Autoimmune Pancreatitis: A Multiorgan Disease Presenting a Conundrum for Clinicians in the West

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Abstract: Autoimmune pancreatitis (AIP), a clinical entity originally described in East Asia and more recently recognized in the United States and Europe, poses a diagnostic conundrum for clinicians in the West due to immunoglobulin G4 seronegativity. Although expert panels classify this disease into 2 types, it remains difficult to stratify the disease given that both types share most clinical, biochemical, and imaging characteristics. The classic presentation of AIP can mimic that of pancreatic carcinoma, which increases the urgency of evaluation, diagnosis, and treatment. In this article, we elucidate the differences between the 2 types of AIP, highlight the shortcomings of the current classification system, and propose a more inclusive view of the disorder.
Classification

AIP is a form of chronic pancreatitis that is clinically characterized by the presentation of cholestasis, obstructive jaundice, and/or a pancreatic mass; histologically characterized by fibrosis and a lymphoplasmacytic infiltrate; and therapeutically characterized by a dramatic response to corticosteroid treatment. In 2011, AIP was formally classified by the International Consensus Diagnostic Criteria into 2 categories: type 1 and type 2 (Table).9,10

Type 1 AIP is characterized by the histologic description of lymphoplasmacytic sclerosing pancreatitis. It is associated with IgG4-positive serology and other organ involvement (sclerosing cholangitis, sclerosing sialadenitis, tubulointerstitial nephritis, and retroperitoneal fibrosis). This type of AIP is more common in older men and people of East Asian ethnicity, and it has a high relapse rate.

Type 2 AIP is characterized by the histopathologic pattern of chronic pancreatitis called idiopathic ductocentric pancreatitis or by the presence of granulocytic epithelial lesions. It is associated with IBD but has no known serologic biomarker. This type is more common in younger people of Western (European and American) ethnicity, does not show a sex predilection, and rarely recurs.

Clinical Presentation

Classically, AIP presents with obstructive jaundice and/or a pancreatic mass.9 There may be an insidious prodrome of feeling unwell, with complaints of a gnawing midline discomfort sometimes associated with ingestion of food, medications, or alcohol. Mild weight loss is not uncommon. A minority of patients present with a more acute, painful pancreatitis. An international, multicenter survey of 731 AIP patients found obstructive jaundice to be a more frequent presentation in type 1 vs type 2 AIP (75% vs 47%; \(P < .001\)), whereas abdominal pain (41% vs 68%; \(P < .001\)) and acute pancreatitis (5% vs 34%; \(P < .001\)) were more frequent in type 2 AIP.10 Patients with type 1 AIP have a high relapse rate, and patients with type 2 AIP rarely experience relapse.11

Imaging

The characteristic findings seen on computed tomography (CT), magnetic resonance imaging (MRI), pancreateography, and endoscopic ultrasound (EUS) are common for both types of AIP.12-15 CT/MRI in AIP shows an enlarged pancreas with featureless borders often described as “sausage-shaped” (Figure 1). Imaging scans frequently demonstrate pancreatic swelling and occasionally show a

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 1 Autoimmune Pancreatitis</th>
<th>Type 2 Autoimmune Pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Asia &gt; United States, Europe</td>
<td>Europe &gt; United States &gt; Asia</td>
</tr>
<tr>
<td>Age</td>
<td>60 years or older</td>
<td>Younger (~40 years)</td>
</tr>
<tr>
<td>Sex</td>
<td>Men &gt; women</td>
<td>Men = women</td>
</tr>
<tr>
<td>Serology</td>
<td>High serum IgG4, autoAb+</td>
<td>Normal serum IgG4, autoAb−</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Marked lymphocyte and plasmacyte infiltration and fibrosis Infiltration of IgG4+ plasma cells</td>
<td>Granulocytic epithelial lesion often with destruction and obliteration of the pancreatic duct</td>
</tr>
<tr>
<td>Symptoms (overall)</td>
<td>Painless/obstructive jaundice Pancreatic exocrine insufficiency New-onset diabetes</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Radiologic findings</td>
<td>Pancreatic swelling (“sausage-shaped”)</td>
<td></td>
</tr>
<tr>
<td>Other organ involvement</td>
<td>Salivary/submandibular/lacrimal glands Bile ducts (sclerosing cholangitis) Kidneys (renal mass, tubulointerstitial nephritis) Retroperitoneal fibrosis</td>
<td>Rare</td>
</tr>
<tr>
<td>Association with IBD</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Response to corticosteroids</td>
<td>Responsive</td>
<td></td>
</tr>
<tr>
<td>Relapse rate</td>
<td>High</td>
<td>Low</td>
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</tbody>
</table>

AutoAb, autoantibody; IBD, inflammatory bowel disease; IgG4, immunoglobulin G4.
mass, both of which affect biliary obstruction and cholestasis (Figure 2). In such cases, the bile duct morphology can be attenuated (stricturing) or dilated, obfuscating the clinical picture because these findings are also present in sclerosing cholangitis and cholangiocarcinoma, which are entities associated with IBD.

