

Autoimmune Pancreatitis

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Summary

Autoimmune pancreatitis (AIP) is a fibroinflammatory condition of the pancreas that can mimic malignancy but usually responds to steroids. Most patients have elevated levels of serum IgG4 and most patients have increased numbers of IgG4-positive plasma cells in the inflamed pancreas. Similar IgG4-rich inflammatory lesions can occur in almost any organ; all such conditions are currently (tentatively!) grouped under the rubric IgG4-related sclerosing disease (IgG4-RSD).

IgG4-RSD disease produces a characteristic but not specific set of histologic changes, modified by the microanatomy of the particular site involved. [1] Lymphoplasmacytic inflammation, fibrosis, phlebitis and increased numbers of IgG4-positive plasma cells make up the characteristic mix, and the resulting pattern is usually sufficient to suggest the correct diagnosis. While the original work on the pathology of AIP was based on resection specimens, the fact that this is a non-neoplastic, steroid-responsive condition means that we are now being asked to contribute to the diagnosis based on findings in needle biopsies.

The literature on the pathology of autoimmune pancreatitis is complicated by the fact that the term encompasses two probably separate conditions. Notohara et al termed them “lymphoplasmacytic sclerosing pancreatitis” and “idiopathic duct-centric pancreatitis” ([2]), while Deshpande et al chose the terms lobulocentric AIP and duct –centric AIP. ([3]) The two patterns have come to be called type 1 and type 2 AIP ([4, 5])

Pathology of AIP, type 1

Type 1 AIP is the pancreatic manifestation of IgG4-related sclerosing disease. Affected patients are generally males (M:F ratio is 4-5:1) in their 7th decade. The usual presentation is painless jaundice, but some patients complain of abdominal pain and rare patients present with pancreatic insufficiency. [5]

Type 1 AIP usually involves the entire pancreas, but can be localized enough to mimic pancreatic tumor. Histologically, focal involvement is not rare; Chandan et al found at least focal sparing in 32/39 resected examples of AIP. [6] When focal involvement does occur, the uninvolved areas are histologically normal and IgG4-positive plasma cells are not increased. Biopsies taken from uninvolved areas will necessarily be non-diagnostic.

Pancreatic tissue involved by AIP has lymphoplasmacytic inflammation.

There is almost always a cuff of lymphocytes and plasma cells surrounding branches of the pancreatic duct. While the inflammatory cuff can be quite dense, the duct epithelium remains intact. Neutrophils are not seen in or around the epithelium; in fact, the presence of intraepithelial neutrophils favors type 2 AIP over type 1.

Lymphoplasmacytic inflammation involves the pancreatic lobule as well. At least a few eosinophils are often present, and may be quite numerous at times. [7] As in the periductal infiltrate, the presence of more than a few neutrophils should raise doubt about the diagnosis of IgG4-RSD.

Lymphoepithelial lesions (infiltration of glands by lymphocytes) are not a feature of this condition. Instead, the infiltrate is concentrated between acini. At first, the dense infiltrate contrasts with interlobular fibrosis to accentuate the lobular architecture, but further damage ultimately obliterates the acini, leaving only islets and small duct branches. The lymphoid infiltrate is dominated by T-lymphocytes, specifically CD8-positive T-suppressor cells. No clonality has been demonstrated in T or B cell subsets. [8] Lymphoid aggregates are sparse in the pancreas itself, but are prominent

in peripancreatic soft tissue. [2] Perineural inflammation is a common feature of type 1 AIP.

The atrophic pancreatic lobule is replaced by a mix of lymphoplasmacytic inflammation and fibrosis, often producing a storiform pattern. This pattern tends not to occur in other forms of chronic pancreatitis (including type 1 AIP) or in the pancreatitis adjacent to neoplasm, making it a very helpful diagnostic feature, particularly in needle biopsies. The distinctive appearance may partly be due to the type of collagen that makes up the fibrotic component: Song et al have demonstrated that AIP tends to have much less type III collagen than alcoholic chronic pancreatitis, and more type IV collagen. [9] They speculate that the collagen profile accounts for the reversibility of fibrosis in some cases of AIP, since type IV collagen is an element of the normal pancreatic stroma rather than a manifestation of scarring. One might further speculate that “burned out” AIP has more collagen III and is therefore irreversible. [10]

Phlebitis is invariably seen in resected examples of type 1 AIP. It is easily located by finding large muscular arteries, then locating the adjacent vein. The vein lumen is narrowed (sometimes completely obliterated) by a dense

infiltrate of lymphocytes and plasma cells. Neutrophils are not a part of this process, nor is there fibrinoid necrosis or nuclear dust that might suggest a vasculitic process. Needle biopsies generally don't contain large veins, but small artery-vein pairs can occasionally be seen. A histochemical stain for elastic is said to be helpful in identifying vein remnants. [11]

