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Review

# Autoimmune pancreatitis / IgG4-associated cholangitis and primary sclerosing cholangitis – Overlapping or separate diseases?☆

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**Autoimmune pancreatitis is a recently described fibroinflammatory disease which is characterised by raised serum levels of IgG4 (in >70% of cases), and an IgG4-positive lymphoplasmacytic tissue infiltrate. A favourable and rapid clinical response to oral steroid therapy is often seen. Biliary involvement is common, and the term IgG4-associated cholangitis has recently been coined. The cholangiographic appearances of IgG4-associated cholangitis and primary sclerosing cholangitis can be difficult to differentiate. Moreover, raised levels of serum IgG4 have been recently found in 9% of patients with primary sclerosing cholangitis (a much higher frequency than for other gastrointestinal diseases), and those with raised levels appear to progress more rapidly to liver failure. Here we review the similarities and differences between the biliary disease in autoimmune pancreatitis and primary sclerosing cholangitis, and address the issue of disease overlap. Improvements in understanding the relationship between these conditions might lead to an enhanced understanding of the aetiopathogenesis, and improved treatment of both conditions.**


***Keywords*: Autoimmune pancreatitis; Primary sclerosing cholangitis; Immunoglobulin G4; IgG4-associated cholangitis**

## 1. Introduction

Primary sclerosing cholangitis (PSC) is a fibrosclerotic disease of bile ducts, in which diffuse stricturing of the intrahepatic and extrahepatic biliary tree is characteristically seen on cholangiography [1]. The disease is usually progressive, with death or liver transplantation occurring a mean of 12–18 years after diagnosis [2,3]. A range of insults may induce similar cholangiographic features to PSC, including bile duct injury, immunodeficiency, and biliary toxins [4]. However, these can usually be differentiated on the basis of the patient's history, and the strong association of PSC with inflammatory bowel disease [5].

Autoimmune pancreatitis (AIP) was originally described in Japan more than 10 years ago [6], but has only recently been recognised as a worldwide condition [7–10]. Characteristic features include pancreatic enlargement or a mass (which may mimic malignancy), a raised serum IgG4 level, a lymphoplasmacytic infiltrate on biopsy, and a response to steroid therapy [6,7]. The name is inadequate, as extrapancreatic disease occurs in more than 45% of patients [9,11,12], and pancreatic disease may be minimal. Intra and extrahepatic biliary stricturing is a particular feature in AIP [11,13–15], which may be confused with PSC, and these biliary changes may develop after initial presentation with pancreatic disease. Bjornsson et al. have recently suggested that the biliary changes in AIP should be redesignated

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*Abbreviations:* PSC, primary sclerosing cholangitis; AIP, autoimmune pancreatitis; IgG4, immunoglobulin G4; IAC, IgG4-associated cholangitis; ERCP, endoscopic retrograde cholangiopancreatography.

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as 'IgG4-associated cholangitis' [16] (IAC). Although differences in biliary abnormalities between PSC and AIP have been reported (including longer biliary strictures in AIP, with more prestenotic dilatation and associated low bile duct stricturing [17]) these distinctions can be subtle and making a firm diagnosis between the two conditions based on cholangiography alone is often difficult.

We wish to outline the clinical similarities and differences between these conditions, propose that some cases previously assumed to be PSC may in fact have been those of AIP with biliary involvement, and discuss whether PSC and AIP/IAC are separate clinical entities or may represent different ends of the same disease spectrum.

### *1.1. Epidemiology and relationship to chronic pancreatitis*

The prevalence of PSC has been reported at approximately 13 per 100,000, with a 2:1 male predominance. AIP is also more common in males (>8:1), but no reliable data on prevalence exists. It has been implicated as the cause of 6% of cases of chronic pancreatitis in Japan, and of the pancreatic mass in 3% of pancreaticoduodenectomies performed for suspected pancreatic cancer [18]. Similar results have been reported from the United States, where 11% of patients with chronic pancreatitis were diagnosed as AIP based on the findings of pancreatic histology [19].

