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Pathophysiology, Diagnosis and Management of Primary Sclerosing Cholangitis

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Abstract

Primary sclerosing cholangitis is a chronic inflammatory disease described by cholestasis and progressive stricturing and destruction of the intrahepatic and extrahepatic biliary tree. There is growing evidence suggesting the involvement of multiple genetic, environmental, microbiological and particularly autoimmune factors contributing to disease development. Primary sclerosing cholangitis is described by the interplay of inflammation, fibrosis, and cholestasis. A cholestatic picture of liver function with an elevation in serum alkaline phosphatase level is the biochemical hallmark of primary sclerosing cholangitis, although certain patients perhaps have normal alkaline phosphatase levels. Effective medical treatment of primary sclerosing cholangitis has been inhibited by uncertainty regarding the pathogenesis of the disease and the factors responsible for its progression. Ursodeoxycholic acid is a hydrophilic bile acid which, in moderate doses, is thought to exert its mechanisms of action chiefly through protective effects on cholangiocytes by decreasing hydrophobicity and toxicity of bile via the stimulation of hepatobiliary synthesis, and a direct effect on adaptive immunity e.g. by preventing dendritic cells.

Introduction

Primary sclerosing cholangitis is a chronic cholestatic liver disease described by intrahepatic or extrahepatic (or both) bile duct damage (Wilde et al., 2022). PSC can occur in association with autoimmune diseases such as autoimmune hepatitis and autoimmune pancreatitis; frequently referred to as the PSC overlap syndromes (Dyson et al., 2018). PSC is a chronic liver disease initially affecting the bile ducts, but as the disease progresses, liver fibrosis and cirrhosis perhaps advance (Laborda et al., 2019). PSC occurs more frequently in men than in women (2:1). The mean age at the time of diagnosis is approximately 40 years (Bossen et al., 2021).

Risk Factors

There is growing evidence suggesting the involvement of multiple genetic, environmental, microbiological and particularly autoimmune factors contributing to disease advancement. The etiology of PSC is complex and includes both genetic and environmental factors. Genetic risk factors in multifactorial diseases by means of genome-wide association studies have shown an unprecedented insight into molecular factors of importance for disease development. The heritability of PSC is in the identical range as for multiple of the autoinflammatory circumstances that have been studied so far (relative risk in siblings approximately 10 times that of the overall population), and in a current genome-wide association study in PSC a genetic architecture typical for such situations was also observed (Lindor et al., 2019; Banales et al., 2019; Strazzabosco et al., 2018). The most robust resulting was the associations within the HLA complex on chromosome 6p21, but additional susceptibility loci at chromosomes 2q35, 3p21 and 13q31 were also detectable. When compared to IBD, the HLA resulting seem to be specific for PSC. Many abnormalities along the "gut-liver axis" have been identified involving defects in: immune regulation, hepatobiliary protection mechanisms, bile acid metabolism, microbiome and intestinal permeability. Patients undergo a variable progression through hepatobiliary fibrosis, cirrhosis, and end-stage liver disease (ESLD) with a greatly elevated risk for cholangiocarcinoma (CCA) (Trampert et al., 2021; Musayeva et al., 2021). Biliary fibrosis obstructs bile flow, which results in accumulation of "toxic bile" in the liver; this is thought to be a major contributor to the pathogenesis of this disease (Greverath et al., 2020).

Pathophysiology

Primary sclerosing cholangitis is described by the interplay of inflammation, fibrosis, and cholestasis. The typical fibrosing cholangitis with irregular narrowing and scarring of the biliary tree is likely, in light of genetic associations, immune-mediated and triggered by HLA-restricted T cells leading to release of

profibrogenic cytokines (eg, transforming growth factor β). To what extent other immune cells, such as natural killer cells and natural killer T cells, play a function is largely unfamiliar. Inflammation and fibrosis lead to cholestasis and parenchymal damage. Biliary obstruction might facilitate cholangitis. Although primary sclerosing cholangitis in its early stages might be chiefly autoimmune mediated, superinfection perhaps represent a significant factor for disease progression. Therefore, treating superinfection aggressively and dilating dominant strictures are probably to be effective management approaches, especially in developed disease. Cholestasis can become self-sustaining, with the toxic biliary milieu leading to a cycle of progressive damage. The importance of the cholestatic process is indicated by the putative primary sclerosing cholangitis susceptibility genes encoding the apical bile salt receptor TGR5 (also known as GPBAR1) and the glycocalyx stabilising enzyme fucosyltransferase 2 (FUT2),30,44 which result in protection of cholangiocytes against potentially toxic bile acids such as glycochenodeoxycholic acid. Cholangiocytes are exposed to bile salt monomers at millimolar concentrations about 1000 times higher than other cells in the body. A so-called alkaline biliary bicarbonate umbrella on the cell surface might keep bile salt molecules in a negatively loaded state inhibiting protonation and uncontrolled invasion of polar bile acids into the cholangiocytes with subsequent cell injury and death (Durchschein et al., 2018; Mayer et al., 2020; Wilde et al., 2021; Goet et al., 2019; Feng et al., 2018).

