

Differentiating Primary Sclerosing Cholangitis from Similar Diseases of Autoimmune Origin

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ABSTRACT

Background & Aims: Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease. Differential diagnostics can confuse it with immunoglobulin (Ig) G4-related sclerosing cholangitis (SC), an IgG4-related disease with clearly proven autoimmune origin. Differential diagnosis is made even more challenging because PSC with increased IgG4 levels (PSC-increased IgG4) also occurs. In order to facilitate their differential diagnosis, we reviewed recent literature regarding the etiologies, identifying characteristics, the most useful diagnostics, treatment, and the progression of these partially similar diseases. It is clear that PSC's pathogenesis differs from that of IgG4-related SC. In any differential diagnosis between PSC and PSC-increased IgG4, high IgG1 and low or normal IgG2 levels are characteristic for patients with PSC. Histological examination of the biliary tree wall in patients with IgG4-related SC typically reveals such changes as storiform fibrosis, obliterative phlebitis, and venulitis. These are absent in PSC-increased IgG4, which is characterized by a typical circular thickness in different parts of the biliary ducts. Finally, PSC is associated with inflammatory bowel disease, which is rare in IgG4-related SC, and more frequently is associated with cholangiocarcinomas and colon cancers. As distinct from IgG4-related SC, PSC is not a primary autoimmune disease.

Key words: autoimmune diseases – IgG4-related sclerosing cholangitis – primary sclerosing cholangitis – primary sclerosing cholangitis with increased IgG4.

Abbreviations: IBD: inflammatory bowel diseases; Ig: immunoglobulin; PSC: primary sclerosing cholangitis; SC: sclerosing cholangitis; Tfh: follicular helper T; Tregs: Regulatory T cells; UC: ulcerative colitis.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease [1, 2]. In clinical practice, it should be differentiated from immunoglobulin (Ig) G4-related sclerosing cholangitis (SC), which is one of the IgG4-related diseases with a clearly proven autoimmune origin [3]. Moreover, PSC with increased IgG4 serum levels (PSC-increased IgG4) has been described and can make differential diagnosis challenging.

PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis is a rare biliary tract-affecting

disease, characterized by inflammation and destruction of intra- and extrahepatic bile ducts. As a result, hepatic fibrosis or even cirrhosis can occur [4]. There is a very close association between PSC and inflammatory bowel disease (IBD), most typically ulcerative colitis (UC) [4–6]. Approximately 70% of patients with PSC also have IBD [6], but only about 5% of patients with IBD suffer also from PSC [4]. Interestingly, concomitant UC seems to be a negative prognostic factor regarding the risk of malignancy development and liver disease leading to liver transplantation or death [6].

Recently, three important pathogenic mechanisms typical of PSC have been discussed: 1) intestinal dysbiosis with possible production of toxins or immunostimulating substances; 2) increased intestinal permeability resulting in translocation of microbial toxins and bacteria to the hepatobiliary system; 3) stimulation of an immune response against hepatocytes and cholangiocytes by translocated bacteria, causing biliary injury and fibrosis [7].

As proof of the involvement of intestinal dysbiosis in PSC pathogenesis, there is also increased microbe-associated expression of toll-like receptors and T helpers type 17 in PSC patients [8].

In the pathogenesis of chronic inflammatory diseases of the bile duct, including PSC, inappropriate recruitment of mucosal lymphocytes within portal tracts due to chemokines and adhesion molecules secreted by cholangiocytes has been described. As a result, the bile ducts are destroyed by infiltrating leukocytes, mostly by the mechanism of Fas-dependent apoptosis [9].

Regarding etiology, according to a large genomic study (4,796 cases and 19,955 population controls) there are at least 23 regions of the genome associated with PSC [10]. Nevertheless, many other factors apart from genetic factors, such as environmental influences, are thought also to play roles in the etiology of the disease.

Unfortunately, no effective treatment is known to date that can stop, or even slow, the progression of the disease [5].

In the long term, PSC patients are at a significantly greater risk of cirrhosis and cholangiocarcinoma than are patients with IgG4-related SC [11].

IgG4-RELATED SCLEROSING CHOLANGITIS

IgG4-related SC is an autoimmune disease of the biliary tract. It is characterized by IgG4 serum elevation and tissue infiltration by IgG4+ plasma cells [12]. In its pathogenesis, two parallel immunological responses are described [13]: a) proinflammatory tissue destruction, and b) anti-inflammatory feedback response.