### *1.2. Inflammatory bowel disease, cholangiocarcinoma, and other immune mediated diseases*

Inflammatory bowel disease (IBD) is found in approximately 75% of Northern European cases of PSC, although the association is much less common in Japan, where only 20% of PSC patients have IBD. The majority of patients with PSC and IBD have ulcerative colitis, although Crohn's disease is also associated. Whereas small series from Europe have found IBD in approximately 30% of cases of AIP [9,12], it has been found at very low frequency in Japanese series of AIP [17]. Cholangiocarcinoma is a common complication of PSC which develops in 10–30% of patients, but to date no cases of cholangiocarcinoma complicating bile duct involvement in AIP have been described. Other autoimmune-type conditions, including Sjogren's syndrome, thyroid disease, psoriasis, and retroperitoneal fibrosis are associated with AIP.

## 2. Diagnostic criteria

A pancreatic mass or diffuse enlargement ('sausage pancreas') is a diagnostic criteria for AIP, in association with diffuse pancreatic duct abnormalities [6]. Whilst the pancreatic enlargement usually spontaneously resolves, pancreatic duct abnormalities persist in the majority not given steroid treatment [20], and pancreatic atrophy is a common outcome. Whilst a pancreatic mass is not a feature of classical PSC, pancreatic duct abnormalities have been reported in 7–15% of patients [21,22] with impaired exocrine function in 36% (although this is usually subclinical) [22].

A raised serum IgG4 was initially reported as >95% specific and sensitive for AIP [23]. More recent data suggests that although serum IgG4 is indeed highly specific in the correct clinical setting, it is only 71–82% sensitive for AIP [9,11]. Raised serum IgG4 levels have recently been demonstrated in 9–36% of patients with PSC [24,25], but are rare in other types of pancreaticobiliary disease [25], including malignancy. High concentrations of IgG4-positive plasma cells are found within a range of involved tissues in AIP, including liver, kidneys, gallbladder, and extrahepatic bile ducts [12,26] (Fig. 1). In a recent study of 99 patients who had undergone liver transplantation for PSC (published in abstract) [27], increased intrahepatic IgG4+ plasma cells were found in 23% of explanted livers, closely correlated with a moderate-marked periductal lymphoplasmacytic infiltrate.

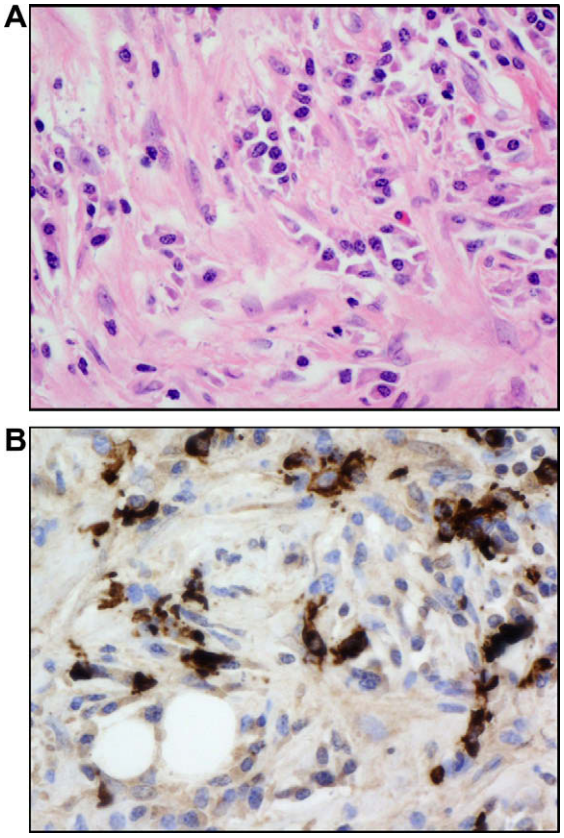


**Fig. 1. Histology from the liver hilum in a patient with complex hilar stricturing and an associated mass. A diagnosis of IgG4-associated cholangitis was made. (A) H + E showing extensive fibrous stroma, with associated plasma cell infiltrate. (B) IgG4 immunostaining showing >20 IgG4+ plasma cells per high power film.**

## 3. Aetiopathogenesis

Both conditions are suspected of having an immune basis, but no specific autoantibodies have been linked to either PSC or AIP. Pericellular anti-neutrophil cytoplasmic antibody (pANCA) is found in 70–80% of patients with PSC [28], but it is also found in 50% of patients with type 1 autoimmune hepatitis and 30% of patients with ulcerative colitis. In contrast, it appears to be rarely found in AIP. Antinuclear, anti-carbonic anhydrase and anti-lactoferrin antibodies have been reported in the majority of Japanese patients with AIP [29], but in a minority of patients from Europe and USA. Several human leukocyte antigen (HLA)- and non-HLA-associated genes have been implicated in the development of PSC, and genetic variants on chromosome 6p21 seem to be important [30]. An association of HLA DRB10405-DQB10401 haplotype in Japanese patients with AIP has been reported [31], but susceptibility alleles among HLA class I and II antigens for AIP have not been shown by other groups [32].