Diagnostic Criteria

A diagnosis of PSC is made in patients with a cholestatic biochemical profile, when cholangiography (e.g., magnetic resonance cholangiography [MRC], endoscopic retrograde cholangiography [ERC], percutaneous transhepatic cholangiography) reveals characteristic bile duct alters with multifocal strictures and segmental dilatations, and secondary causes of sclerosing cholangitis have been excluded. Patients, who present with clinical, biochemical and histological features compatible with PSC, but have a normal cholangiogram, are categorized as small duct PSC (Hering et al., 2021; Ayers et al., 2022).

Biochemical features: A cholestatic picture of liver function with an elevation in serum alkaline phosphatase level is the biochemical hallmark of PSC, although certain patients perhaps have normal alkaline phosphatase levels. Elevates in serum aspartate and alanine aminotransferase levels are frequently only mild to moderate. Patients with PSC usually have fluctuations in bilirubin and alkaline phosphatase levels during the course of the disease (Wilde et al., 2022).

Radiographic features: Diagnostic features involve diffuse multifocal strictures, often including both the intrahepatic and extrahepatic ducts. Strictures are typically short and annular, alternating with normal or minimally dilated segments to generate a characteristic ‘beaded’ appearance (Banales et al., 2019).

Liver Histology: Typically, a liver biopsy is not required to diagnose PSC, unless small-duct PSC is suspected or if there are concerns that a patient also has AIH. Histologic features of PSC are usually nonspecific and prone to sampling variations, owing to the heterogeneous involvement of the biliary tree. Use of histologic analysis to determine the stage of liver fibrosis requires a specialized scoring system (Batts-Ludwig). However, noninvasive methods to ascertain fibrosis and cirrhosis, such as elastography imaging, are emerging as useful tools for subjects with PSC (Strazzabosco et al., 2018; Trampert et al., 2021).

Serological features: Recently, testing for specific autoimmune antibodies does not contribute to the diagnosis of PSC. Many autoantibodies can be detected in PSC. Antinuclear antibodies and smooth muscle antibodies can be resulted in 20% to 60% of patients, often in lower titres than those demonstrated in autoimmune hepatitis (Cabral-Marques & Riemekasten, 2017).

Imaging: Cholangiography is the best way to distinguish patients with PSC. The classic features involve multi-focal angular structuring within the intrahepatic and/or extrahepatic bile ducts, with alternating normal or slightly dilated segments. Typically there is diffuse involvement. However, up to 25% of individuals have only intrahepatic disease (Musayeva et al., 2021).

Pharmacological Treatment

Effective medical treatment of PSC has been blocked by uncertainty regarding the pathogenesis of the disease and the factors responsible for its progression (Greverath et al., 2020).

Ursodeoxycholic acid (UDCA): UDCA is a hydrophilic bile acid which, in moderate doses, is thought to exert its mechanisms of action chiefly through protective effects on cholangiocytes by decreasing hydrophobicity and toxicity of bile via the stimulation of hepatobiliary production, and a direct effect on adaptive immunity e.g. by preventing dendritic cells. Hydrophobic bile acids perhaps hepatotoxic and high concentrations available in PSC appear to be cytotoxic within the biliary tree. PSC patients perhaps lack an effective “bicarbonate umbrella” buffer layer between cholangiocytes and the biliary lumen, compounding this effect. UDCA is a hydrophilic bile acid with cytoprotective effects that is readily absorbed orally. UDCA elevates levels of hydrophilic bile acids in bile and reduces histocompatibility antigen display by hepatocytes. UDCA is effective for adults with primary biliary cholangitis, another immunemediated disease targeting bile ducts. Its function in PSC is controversial. Ursodeoxycholic acid, typically at moderate doses of 15–20 mg/kg daily, remains broadly used (Vesterhus & Karlsen, 2020; Aabakken et al., 2017; Bowlus et al., 2019).

Immunosuppressive agents: Immunosuppressive and biologic medications, independent of their effect on concomitant IBD or Autoimmune hepatitis (AIH), have not revealed a benefit for PSC. Small pilot trials have been performed in adult PSC patients with a variety of agents involving: Prednisone,

budesonide, methotrexate, mycophenolate mofetil, tacrolimus, infliximab, and etanercept, with none observing particular efficacy. When biologic agents are used to manage IBD in PSC-IBD patients, there is no benefit to the liver. Aspartate aminotransferase, alanine aminotransferase, bilirubin, elastography and cholangiography were not ameliorated on adalimumab, infliximab or vedolizumab in PSC-IBD patients. Of note, IBD patients without usual PSC who were treated with vedolizumab were more probably to advance PSC than those treated with anti-tumor necrosis factor agents, an effect that was especially pronounced in those with a crohn disease phenotype (Ali et al., 2018; Grimsrud & Folseraas, 2019). Ciclosporin prevents IL-2 transcription and hence T-cell response and possibly T regulatory cell production, while methotrexate exerts anti-inflammatory properties through inhibition of T-cell activation and adhesion molecule expression. Vedolizumab, a selective humanized monoclonal antibody to the a4b7 integrin expressed on lymphocytes; prevents gut lymphocyte trafficking through suppression of the binding of a4b7 integrin to MadCAM-1. In the bowel, this leads to decreased intestinal inflammation and induction of mucosal healing and vedolizumab has emerged as an effective treatment option in refractory IBD. Infliximab is a monoclonal antibody preventing TNF-a, frequently used in the treatment of severe IBD. In PSC, one small pilot study was conducted in which infliximab failed to observe any effect on ALP, histology or liver related symptoms (Chung et al., 2018).

