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Review

The challenges in primary sclerosing cholangitis – Aetiopathogenesis, autoimmunity, management and malignancy☆

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Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease, characterized by progressive inflammation and fibrosis of the bile ducts, resulting in biliary cirrhosis and is associated with a high risk of cholangiocarcinoma. The majority of patients are young, male and have coexisting inflammatory bowel disease. PSC is found with a prevalence of 10/100,000 in Northern European populations. The pathophysiology of PSC is a complex multistep process including immunological mechanisms, immunogenetic susceptibility and disorders of the biliary epithelia. The diagnosis is primarily based on endoscopic cholangiography although magnetic resonance imaging is increasingly used; biochemistry and immunoserology as well as histology play only a minor role. Due to the high risk of developing cholangiocarcinoma and also other tumours of the GI tract, surveillance strategies are essential, however they have yet to be established and evaluated. Biochemical parameters, clinical risk factors, endoscopic procedures and imaging techniques contribute to the early identification of patients at risk. Since medical therapy of PSC with ursodeoxycholic acid does not improve survival, to date, liver transplantation is the only option with a cure potential; if transplantation is accurately timed, transplanted PSC patients have an excellent rate of survival. However if cholangiocarcinoma is detected, a curative treatment is not possible in the majority of cases. The present review critically summarizes the current knowledge on the aetiopathogenesis of PSC and gives an overview of the diagnostic approaches, surveillance strategies and therapeutic options. Primary sclerosing cholangitis is a disease of unknown aetiology and without any further curative treatment options apart from liver transplantation. Therefore it may be regarded as the greatest challenge in hepatology today.

***Keywords*: PSC; Primary sclerosing cholangitis; Aetiology; Pathogenesis; Immunology; Surveillance; Diagnosis; Therapy; Transplantation; Malignancy; Cholangiocarcinoma**

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Abbreviations: PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; UC, ulcerative colitis; MHC, major histocompatibility complex; HLA, human leukocyte antigen; MIC, MHC class I chain-like; CR5Δ32, 32-bp deletion of the chemokine receptor 5; ICAM-1, intercellular adhesion molecule-1; CFTR, cystic fibrosis transmembrane conductance regulator; ANA, antinuclear antibodies; p-ANCA, perinuclear-staining, antineutrophil cytoplasmic antibodies; AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; p-ANNA, peripheral antineutrophil nuclear antibodies; TNF-α, tumour necrosis factor-α; VAP-1, vascular adhesion protein-1; MadCAM-1, mucosal addressin cell adhesion molecule-1; BEC, biliary epithelial cells; MDR, multidrug resistance protein; UDCA, ursodeoxycholic acid; IL, interleukin; TLR, toll-like receptors; IFNγ, interferon γ; CC, cholangiocarinoma; iNOS, inducible nitric oxide synthase; ERC, endoscopic retrograde cholangiography; ERCP, endoscopic retrograde cholangiopancreatography; MRC, magnetic resonance cholangiography; MRCP, magnetic resonance cholangiopancreatography; AMA, antimitochondrial antibodies; sdPSC, small-duct PSC; IgG, immune globulin G; MELD, model for end-stage liver disease; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; MRI, magnetic resonance imaging; CT, computed tomography; FDG-PET, positron emission tomography with ^{18}F-fluorodeoxyglucose; US, ultrasound; IDUS, intraductal US; IGF-I, insulin-like growth factor I; CRC, colorectal cancer; OLT, orthotopic liver transplantation; PDT, photodynamic therapy.

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1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic and progressive cholestatic liver disease, which is characterized by inflammation and fibrosis of mainly the large bile ducts leading to biliary cirrhosis in a high percentage of patients. It is associated with inflammatory bowel disease (IBD) in the majority of cases and is associated with a high risk of hepatobiliary as well as extrahepatic malignancies.