Despite the diagnostic importance of elevated serum and tissue IgG4 in AIP/IAC (and its recent association with PSC), the exact role of IgG4 in disease pathogenesis remains uncertain. Recent studies have shown that Th2 and regulatory T cell immune reactions are uniquely increased in AIP/IAC when compared with other biliary diseases, including PSC [33]. This type of pattern has also been observed in allergic disorders such as bronchial asthma and atopic dermatitis, suggesting that an allergic reaction may play an important part in the pathogenesis of AIP. It has been postulated that IgG4 plays no pathogenic role, but that it is upregulated in response to chronic exposure to microbial [34] or non-microbial antigens [35,36]. The recruitment of IgG4-committed B cells (with the subsequent maintenance of an IgG4 positive plasma cell infiltrate) may result from an excessive production of anti-inflammatory cytokines (e.g. TGF and IL-10) at the site of chronic inflammation [35]. This might also explain why serum IgG4 levels in AIP fall spontaneously, and in response to steroids [23], in parallel with resolution of active inflammation. It is not as yet established whether serum IgG4 levels should be used to guide the introduction or continuation of immunosuppression in AIP/IAC. The functioning of IgG4 also appears to be unusual, in that IgG4 engages the Fc (constant) portion of IgG through its own Fc, rather than through its variable, antigen binding Fab [37]. The relevance of this to disease remains unclear.

## 4. Response to treatment

A response to steroid therapy appears to fundamentally distinguish AIP from PSC, and suggests an absence of commonality between the conditions. No randomised trials of therapy in AIP/IAC have been performed, but biliary stricturing may dramatically improve within two months of commencing steroids [9,38,39] (Fig. 2), and the disease course appears to be less favourable in those who do not receive steroids [40]. In contrast, randomised controlled trials of systemic and endobiliary steroids (and other immunosuppressants) in PSC have shown no statistical benefit [41].