Proinflammatory tissue destruction: In IgG4-related disease (and in autoimmune pancreatitis), there is an abnormal expansion of some typical subsets of lymphocytes. First, the balance between the numbers of T helper cells Th1 and Th2 is shifted toward Th2 cells, which could explain eosinophilia and increased IgE concentrations in patients with IgG4-related disease [13]. Further, a role of follicular helper T (Tfh) cells in the pathogenesis of IgG4-related disease has been noted. Tfh2 cells constitute the most expanded population of Tfh subsets [13] and induce the differentiation of naïve B cells into plasmablasts with enhanced production of IgG4 [14]. Generally, circulating Tfh2 cell counts correlate with disease activity and heightened IgG4 serum concentrations [13].

In a global proteomic study, tissue proteomes and phosphoproteomes in frozen large bile duct samples were analyzed [15]. Analysis based on the expression profiles of peptides did not discriminate between IgG4-related SC and PSC, but the profiles of phosphopeptides were able to distinguish between these two diseases. This indicates that proteins expressed in the two diseases overlap, whereas their functional states differ [13]. In the pathway analysis in IgG4-related SC, 11 more activated signal cascades have been found, including 3 immunological pathways, all of which are B cell or immunoglobulin-related. This suggests crucial roles for B cells and macrophages in IgG4-related SC [15].

Anti-inflammatory feedback response: Normally, immunoglobulins mediate proinflammatory activity. They are produced by clonal B cell populations, where each population of B cells produces only one type of immunoglobulin recognizing a single type of antigen. Interestingly, in contrast with all the other IgG subclasses, IgG4 antibodies mediate anti-inflammatory activity through a mechanism known as Fab-arm

exchange [16]. Fab-arm exchange is a process whereby a pair of heavy and light chains in the IgG molecule exchange places. This causes IgG4 molecules to lose their antigen cross-linking ability so that they are not able to form an immune complex. By competing against other immunoglobulins, IgG4 is a factor that suppresses inflammatory reactions [17]. In conclusion, IgG4 seems to be one of the factors in an organism that helps the immune system to dampen inappropriate inflammatory reactions in different pathological situations [18].

Another factor involved in the suppressive process is the expansion of circulating and tissue resident regulatory T cells (Tregs). Histologically, large numbers of Tregs are found in tissues affected by IgG4-related disease [13]. By the expression of regulatory cytokines, such as interleukin 10 and transforming growth factor β , they probably link the tissue-destructive and anti-inflammatory processes in patients with IgG4-related diseases [17].

The relationship of pathophysiological proinflammatory and anti-inflammatory processes in IgG4-related SC can be seen in Fig. 1.

IgG4-related SC is commonly associated with autoimmune pancreatitis type 1 [19]. Histopathological criteria of the IgG4-related SC include obliterative phlebitis, storiform fibrosis, and tissue infiltration with IgG4 positive plasma cells (>10 IgG4 + plasma cells per high-power field, defined as the microscopically visible area under $400\times$ magnification) [20].

IgG4-related SC can be classified into four types, according to morphological images observed under cholangiography and the location of strictures in the biliary tree [21]. Fig. 2 describes this classification and differential diagnosis.

Even though diagnostic criteria were published already in 2012 [22] and then again in 2016 [23], the correct diagnosis of IgG4-related SC is still very challenging. This is because we must differentiate between PSC, IgG4-related SC, and cholangiocarcinoma, all of which can mimic one another. What is more, intrapancreatic biliary strictures can occur also in patients with autoimmune pancreatitis. These are thought to be caused by pancreatic edema, and it is necessary to distinguish this from any primary biliary diseases [24]. Moreover, a recently published study from Ali et al. [11] proved that the risk of cirrhosis and cholangiocarcinoma was significantly lower in IgG4-related SC patients treated via immunosuppressive therapy than in PSC patients [11]. Determining the correct diagnosis is therefore crucial for the outcomes of the patients. A comparison of cholangiographic findings in differential diagnostics for IgG4-related SC and PSC are summarized in Fig. 3 [25].

In contrast with cases of PSC and PSC-increased IgG4, glucocorticoids display very good results in the treatment of IgG4-related SC [26].

PRIMARY SCLEROSING CHOLANGITIS WITH INCREASED IgG4 LEVELS

There are several subtypes of PSC: “classical” large-duct PSC, small-duct PSC, “overlap syndrome” with autoimmune hepatitis, and, finally, PSC-increased IgG4 [27].

