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Type 2 autoimmune pancreatitis

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Introduction

Autoimmune pancreatitis (AIP) encompasses at least two entities, one related to a systemic disease referred to as IgG4-related disease (type 1 AIP) and the other is an isolated pancreatic disorder (type 2 AIP). Importantly, histology can generally separate these two diseases. The following discussion describes characteristics of type 2 AIP.

Histopathology of type 2 AIP

The pancreas of patients with type 2 AIP is often only focally involved. The region that seems to be most often affected is the pancreatic head including the pancreatic portion of the distal bile duct. As in type 1 AIP, the outstanding histologic feature is a periductal lymphoplasmacytic infiltrate usually affecting some or all of the medium sized ducts **(Figure 1)**. It is often accompanied by a collar-like periductal fibrosis, with narrowing of the affected duct. The lymphoplasmacytic infiltrate may extend from the periductal area to the acinar tissue. In addition, there is a perilobular fibrosis, occasionally of the storiform-type. These histological changes can also be found in type 1 AIP, but are usually less pronounced in type 2 AIP. Conversely, the finding of the so called granulocytic epithelial lesion (GEL) is specific to AIP 2 (19). This lesion is characterized by focal disruption and destruction of the duct epithelium due to the invasion of neutrophilic granulocytes. GELs affect medium sized and small ducts **(Figure 2)**, and may also be recognized in the acinar tissue. In the ducts they often cause destruction and obliteration of the duct lumen. The number of GELs and their severity differs from patient to patient. If a GEL is included in a biopsy specimen from the pancreas it is diagnostic for type 2 AIP (4). Another, though less specific, criterion for the diagnosis of type 2 AIP is the absence or scant (<10 cells/HPF) IgG4-positive staining plasma cells in the inflamed pancreatic tissue **(Figure 3)** (4, 20).

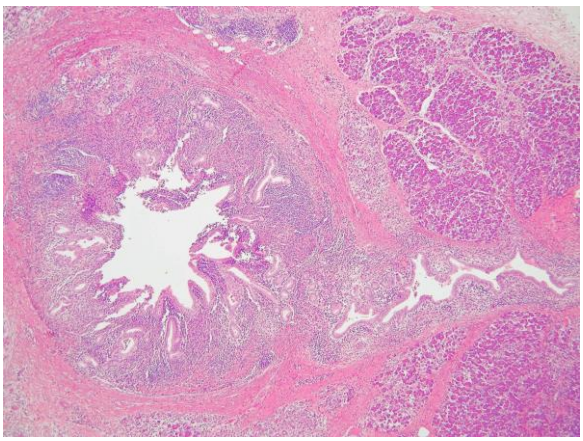

Figure 1. **Resected pancreatic specimen from a patient with type 2 AIP demonstrates an intense periductal lymphoplasmacellular infiltrate and fibrosis, extending into the surrounding interlobular tissue.** The epithelium of the large duct is focally destroyed by granulocytic infiltrates.

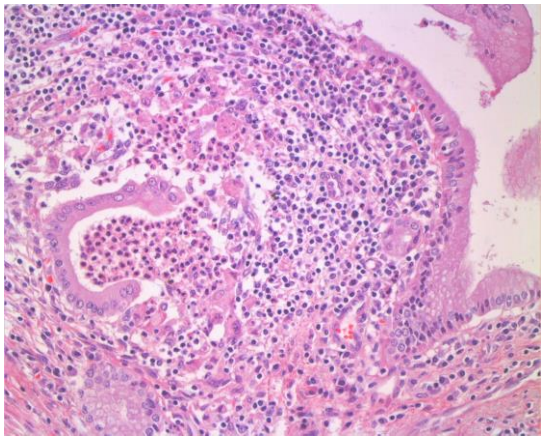

Figure 2. **A small pancreatic duct is seen next to a large duct containing a granulocytic epithelial lesion (GEL), which causes duct disruption.**