Endoscopic therapy: Some patients present with clinical and biochemical deterioration, and exhibit a dominant stricture that includes the larger extrahepatic biliary ducts. The incidence of dominant strictures in patients with PSC has been estimated to be as high as 45% to 58%, whereas others have found a much lower frequency. Such lesions perhaps amenable to endoscopic or radiological dilation with or without a biliary drainage procedure, such as sphincterotomy and stenting. This leads to symptomatic, biochemical and radiographic improvement. The use of endobiliary stents in PSC has been associated with greater frequency of intervention-related complications involving acute cholangitis; balloon dilation alone is preferred in this population (Petersen et al., 2020; Dhillon et al., 2019; Liao et al., 2019; Strazzabosco et al., 2018).

Oral vancomycin therapy: PSC patients are familiar to have decreased bacterial diversity and microbiome profiles that are distinct from healthy controls and from patients with isolated IBD. Enterococcus, Fusobacterium and Lactobacillus species are over-represented in the stool of PSC patients. An operational taxonomic unit of the Enterococcus genus was associated with increased serum ALP levels, a disease severity marker in adult patients. Even the oral microbiome is abnormal in PSC, with dysbiosis revealed in the saliva. Because of this, several antimicrobial agents have been used and studied in the treatment of PSC involving rifaximin, tetracycline, minocycline and metronidazole, with mixed results (Ruhlemann et al., 2019; Nakamoto, et al., 2019). Vancomycin functions against gram positive bacteria by preventing cross-linking of cell wall substrates. When given orally, the medication has minimal systemic absorption. While the medication is potent against clostridium difficile and other gram positive organisms within the gastrointestinal tract, vancomycin may also act as an immunomodulator. OVT use in children with PSC was revealed to elevate transforming growth factor beta levels and peripheral T-regulatory cell counts. OVT is presently used in at least 7% of patients with PSC. Practice patterns at different centers vary broadly. Most frequently OVT is reserved for select patients with persistently increased biochemical markers who failed trials of UDCA. At certain centers however, OVT is used as initial therapy in virtually all new PSC patients, irrespective of biochemical markers (Allegretti et al., 2019; Damman et al., 2018; Shah et al., 2019; Liwinski et al., 2019).

Liver transplantation: The timing and selection of patients with primary sclerosing cholangitis for liver transplantation remains a problem. Primary sclerosing cholangitis is a well-established indication for liver transplantation in patients with decompensated liver disease, intractable pruritus, or recurrent bacterial cholangitis. Liver transplant indications for patients with PSC do not differ substantially from those with other forms of chronic liver disease and relate initially to complications of portal hypertension, damaged quality of life, and chronic liver failure (Keitel et al., 2019; Younossi et al., 2019; Hirschfield et al., 2019).

Surgical treatment: Before the widespread use of liver transplantation and endoscopic balloon dilation to treat PSC, surgical resection was used as the predominant method of treatment. Operative management of PSC entails resection of the extrahepatic biliary tree involving hepatic duct bifurcation and postoperative transhepatic stenting. In carefully selected patients without cirrhosis and with predominantly extrahepatic biliary strictures, resection of the extrahepatic biliary tree perhaps prolongs the interval to liver transplantation and provides relief of jaundice (Rokkas et al., 2019).

Conclusion

Primary sclerosing cholangitis is a progressive liver disease described by ongoing destruction of the intra- and extra-hepatic bile ducts leading to cholestasis, developed fibrosis, liver cirrhosis and eventually liver failure with its consequent complications such as portal hypertension and an increased risk of malignancy. Inflammation and fibrosis lead to cholestasis and parenchymal injury. Biliary obstruction might facilitate cholangitis. Cholangiography is the best way to distinguish patients with PSC. UDCA is a hydrophilic bile acid with cytoprotective effects that is readily absorbed orally. UDCA elevates levels of hydrophilic bile acids in bile and reduces histocompatibility antigen display by hepatocytes.

Abbreviations

AIH: Autoimmune hepatitis; ALP: Alkaline phosphatase; CCA: Cholangiocarcinoma; ERC: Endoscopic retrograde cholangiography; ESLD: End-stage liver disease; FUT2: Fucosyltransferase 2; HLA: Human leukocyte antigen; IBD: Inflammatory bowel disease; MRC: Magnetic resonance cholangiography; OVT: Oral vancomycin therapy; PSC:

Primary sclerosing cholangitis; UDCA: Ursodeoxycholic acid;

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Availability of Data and Materials

The datasets generated during the current study are available with correspondent author.

Competing Interests

The author has no financial or proprietary interest in any of material discussed in this article.

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