower compared to Western countries), 2.59% after 15 years, and 3.35% after 20-25 years[13].

To a lesser extent, PSC is associated with autoimmune thyroid diseases, sarcoidosis, and psoriasis. The most frequent autoimmune diseases were psoriasis (3.6%), autoimmune thyroiditis (2.6%), sarcoidosis (2.1%), and diabetes mellitus type 1(2.1%). Other autoimmune diseases include celiac disease (1.0%), autoimmune anemia (1.0%), vitiligo (0.5%), Sjogren syndrome (0.5%), autoimmune thrombocytopaenia, and ankylosing spondylitis (both 0.5%)[14].

Types of PSC

There are two types of PSC distinguished: Small Duct PSC (sdPSC), which has a better prognosis and involves small bile ducts. When it affects ducts with a diameter up to 400 nm, it

is not detectable in MRCP or ERCP Patients with small-duct disease typically have better prognoses than those with the classic form of the disease. Furthermore, patients who have Primary Sclerosing Cholangitis without inflammatory bowel disease may have a different subtype than those with PSC and concurrent inflammatory bowel disease. Nevertheless, determining whether this combination is more than a coincidence is challenging, as inflammatory bowel disease may develop years after the diagnosis of Primary Sclerosing Cholangitis and may even occur after liver transplantation[15].

However, indirect imaging findings have been described (periductal enhancement, periportal lymphadenopathy, heterogeneous parenchymal signal intensity, gallbladder dilatation, and inhomogeneous liver enhancement) that may suggest this diagnosis [16] . Large Duct PSC affects larger bile ducts and is associated with a higher risk of malignancy [5] . SdPSC can progress to large duct PSC, occurring in 33-55% of cases[16,17].

In the diagnosis, one must not forget about the overlap syndrome with autoimmune hepatitis (PSC-AIH), which is confirmed by histology. PSC-AIH occurs more frequently in young patients and responds to immunosuppressive treatment, resulting in a better prognosis. An elevation in serum transaminases, high titers of antinuclear antibodies (ANA) or anti-smooth muscle antibodies (ASMA) (>1:40), and elevated levels of IgG should raise suspicion of autoimmune hepatitis. Typically, syndromes involving both PSC and AIH tend to present with features of AIH first, and the diagnosis of PSC occurs several years later in some cases[18].

Primary Sclerosing Cholangitis (PSC) and Primary Biliary Cirrhosis (PBC) are slowly progressive chronic cholestatic diseases that can ultimately cause cirrhosis and liver failure, generally over many years. Although both diseases cause damage to the bile ducts, 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. In the majority of cases, these criteria are sufficient to make the correct diagnosis. Most overlap syndromes were found in females, ranging from 49-72 years old.

Theories regarding the pathogenesis of PSC include autoimmune, inflammatory, and immunological recurring damage to biliary ducts, likely modulated by genetic and environmental factors. However, rarely, cases have been reported in which there are features of more than a single autoimmune entity, including autoimmune hepatitis, PBC, or PSC. In

particular, Primary Sclerosing Cholangitis-and-Primary Biliary Cirrhosis (PSC-PBC) overlap cases have been reported, albeit rarely. 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[19].

Imaging

In MRCP and ERCP, beaded bile ducts are usually present both extrahepatically and intrahepatically, although only intrahepatic (15-25%) or only extrahepatic involvement (5-10%) may occur. Initially, MRCPmay reveal subtle dilations of small ducts at the periphery of the liver, and in advanced stages, changes may be well visualized in ultrasound as segmental ductal dilations, thickening of the walls, and echogenic portal triads. Magnetic Resonance Imaging (MRI/MRCP) is the diagnostic test of choice for detecting large-duct PSC. MRCP combined with abdominal MRI (MRI/MRCP) has the advantage of visualizing not only the bile duct lumen but also the duct wall, liver parenchyma, and extrahepatic abdominal structures. In T2-weighted (T2W) and diffusion-weighted imaging (DWI), parenchymal hyperintensity and periportal T2 hyperintensity can be observed in patients with PSC. Increased hepatic parenchymal enhancement, predominantly in the periphery of the liver and in areas of regional atrophy, early peribiliary enhancement, and delayed parenchymal enhancement have also been observed. These imaging findings likely correspond to focal or zonal areas of fibrosis and/or inflammation. There are no specific reports describing the imaging findings of Small Duct Primary Sclerosing Cholangitis (SD-PSC), except for a study using MR elastography, which showed no significant difference in liver stiffness between Large Duct PSC (LD-PSC) and SD-PSC[15].

Risk of Cancer

The pathophysiology of cholangiocarcinoma (CCA) development in the context of Primary Sclerosing Cholangitis involves inflammation-driven carcinogenesis concomitant with various genetic and epigenetic abnormalities, serving as underlying factors. PSC is associated with a significantly increased risk of cholangiocarcinoma, estimated to be 40 times higher than in the general population. The cumulative 5-year and 10-year risks after PSC diagnosis,

and the lifetime risk of developing CCA, are estimated to be 7%, 8–11%, and 9–20%, respectively.

Nevertheless, a consistent finding in many studies is the higher frequency of cholangiocarcinoma occurrence within the first 2 years after the primary diagnosis of primary sclerosing cholangitis. Importantly, a substantial percentage of cholangiocarcinoma cases (around 30–50%) are observed within the first year following the diagnosis of primary sclerosing cholangitis.