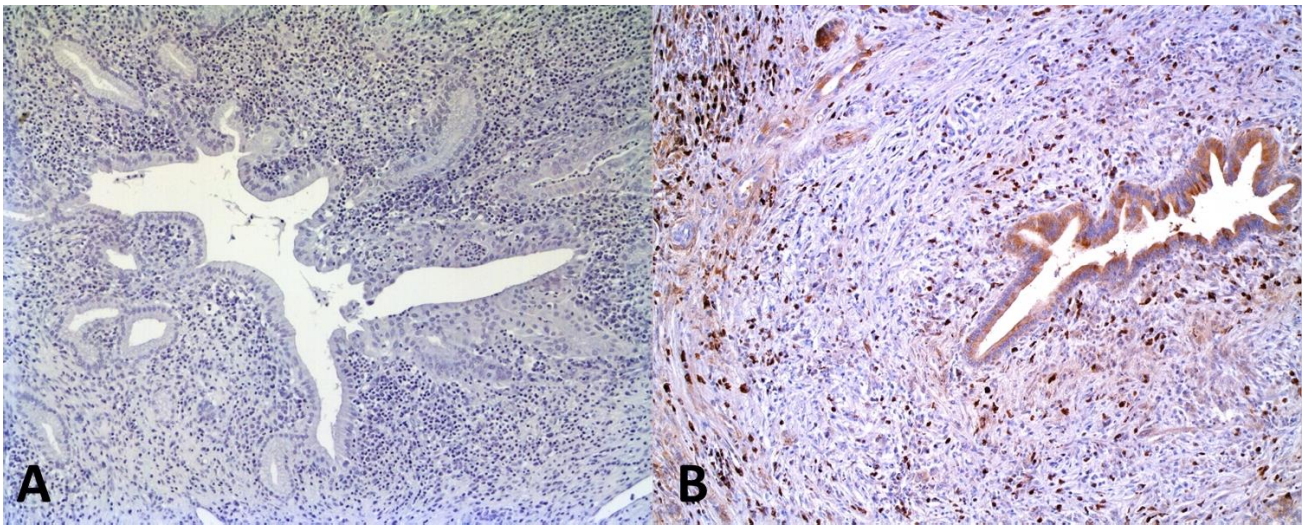

Figure 3. **Immunostaining for IgG4 reveals no positive-staining plasma cells in type 2 AIP (A), but abundant IgG4-positive plasma cells in type 1 AIP (B).**

Differential diagnosis of type 1 versus type 2 AIP

Macroscopically, the subtypes of AIP are indistinguishable. In approximately 80% they present as a tumorous mass in the head of the pancreas mimicking ductal adenocarcinoma (14,19). The inflammatory infiltration of the pancreas head and the wall of the extrahepatic bile duct can cause narrowing of the distal bile duct and main pancreatic duct. In both types of AIP pseudocysts and calculi are uncommon (1,19).

The histopathology of the two types of AIP differs. Type 2 AIP is characterized by the presence of GELs which are absent in type 1 AIP (1,19) . The second distinctive feature is the absence or only very low number (<10 cells/hpf) of immunostained IgG4 positive plasma cells in type 2 AIP, in contrast with the abundant (>10 cells/hpf) IgG4 positive plasma cells in type 1 AIP. Other features that are not specific but usually more pronounced in type 1 AIP are: i.) the presence of an intense lymphoplasmacytic infiltration not only around ducts, but also in the acinar tissue, ii.) swirling (storiform) fibrosis centered around ducts and extending into the lobules, and iii.) vasculitis with lymphoplasmacytic infiltration surrounding and obliterating the veins (phlebitis) and, to a lesser extent, arteries (arteritis). Immunostaining for CD3, CD4 and CD8 positive lymphocytes, CD79a positive plasma cells and CD68 positive macrophages often reveals a higher number of these cells in type 1 AIP compared to type 2 AIP (12,20).

Extrapancreatic Disease in type 2 AIP

Patients with type 2 AIP usually do not show the immune-mediated diseases, that are observed in about 20 to 40 % of patients with IgG4-related disease (6,9,10). Instead they commonly suffer from chronic inflammatory bowel disease such as ulcerative colitis or Crohn's disease (10,19). Moreover, these patients mostly fail to exhibit elevated IgG4 serum levels and increased IgG4 positive plasma cells.

Epidemiology of type 2 AIP

The subtypes of AIP differ in their clinical features such as gender and mean age at diagnosis (6). Type 2 AIP is associated with an equal gender distribution and a mean age (45 – 48 years) that is considerably lower than that seen in type 1 AIP, which peaks between 60 and 65 years (1,10,19). It is interesting to note that the relative frequency of the two AIP types in Europe and the US seems to differ from that in East Asia. While in Europe each subtype can be expected in about 40-60% of the cases (in biopsy series they amount to 38% and 45%, respectively), type 2 AIP seems to be rare in East Asia (11).