PSC-increased IgG4 was first described by authors from the Mayo Clinic in 2006. Higher IgG4 serum levels were measured in 12 patients (9%) from a group of 127 patients with PSC.

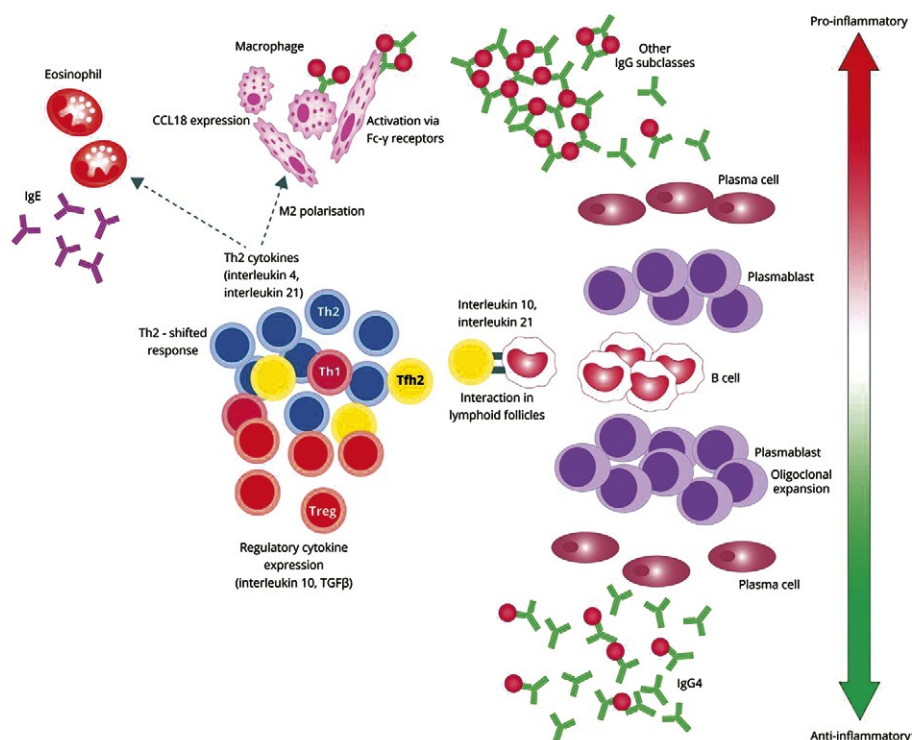


Fig. 1. Relationship of pathophysiological process to proinflammatory and anti-inflammatory processes in IgG4-related SC (prepared in accordance with Kamisawa et al. [13] and created in collaboration with the Service Center for E-Learning at Masaryk University, Faculty of Informatics).

In this small group of 12 patients, higher levels of alkaline phosphatase and total bilirubin were also found. What is more, time to liver transplantation was shorter [28].

Therefore, it is very important – but very difficult – to distinguish patients with PSC-increased IgG4 from other particular subtypes of PSC and IgG4-related SC. In any differentiation between PSC and IgG4-related SC, the estimation of immunoglobulin subtype-1 (IgG1) and subtype-2 (IgG2) could be useful. According to the work of Vujasinovic et al. [29], elevated levels of IgG2 predict autoimmune pancreatitis (AIP) and IgG4-related SC. That is in contrast to elevated levels

of IgG1, which in combination with normal IgG2 and IgG4 is typical for PSC. In that study, IgG2 elevation, predicting AIP and IgG4-related SC, displays a specificity of 97% and a positive predictive value of 91% [29].

After validation in larger cohorts, a novel IgG4:IgG RNA ratio might also be helpful in discriminating between IgG4-related SC and PSC-increased IgG4 [30].

These and several other features that distinguish classical PSC from PSC-increased IgG4 and from IgG4-related SC are summarized in Table I (modified according to Manganis et al. [30] and Nakazawa et al. [31]).

