Autoimmune Pancreatitis and Retroperitoneal Fibrosis

Thomas C. Smyrk, MD

Associate Professor of Pathology

Mayo Clinic, Rochester MN 55902

smyrk.thomas@mayo.edu
Summary

Retroperitoneal fibrosis complicated by ureteral obstruction and hydronephrosis can be a manifestation of IgG4-related sclerosing disease. Affected patients almost always have similar fibroinflammatory lesions at other sites, with the pancreas being the best-known. This review will detail the histologic features of autoimmune pancreatitis (with a digression on subtypes of the condition) and summarize the extra-pancreatic manifestations of IgG4-related disease, with emphasis on retroperitoneal fibrosis.

Autoimmune pancreatitis

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 or IgG4-related systemic disease (IgG4-RSD).
IgG4-RSD produces a characteristic but not specific set of histologic changes, modified by the microanatomy of the particular site involved. Cheuk and Chan have provided a superb recent review of the topic. [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 Despande 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 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 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 Despande 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

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60-70</td>
<td>50-60</td>
</tr>
<tr>
<td>Sex</td>
<td>4-5M:1F</td>
<td>M=F</td>
</tr>
<tr>
<td>Jaundice</td>
<td>common</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>rare</td>
<td>usual</td>
</tr>
<tr>
<td>IgG4-RSD</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Periductal inflammation</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>GELs</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Storiform pattern</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>IgG4 IHC</td>
<td>+++</td>
<td>0 to +</td>
</tr>
</tbody>
</table>

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.

**Retroperitoneal 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. IgG4 disease also seems to account for a substantial subset of retroperitoneal fibrosis.

Retroperitoneal fibrosis is an idiopathic chronic inflammatory fibrosing condition, probably with multiple causes. Affected patients can have similar fibrosing lesions at other sites; this condition has been referred to as multifocal fibrosclerosis. [20] Even before the IgG4 story developed, pancreatic disease was noted as a sometime association with multifocal fibrosclerosis. [21] Now, it appears that IgG4 disease accounts for many examples of multifocal fibrosclerosis. [22, 23] Zen et al recently described 17 patients with retroperitoneal fibrosis, 10 of whom were thought to be IgG4-related. [24] In general, there were no histologic features specific for IgG4-related fibrosis: both set of patients had variable degrees of inflammation, with or without lymphoid aggregates. Multinucleated giant cells were present in about 20% of both groups. Phlebitis, however, was much more common in the IgG4-related group (6/10 vs 1/7). IgG4 immunohistochemistry showed significant differences, both in terms of IgG4-positive plasma cells (68/hpf vs 3/hpf) and IgG4/IgG ratios (62% vs
4%). Strikingly, all 10 patients with IgG4-related disease were male, while 6 of the other 7 were female.

The male predominance noted by Zen et al has also been a feature of other cases described in the literature, mostly in the form of case reports. In fact, all 14 cases collected in a recent review of the literature were male. [25] Among those 14 patients, 11 also had pancreatitis, two had salivary gland involvement and one had mediastinitis. All 11 patients for whom treatment was described were said to have a positive response to corticosteroid treatment.

**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.
Retroperitoneal fibrosis (and other conditions linked to multifocal fibrosclerosis) often feature IgG4-rich infiltrates and are associated with other manifestations of IgG4-related sclerosing disease. Thus far, there is a striking male predominance in this subset of IgG4-RSD (a condition in which males already predominate). The etiology remains unknown.