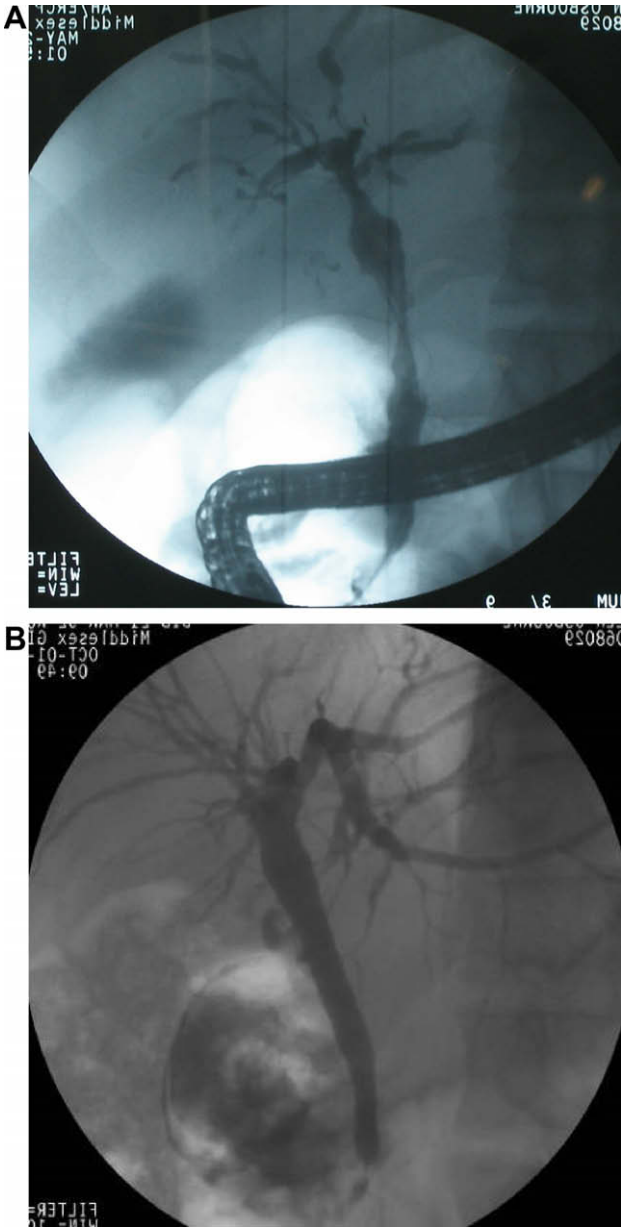


**Fig. 2. Cholangiographic response to steroid therapy in autoimmune pancreatitis/IgG4-associated cholangitis. (A) ERCP showing complex hilar stricture with associated intrahepatic biliary stricturing in a patient with biliary obstruction and raised serum IgG4. The patient also had renal impairment, focal renal abnormalities on imaging, and an IgG4+ plasma cell renal infiltrate. (B) Repeat ERCP 3 months following commencement of oral steroid therapy. Marked improvement in hilar and intrahepatic stricturing is seen.**

Why might the findings be so different? We hypothesise that one explanation may be the duration of disease. In the majority of patients PSC is an indolent disease, with established fibrosclerotic changes and minimal inflammatory infiltrate on liver biopsy at presentation, which progresses over a period of many years. Only a minority present with jaundice due to a benign dominant extrahepatic biliary stricture. In contrast, obstructive jaundice is the presenting feature in most patients with AIP, usually due to an intrapancreatic common bile duct stricture associated with the pancreatic mass. Histologically, an active lymphoplasmacytic infiltrate is seen, with varying degrees of fibrosis. It may be that stricturing is reversible in these patients because the clinical presentation occurs at a relatively early stage of the inflammation-to-fibrosis process, because of obstructive jaundice. In the light of this theory, it is of interest that steroids may be of benefit in children with PSC [42], although the natural history of the disease in children appears to be different to that seen in adults. Idiopathic sclerosing cholangitis in children is commonly associated with a lymphocytic inflammatory liver infiltrate (hence the proposed term autoimmune sclerosing cholangitis) [43]. Clinical and histological improvement in these patients occurs in nearly 90% with immunosuppression. In a Norwegian review of immunosuppression in adults with PSC, the small proportion who responded to steroids were younger, with a shorter duration of disease, and higher pre-treatment ALT, than non-responders [44]. It is of interest that one of the earliest descriptions of steroid benefit in PSC related to a patient with florid biliary and pancreatic duct abnormalities [45], suggesting AIP with biliary involvement. Whilst it may be argued that these latter two reports relate to patients with a different disease to PSC (i.e. overlap PSC/autoimmune hepatitis, or 'autoimmune sclerosing cholangitis') an alternative explanation is that, as with biliary involvement in AIP, steroids were having their benefit during the early inflammatory phase of PSC. It is of note that in patients with PSC, both raised serum [24] and liver IgG4 [27] appears to be associated with more rapid progression to liver transplantation. This has led to a proposal, as yet unproven, that these patients might warrant, and respond to, steroids [24]. We certainly recognise that in patients with long-standing 'burnt-out' AIP, serum IgG4 is normal, histology is markedly fibrosclerotic with little inflammatory infiltrate, and objective treatment response may be disappointing.

## 5. Conclusion

AIP/IAC is unlikely to be a new disease, but one that has masqueraded as others, and has been both underdiagnosed and in some cases wrongly labelled as PSC.

**Table 1**
**Evidence for and against PSC and AIP/IAC as the same disease entity.**

| Evidence for | Evidence against |
|---|---|
| Male predominance | Weak association between AIP & IBD |
| Similar cholangiographic changes | No association of AIP with cholangiocarcinoma |
| Associated immune-mediated diseases | Different T cell populations |
| Pancreatic duct stricturing | Response to treatment with steroids |
| Increased frequency of raised serum and tissue IgG4 in both conditions | Pancreatic masses in AIP, not PSC |

Distinguishing between biliary involvement due to AIP/IAC and classical PSC is not simply an academic exercise, in view of the clinical improvement with steroids that is seen in most patients with AIP, but not in PSC. It is unclear whether PSC and AIP/IAC represent completely separate conditions or variations of the same disease spectrum (see Table 1), and further information about the aetiology, pathogenesis, and diagnostic criteria for these conditions is required. Nevertheless, emerging evidence of elevated serum and intrahepatic IgG4 levels in patients with PSC raises further questions as to the inter-relationship between PSC and AIP/IAC, and perhaps reinvigorates the issue of the role of immunosuppression in these conditions.

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