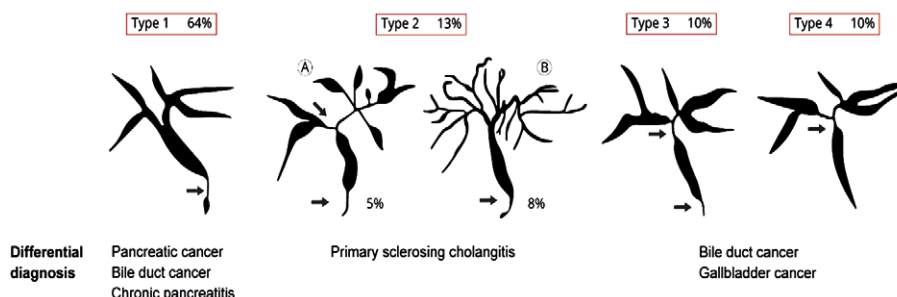


Fig. 2. Cholangiographic classification of IgG4-related SC: Type 1 – stenosis only in lower part of bile duct; Type 2 – includes two subtypes, stenosis is diffusely distributed in intrahepatic and extrahepatic bile ducts, Type 2a – narrowing of the intrahepatic bile duct with prestenotic dilation, Type 2b – narrowing in intrahepatic bile ducts without prestenotic dilation and with reduction of bile duct branches; Type 3 – stenosis in the hilar hepatic lesions and lower part of the common bile duct; Type 4 – strictures only in the hilar hepatic lesions. Prepared in accordance with Nakazawa et al. [21] and created in collaboration with the Service Center for E-Learning at Masaryk University, Faculty of Informatics.

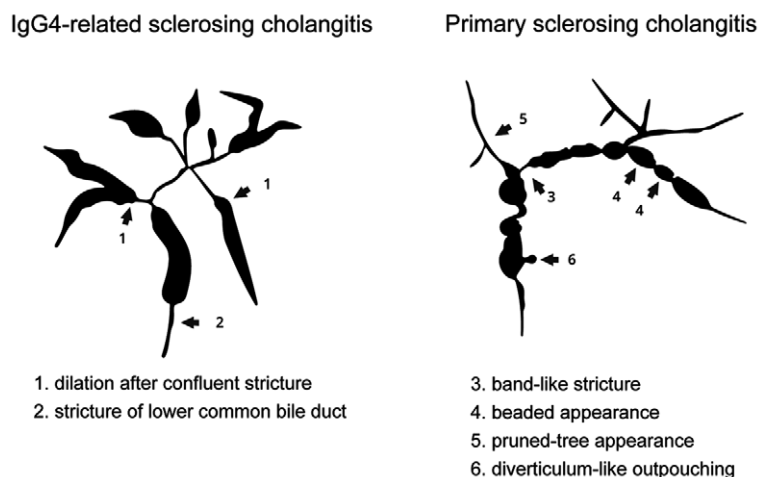


Fig. 3. A comparison of cholangiographic findings in differential diagnostics of IgG4-related SC and PSC (prepared in accordance with Ohara et al. [25] and created in collaboration with the Service Center for E-Learning at Masaryk University, Faculty of Informatics).

Regarding gender differences, PSC-increased IgG4 occurs more frequently in men than in females in a ratio of 7:1, and IgG4-related SC in a ratio of 1.5:1 [29,31,32]. Age at diagnosis of PSC-increased IgG4 is usually below 50 years, while in patients with IgG4-related SC the age is typically over 60 years [30].

In PSC-increased IgG4, similar to IgG4-related SC, overexpression of the chemokines CCL1, mainly in peribiliary epithelium, CCR8, and interleukins IL-4 and IL-10, compared with the normal IgG4 levels in PSC, has been identified. All these factors seem to play crucial roles in IgG4 induction [33]. High IgG4 levels in both these diseases may represent an immunoreaction to an as-yet unidentified antigen [32]. Nevertheless, the specific factors that induce the CCL1 production in each of these diseases seem to differ [33].

In comparison with other subtypes of PSC (with normal IgG4 serum levels), PSC-increased IgG4 could be considered a special clinical phenotype, with different human leukocyte antigen (HLA) associations, cytokine and chemokine profiles,

and post-translational antibody modifications [30, 34]. Pathogenic factors impacting on PSC-increased IgG4 are shown in Fig. 4.

Finally, the outcomes of patients differ. In PSC-increased IgG4, there is usually a more rapid progression of the disease and shorter times to liver transplantation, even compared to patients with PSC without any elevation of IgG4 levels [28]. In patients with IgG4-related SC, we note the excellent therapeutic effect of steroids. Relapses are nevertheless common, and most of the patients need long-term immunosuppressive therapy [35].