Symptoms associated with bile duct cancer related to PSC include jaundice, pain, cholangitis, fatigue, pruritus, weight loss, ascites, hepatomegaly, splenomegaly, and abnormal liver laboratory tests. These symptoms often occur in PSC patients, making them less specific for the presence of CCA. Nevertheless, a sudden worsening of these symptoms, especially abnormal liver biology, is more indicative of bile duct cancer[18]. There is also an elevated risk of gallbladder carcinoma, hepatocellular carcinoma (HCC), and pancreatic cancer[20].

Differentiation of PSC

It is important to differentiate PSC from IgG4-related sclerosing cholangitis, which can be challenging because PSC can also present with increased IgG4 levels (PSC-increased IgG4). Epidemiology can aid in the differentiation, as IgG4-related sclerosing cholangitis typically occurs in individuals over 60
years of age. Additionally, there may be elevated IgG4 levels, and other organs such as the pancreas and salivary glands may be involved. The prognosis for IgG4-related sclerosing cholangitis is generally favorable. Unlike cases of PSC, PSC with increased IgG4 levels, glucocorticoids show very good results in the treatment of IgG4-related SC. In any differential diagnosis between PSC and PSC-increased IgG4, high levels of IgG1 and low or normal levels of IgG2 are characteristic for patients with PSC[5].

If other infectious, ischemic, toxic, or inflammatory causes of bile duct narrowing have been identified, the diagnosis may appear to be secondary sclerosing cholangitis (SSC). Symptoms of SSC may similar to those of PSC, including asymptomatic laboratory abnormalities, symptoms related to bile duct obstruction such as jaundice and pruritus, as well as features of active cholangitis, such as pain in the right upper quadrant of the abdomen and fever. Even if

a specific diagnosis cannot be made based on imaging alone, the etiology of SSC can usually be identified clinically[21].

TREATMENT

The most common form of PSC is classic "large duct" PSC - it accounts for 90% of cases. The remaining 10% are "small duct" PSC - with a slower progression of the disease, better prognosis, a lower risk of cholangiocarcinoma[22], and later cirrhosis. Unfortunately, the only effective therapeutic option in the late stage of the disease remains liver transplantation. Nevertheless, symptomatic treatment remains a matter of consideration, and ongoing efforts are being made to develop drugs that can modify the course of the disease. Procedural treatment is also in use[23].

The most important strategies used in pharmacological treatment include: 1) bile composition modifiers (UDCA, nor-UDCA, obeticholic acid, Cilofexor), 2) immune response modulators (Aldafermin, Vedolizumab), 3) anti-fibrotic drugs (statins, simtuzumab, setanaxib), 4) drugs modifying the microbiome of the bile ducts (e.g., antibiotics, fecal transplants)[1].

As mentioned in the Introduction, there is still no standard, approved medical treatment known to affect the natural history of PSC, and the only widespread drug that is the Ursodeoxycholic acid (UDCA) lacks documented efficacy[23].

The most promising drugs currently undergoing clinical trials include norursodeoxycholic acid, obeticholic acid, Cilofexor (a non-steroidal FXR agonist), and Aldafermin - a synthetic analogue of FGF-19. There is also some hope, especially in children, with the use of vancomycin, but adequate research on its efficacy is still lacking. Additionally, a decreased level of ALP has been observed in patients with IBD/PSC receiving adalimumab, but more data is needed to assess the usefulness of this drug[23].

As for procedural treatment, ERCP with balloon dilation and stenting is the dominant approach. It is used in the presence of dominant strictures, and due to the lower adverse effect rate, balloon dilatation is the first-line treatment for patients with dominant strictures. Endoscopic stent placement is reserved for selected patients and is not routinely undertaken. Endoscopic treatment allows for a rapid improvement in symptoms such as jaundice, cholangitis, and pruritus. It is also important to note the significant role that ERCP plays in the diagnosis of PSC.

The last line of treatment remains liver transplantation, and it is currently the only known method that affects the natural history of PSC. Liver transplantation prolongs the survival of a recipient by more than 10 years in 70–80% of cases[1], although it is important to note the possibility of recurrence after transplantation, especially in patients under 40 years old[23]. In general, around 20%, recurrent PSC (rePSC) occurs in less than 5 years after liver transplantation, negatively impacting patient survival[1].

Various prognostic scores have been developed until the recent past to adequately predict the individual prognosis for patients with PSC.

The best known one are Mayo risk score, Amsterdam-Oxford score and the Primary sclerosing cholangitis risk estimate tool (PREsTo). Prognostic scores vary from each other but have some parameters in common such as a level of bilirubin, albumin and aspartate transaminase.

CONCLUSION

Primary sclerosing cholangitis (PSC) remains a challenging hepatobiliary disease characterized by multifocal strictures and dilatations of the bile ducts, leading to cholestasis and liver fibrosis. Despite extensive research, the aetiology of PSC remains elusive, with current understanding suggesting autoimmune mechanisms. Diagnosis is often challenging, requiring a combination of clinical, serologic, imaging, and histologic findings. PSC commonly coexists with inflammatory bowel disease (IBD), further complicating its clinical course and prognosis.

However a number of drugs is in clinical trials, we still lack effective treatment options and further research is necessary to establish the efficacy and safety of these treatments.

Prognosis in PSC varies widely, influenced by factors such as disease severity, presence of complications, and response to therapy. Prognostic scoring systems aid in predicting individual outcomes and guiding clinical management. Liver transplantation remains the definitive treatment for end-stage PSC, providing significant improvements in survival, although the risk of disease recurrence post-transplantation underscores the need for ongoing monitoring and research in this field.

Overall, the management of PSC requires a multidisciplinary approach involving hepatologists, gastroenterologists, radiologists, and transplant surgeons. Continued efforts in understanding the pathogenesis, refining diagnostic techniques, and developing effective therapies are essential in improving outcomes for patients with PSC.

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