In 1929, J.A. Bargen described a case of a biliary cirrhosis in a patient with ulcerative colitis (UC); this was the first description of this disease in English [1] and subsequently he observed further cases of hepatic lesions in UC. In a series of 93 patients with UC, Kimmelstiel et al. reported in 1950 an increased frequency of liver damage [2], including bile casts and interlobular hepatitis. The term "Primary sclerosing cholangitis" was first coined in the early 1960s, when the diagnosis of this disease was based primarily on findings at laparotomy; but it was not until retrograde cholangiography by fiber duodenoscope introduced in 1970, that this disease became easier to diagnose and later also easier to treat. During the last three decades significant progress was made regarding the diagnostic and therapeutic methods, but still we are facing important challenges: the aetiopathogenesis of PSC remains poorly understood, the medical treatment of PSC is insufficient and the early detection of malignant complications to allow timely therapy, namely, liver transplantation is difficult.

Data on the epidemiology of PSC are rare and originate from a few major tertiary referral centres in Northern Europe or North America. In addition, the studies available mostly have methodological limitations [3]. Furthermore, PSC obviously does not occur with the same frequency worldwide. In Northern Europe, Canada or Minnesota incidence rates between 0.9 and 1.3/100,000/year and prevalence between 8.5 and 13.6/100,000 have been reported [4–7], while in southern Europe, Asia or Alaska this disease is seen much less frequently [8–11]. Between 55% and 71% of the patients are male and the mean age at diagnosis is around 40 years; a concomitant IBD can be found in 62–73% of patients and conversely 3–4% of patients with IBD have also PSC [3,12]. Ulcerative colitis (UC) is most common, but an association with Crohn's disease has been described in 1–14% of all PSC patients. However, in Japan [10] and Singapore [9] patients appear to be older at diagnosis and an associated IBD is less frequent. As numerous studies demonstrated, PSC is a disease of non-smokers, since current smokers have a decreased risk with an odds-ratio of 0.13–0.17 for the development of PSC [13,14].

The clinical course of PSC is characterized by recurrent episodes of cholangitis, during which the disease slowly progresses. While patients are initially often asymptomatic, they suffer over the years from jaundice, pruritus, fever and finally all the symptoms of end-stage liver disease can appear. Nevertheless in some patients the disease can also rapidly progress when after a period of stability septic biliary complications occur. The main causes of death are cholangiocarcinoma and liver failure. The mean time from diagnosis to death or liver transplantation ranges from 9.6 to 12 years and cholangiocarcinoma develops in 8–13.2% [15–17].

2. Aetiology and pathogenesis

While the cause of PSC still remains unknown, there are currently numerous approaches evolving that help us to understand the multiple mechanisms involved in aetiopathogenesis [18]. Based on an adequate immunogenetic background, immunopathogenetic mechanisms occur, which cause inflammatory changes of the bile ducts possibly triggered or intensified by infectious pathogens [19,20]. The following review describes several aspects of the aetiopathogenesis of PSC, i.e. PSC as a genetic disease, as an autoimmune disease, as an inflammatory disease triggered by infectious agents and as a cholangiopathy (Table 1).

2.1. PSC as a genetic disease

First-degree relatives of PSC patients have a PSC prevalence of 0.7% and siblings have an even higher prevalence of 1.5% [21]; this approximately 100-fold increased risk of PSC between genetically related individuals illustrates the importance of a genetic predisposition for the development of the disease. However, PSC is a complex non-mendelian disorder and the susceptibility to the disease is probably based on a combination of certain alleles of the major histocompatibility complex (MHC) and other non-MHC gene-polymorphisms.

The MHC encodes among others the human leukocyte antigen (HLA) class I and HLA class II molecules, which are involved in T-cell response, as well as the MHC class I chain-like (MIC)α-molecules, which play a role for the innate immune response, especially as ligands for natural killer cells [18,19,22]. MHC-haplotypes with an increased risk of PSC include several risk alleles like MICA * 008, DRB1 * 0301, DRB1 * 1301 or DRB1 * 1501; the strongest association was found for the MICA * 008-homozygosity with an odds-ratio of 5.01. Other haplotypes like DRB1 * 0701, DRB1 * 0401 and MICA * 002 are found in lower frequency in patients with PSC compared with controls and hence they are designated as protective haplotypes with an reduced risk of PSC development [23–25].

Genes outside the MHC-region also contribute to the susceptibility to PSC or influence the disease progression; most of them are involved in immune regulation. Unfortunately, most of the studies describing an influence of