Immunohistochemical staining for IgG4

Antibodies against IgG4 perform very well in formalin-fixed, paraffin-embedded tissue, and provide a useful adjunct to the diagnosis of type 1 AIP. Plasma cells producing IgG4 are decorated with a very dense cytoplasmic stain, leaving the nucleus unstained and visible. An IgG4-positive infiltrate alone is not specific for a diagnosis of type 1 AIP (or any particular manifestation of IgG4-RSD), but in the appropriate clinicopathologic setting, positive staining for IgG4 can clinch the diagnosis. The first attempt to quantify the IgG4 infiltrate in this setting used a semiquantitative scale with irregular breakpoints and considered a density of 10 IgG4-positive plasma cells/high power field (hpf) as a positive result. [12] We used this scoring system in a study of pancreatic resections, and found that 21/29 AIP cases had a positive score, compared to 1/9 examples

of alcoholic chronic pancreatitis and 3/25 pancreatic cancers. [13]

Deshpande et al used a slightly different scale, but found similar results. [3]

A recent study from Memorial Sloan-Kettering found that a cut-off value of 50 IgG4-positive cells/hpf gave a sensitivity for AIP of 84% and a specificity of 100%. [14] The authors also emphasized that the IgG4-positive infiltrates tend to be diffuse in AIP and patchy in peritumoral infiltrates.

Diagnosing type 1 AIP in small biopsies

Because this condition generally responds to medical management, the goal is to avoid surgical resection of the pancreas. The tissue-based component of the clinical work-up has come to depend on needle biopsy; most of the documented experience in this area has been with trucut biopsies obtained under endoscopic ultrasound guidance. [15, 16] Naturally, this makes the pathologist's task more difficult, but assuming that the biopsy shows chronic pancreatitis and no evidence of malignancy, one can usually point the diagnosis in favor of or against type 1 AIP. Even small duct branches, if present, will often show a dense periductal lymphoplasmacytic infiltrate. If vein branches are present, phlebitis is a characteristic finding. In practice,

neither ducts nor veins are commonly seen in needle biopsy; in that case the cell-rich storiform fibrosis becomes the critical finding.

Immunohistochemistry for IgG4 is invaluable in this setting. Increased numbers of IgG4-positive plasma cells (more than 10/hpf), particularly if they are diffuse, strongly support the diagnosis of type 1 AIP.

Some studies have shown that fine needle aspiration of the pancreas can provide sufficient diagnostic material in this clinical setting. [17] This diagnosis depends on recognizing stromal fragments on cytology preparations. Carcinoma can also have stromal fragments, but AIP lacks atypical epithelial cells. The inflammation typical of type 1 AIP makes the stromal fragments more cellular in AIP than in carcinoma.

Type 2 AIP

A subset of patients originally grouped under the heading of autoimmune pancreatitis seems to be different on both clinical and histologic grounds. ([2, 3] Table 1 highlights the observed differences between type 1 and type 2 AIP. Briefly, patients with type 2 AIP tend to be younger than those with type 1, and have an equal sex distribution. The disease is confined to the

pancreas. Some patients have inflammatory bowel disease, but systemic manifestations of IgG4-RSD are absent. A very recent review by Deshpande emphasized the importance of making this distinction, and highlighted the fact that peripancreatic lymph nodes almost always show a distinctive IgG4-rich hyperplasia in AIP1, but are not abnormal in AIP2. [18]

Table 1: Clinical and Pathologic comparison of Type 1 and Type 2 AIP

	Type 1	Type 2
Age	60-70	50-60
Sex	4-5M:1F	M=F
Jaundice	common	<20%
Abdominal pain	rare	usual
IgG4-RSD	yes	no
Periductal inflammation	yes	yes
GELs	no	yes
Phlebitis	yes	no
Storiform pattern	yes	no
IgG4 IHC	+++	0 to +

In resected specimens, the diagnosis is usually easy – the ducts are made prominent by a dense cuff of lymphoplasmacytic inflammation and the epithelium contains neutrophils. The epithelium may be eroded. The neutrophils often form microabscesses, producing the very characteristic “granulocytic epithelial lesion.” [19] Features of type 1 AIP (storiform fibrosis, phlebitis, lymphoid aggregates in peripancreatic parenchyma) are either poorly developed or absent. IgG4-positive cells are either absent or sparse. I often struggle with the diagnosis in needle biopsies; unless the needle happens to catch a duct with neutrophils, the biopsy can look very non-specific. Often, the best one can do is to say that there are no malignant cells and no features of type 1 AIP.