CONCLUSIONS

Primary sclerosing cholangitis is a chronic cholestatic disease characterized pathologically by a chronic inflammatory and fibrosing process, leading to diffuse stenosis and wall thickening of intra- and extrahepatic biliary tracts. The pathogenetic mechanism is unknown. Inflammatory changes

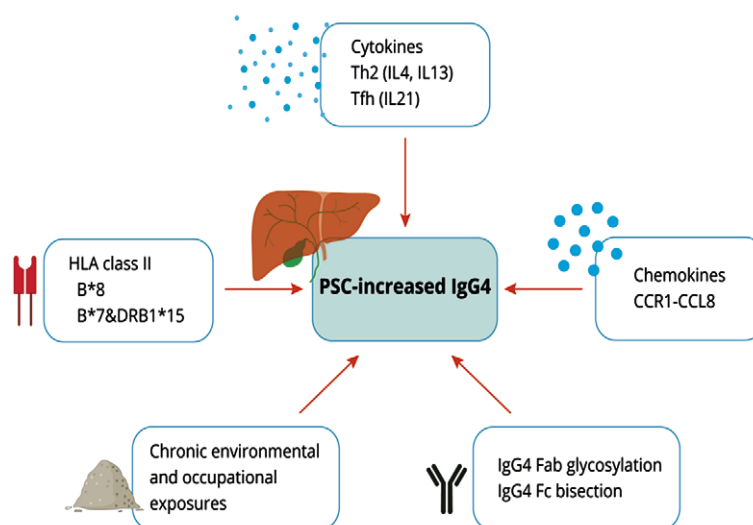


Fig. 4. Pathogenic factors impacting on PSC-increased IgG4 (modified according to Manganis et al. [30] and created in collaboration with the Service Center for E-Learning at Masaryk University, Faculty of Informatics).

Table I. Differences between classical primary sclerosing cholangitis (PSC), PSC-increased immunoglobulin (Ig) G4, and IgG4-related sclerosing cholangitis (SC) according to Manganis et al. [29] and Nakazawa et al. [30]

Item	Classical PSC	PSC-increased IgG4	IgG4-related SC
Age	Younger age	Younger age (<50 years)	>60 years
Gender	Male:female 2:1	Male:female 7:1	Male:female 3:2
Autoantibodies	PR3-ANCA	PR3-ANCA	No specific antibodies
Serology	Normal serum IgG4	Serum IgG4 $\leq 2 \times \text{ULN}$	Serum IgG4 > 5.6g/l Serum IgE raised IgG4:IgG RNA ratio Serum IgG4:IgG1 ratio > 0.24
Histology – hepatobiliary	Periportal sclerosis Onion-skin fibrosis	Periportal sclerosis Onion-skin fibrosis	Obliterative phlebitis Lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells Storiform fibrosis
Pancreatic involvement	Atypical, only in less than 5% azathioprine induced acute pancreatitis	Atypical, only in less than 5% azathioprine induced acute pancreatitis	Autoimmune pancreatitis
Other organs	IBD-colitis	IBD-colitis	Salivary gland, pancreas
Cholangiography	Short band-like strictures Beaded appearance Pruned-tree appearance CBD wall thickness	Short band-like strictures Beaded appearance Pruned-tree appearance CBD wall thickness	Long strictures, skip lesions Stricture of lower CBD Prestenotic bile duct dilation
Diagnostic criteria	Cholestasis Cholangiogram	Cholestasis Cholangiogram High serum IgG4	Histology, imaging, serology Organ involvement, response to steroid HISORt criteria for IgG4-SC
Malignancy	Increased risk of hepatobiliary malignancy and colorectal carcinoma in IBD patients	Increased risk of hepatobiliary malignancy and colorectal carcinoma in IBD patients	Increased risk of any malignancy
Treatment	UDCA, liver transplant	UDCA, liver transplant	Steroid
Prognosis	Progressive	Progressive	Good

CBD: common bile duct; IBD: inflammatory bowel disease; IgG4: Immunoglobulin G4; PR3-ANCA: proteinase 3/anti-neutrophil cytoplasmic antibodies; UDCA: ursodeoxycholic acid; ULN: upper limit of normal.

are found on the biliary epithelium. Distinct from IgG4-related SC, PSC is not a primary autoimmune disease.

Primary sclerosing cholangitis-increased IgG4 could be defined as a distinct clinical phenotype, with human leukocyte antigen associations, cytokine and chemokine profiles, and antibody modifications compared to patients with PSC and normal IgG4 levels. From the clinical point of view, we must separate PSC-increased IgG4 from IgG4-related SC and other biliary tree diseases with elevated IgG4 levels.

Conflicts of interest: None to declare.

Authors' contributions: L.K. and P.D. revised the literature and drafted the manuscript, L.H., and P.J. reviewed and edited the manuscript, J.D., M.U., V.K. and A.M. critically reviewed the manuscript, All the authors approved the final version of the manuscript.

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