Clinical Features and Laboratory Data of type 1 versus type 2 AIP

Symptomatically, both types of AIP patients are indistinguishable. Many patients complain of abdominal pain, although the frequency and intensity of pain attacks tend to be lower in patients with type 1 AIP than type 2 AIP (10). Other frequent symptoms are jaundice and weight loss. Corticosteroid treatment resolves strictures of the extrahepatic bile ducts and main pancreatic duct, as well as the pancreatic mass and focal lesions in the lungs, kidneys and retroperitoneal inflammatory pseudotumors. This can be the case already after one to two weeks of steroid therapy (8,10,15).

Long time follow-up in patients with AIP after pancreatic resection revealed that recurrence of the disease is often observed in type 1 AIP, but is very rare in type 2 AIP (1,6,19). Another interesting question is whether pancreatic ductal adenocarcinoma (PDAC), which has recently been described in association with AIP, has a predilection for one of the two AIP types. So far it seems that PDAC is more commonly reported in association with type 1 AIP (7,18).

Among the autoantibodies that may be detected are antibodies against antigens from the pancreatic ducts and acini such as lactoferrin, carbonic anhydrase type II, SPINK1 and trypsinogen (13,17). Other autoantibodies associated with AIP are antinuclear antibody, rheumatoid factor and anti-smooth muscle antibody.

Pathogenesis

The pathogenesis of AIP is still not known, but several findings, common to both types of AIP, are suggestive of an immune-related etiopathogenesis. This assumption is based on the general histopathological features of both AIP types, their frequent association with immune-related disorders such as the systemic manifestations of IgG4-related disease on one hand and idiopathic inflammatory bowel diseases on the other, and the response to steroid treatment. Whether the demonstrated circulating autoantibodies against carbonic anhydrase II, lactoferrin and nuclear and smooth muscle antigens as well as SPINK1 are found in the same frequency in type 1 AIP as in type 2 AIP is unknown.

A clear difference between the AIP subtypes concerns the amount of IgG4-positive plasma cells in the pancreatic tissue, a finding that often correlates with the serum IgG4 levels in patients. Recently it was found that renal tissue from AIP patients with tubulointerstitial nephritis contained granular deposits at the tubular basement membranes that were positive for IgG4 and complement C3, and occasionally IgG1, IgG2 and IgG3 (3). In a similar study on pancreatic tissue and bile duct tissue of six GEL-negative AIP patients, using double immunofluorescence microscopy, deposits of IgG, IgG4 and C3c (but not C1q, IgA and IgM) were identified, that colocalized with basement membrane-associated collagen IV of ducts and acini (5). On the basis of these findings it may be hypothesized that IgG4 could play a role in the deposition of immune complexes at pancreatic structures that seem to be the target of the fibroinflammatory process characterizing AIP. In order to clarify whether this hypothesis is only valid in IgG4 positive patients with type 1 AIP, a patient was included in the study whose clinical features were indistinguishable from those of the other six patients of the series, but whose immunohistochemical staining was more consistent with type 2 AIP (very low numbers of IgG4-positive plasma cells in the pancreatic tissue). This patient did not have any IgG4-positive deposits at the basement membranes of the ducts and acini, but remained positive for C3c and IgG. If this unique finding is confirmed in future studies, it would imply that in type 2 AIP the mechanisms leading to the changes in the ducts and acini and the fibrosis are independent of the effects of IgG4. This then raises the question as to whether the increased number of IgG4 plasma cells, the high IgG4 serum levels and the tissue depositions of IgG4 play a primary and active role in the pathogenesis of AIP or are rather secondary phenomena.

Summary

AIP has two distinct subtypes, which are primarily defined by their pathologic features. The subtypes have different clinical profiles, disease manifestations, and clinical outcomes. Type 2 AIP is histologically defined by the presence of GELs and the lack of abundant IgG4-positive staining plasma cells. Patients with type 2 AIP tend to be younger at the time of diagnosis and the gender distribution is more equal than in type 1 AIP. Unlike type 1 AIP, which is recognized as part of systemic IgG4-related disease, type 2 AIP is an isolated pancreatic disorder. Aside from the frequent association with inflammatory bowel disease there are no characteristic other organ involvement. The disease manifestations of type 2 AIP are extremely sensitive to steroid therapy, and disease relapses are exceedingly uncommon.

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