Systemic manifestations of IgG4-related sclerosing disease

The idea that IgG4 might serve as a marker for a systemic inflammatory condition is relatively recent. [12] Now, the list of sites/organs involved by IgG4-RSD seems to grow by the day. It is not yet clear whether all of these conditions represent a single disease or simply a stereotypic response to various stimuli, but there is absolutely no doubt that individual patients can

have multisystem involvement, either synchronously or metachronously. At many sites, the term IgG4-RSD encompasses or “explains” a subset of a previously named condition. In the salivary gland, for example, some examples of Mikulicz’s disease and some examples of Kuttner’s tumor are IgG4-rich and have histology characteristic of IgG4-RSD. The same can be said for some examples of Riedel’s thyroiditis, orbital pseudotumor and inflammatory pseudotumors in various locations. This topic has been the subject of several recent reviews; the one by Cheuk and Chan is superb. [1] My talk will focus on the pancreatobiliary tract and gastrointestinal tract.

Type 1 AIP is very commonly accompanied by disease elsewhere in the pancreatobiliary tract. While resections for AIP are now uncommon, sclerosing cholangitis can mimic cholangiocarcinoma so convincingly that there continue to be occasional surgical resections for this condition. In resected extra-hepatic bile ducts, the wall is diffusely thickened.

Peribiliary glands are encased in the fibroinflammatory process. Phlebitis is present in adventitial veins. As in the pancreas, the duct epithelium is preserved and neutrophils are unusual. Large duct involvement by primary sclerosing cholangitis (PSC) tends to produce lumen-centered, neutrophil-rich inflammation with erosions, so preserved epithelium can be a clue to the

diagnosis of IgG4-RSD, unless biliary stents have altered mucosal morphology. Immunohistochemistry for IgG4 is invaluable in the biopsy setting; more than 10 IgG4-positive plasma cells/high power field should be considered suspicious for IgG4-related sclerosing cholangitis.

Hepatic involvement can manifest as an inflammatory mass or as portal inflammation resembling PSC. [20, 21] In the liver, the mass lesion of IgG4-RSD tends to be rich in lymphocytes and plasma cells. Zen et al [21] subdivided hepatic pseudotumors into lymphoplasmacytic (lymphocytes, plasma cells, eosinophils, phlebitis) and fibrohistiocytic (histiocytes, multinucleated giant cells, neutrophils) and found that the former always had many IgG4-positive plasma cells (more than 50/hpf) while the latter tended to be IgG4-poor.

Deshpande et al [22] compared liver biopsy findings in PSC and the PSC-like changes of IgG4-related liver involvement. The latter tended to have more portal and lobular inflammation and more plasma cells (90% vs 24%). The authors also described “portal based fibroinflammatory nodules” in IgG4-related disease, which could be construed as a microscopic form of inflammatory pseudotumor. Six of 10 livers with IgG4 disease had

increased numbers of IgG4-positive plasma cells, compared to none of 12 PSC cases. Evaluating liver biopsies in this setting is complicated by the fact that some patients with IgG4-related changes in extra-hepatic ducts can develop intrahepatic changes secondary to chronic incomplete obstruction, without the liver itself being involved by IgG4-RSD.

At least 25% of patients with AIP have gallbladder involvement. [23] The morphology is distinctive: full-thickness inflammation featuring numerous lymphoid aggregates in the adventitia, accompanied by the usual lymphoplasmacytic inflammation, fibrosis and phlebitis. [24]

Some patients with IgG4-RSD have increased numbers of IgG4-positive cells in the gut. An early description of multifocal involvement by IgG4-RSD described increased numbers of IgG4-positive plasma cells in gastric biopsies from 5 of 7 patients and colon biopsies from 2 of 2 patients. [12] More recently, Deheragoda et al described similar findings in stomach, duodenum and colon, albeit in only one patient. [25] The potential benefit here is obvious, as it is much easier to biopsy the colon than the pancreas. My experience hasn't borne out the promise of gut-based diagnosis; only a handful of the dozens of IgG4 stains that I have been asked to do on

gastrointestinal biopsies have been positive. Still, recent reports describe chronic gastritis in some patients with IgG4-RSD. [26] The histologic features of gastrointestinal involvement do not seem to be distinctive, so in most cases the decision to stain gastrointestinal biopsies for IgG4 will be driven by clinical suspicion for IgG4-RSD.

Conclusion

The combination of clinical features and histology can usually establish a diagnosis of type 1 AIP without the need for pancreatic resection. Affected patients will often have other manifestations of IgG4-related sclerosing disease. There is no one histologic feature specific for IgG4-RSD, but a mix of lymphoplasmacytic inflammation, storiform fibrosis and phlebitis is characteristic. Immunohistochemistry for IgG4 is also nonspecific, but large numbers of IgG4-positive cells are a useful adjunct to the diagnosis.

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