Pancreatographic features include segmental or diffuse irregular narrowing of the main duct. CT/MRI can be used to differentiate neoplasms from AIP, which demonstrates clear anatomic surgical planes. Vascular structures are unaffected in most AIP patients, with the exception of venous thrombosis and the development of collateral vessels secondary to the inflammatory process. However, inflammatory changes may extend to peripancreatic lymph nodes, in which case a biopsy is required to rule out neoplasia. In positron emission tomography studies, uptake of fluorodeoxyglucose in organs known to be affected by IgG4-related disease other than the pancreas suggests AIP. The classic EUS finding in AIP is hyperchoic parenchyma of a pancreatic mass with clear margins. However, with EUS, a definitive diagnosis must be established histologically via multiple fine-needle aspirations or a core biopsy of the lesion.

**Other Organ Involvement**

Both types of AIP can be associated with extrapancreatic disease. Type 1 commonly has other organ involvement related to IgG4 infiltration. Although previously regarded as isolated single-organ diseases without any known underlying systemic condition, IgG4-related diseases were recently recognized as a unified entity. These diseases can manifest as sclerosing cholangitis, sclerosing sialadenitis, tubulointerstitial nephritis, and/or retroperitoneal fibrosis. Other affected areas include the lung, prostate, aorta, pericardium, pituitary gland, and lymph nodes. This involvement can present at any time before or after the diagnosis of AIP.

Both types of AIP are associated with IBD, although much less commonly in type 1. This association is predominantly with ulcerative colitis; however, there are reports of AIP associated with Crohn’s disease. The incidence is much greater in type 2 AIP (seronegative patients in the West) compared with type 1 AIP (seropositive Asian patients).

**Histopathology**

Given the clinical and radiologic similarities between AIP and pancreatic carcinoma, a tissue sample is essential for establishing a definitive diagnosis. This requires EUS, CT guidance, or surgical intervention. The find-
If the results are equivocal and the lesion is resectable, surgery is recommended. However, in our institution, where we have experienced pancreatic surgeons, surgery is performed very infrequently.

Analysis

The original diagnosis of AIP was one of exclusion until the 1960s when hypergammaglobulinemia was determined to be a more objective marker for diagnosis. Decades later, investigators noted 2 distinct patterns of the disease. It was not until the early 2000s that a more definitive set of guidelines and classifications were established. The guidelines defined 2 types of AIP, classifying them by their serologic and histologic characteristics, and discussing other distinguishing features of each type (Table). Our intention is to alter the strict classifications accepted today and demystify these associations. The 2 types of AIP are interrelated, but we feel that classification into 2 simple but tightly defined groups is misguided.

Figures 1 through 3 are from a patient who has the potential to manifest characteristics from both types 1 and 2 AIP (an elderly white man with a history of Crohn’s disease, nonsarcoid hilar adenopathy, and recurrent AIP).

Neoplasms Associated With Autoimmune Pancreatitis

Patients with IgG4-related disease are suspected to have an increased risk of malignancies. A report from Japan revealed that, over a 3-year period of observation, 11 of 106 patients with IgG4-related disease were diagnosed with cancer, including colon cancer, lung cancer, and lymphoma. This is 3.5 times more frequent than in the general population. Another report from Japan similarly demonstrated that 15% of their cohort of 108 patients developed cancer within the first year of diagnosis. An issue of whether to distinguish AIP from cancer on initial presentation remains a dilemma. This dilemma is especially imposing in patients who present with seronegative studies, as most patients do in the West. When other imaging studies and core biopsies are completed, and the results are negative, most experts recommend a short course of corticosteroids. The follow-up imaging studies and the patient’s response should verify the diagnosis.

Figure 4. Resolution of a pancreatic mass on a repeat computed tomography scan.

If the results are equivocal and the lesion is resectable, surgery is recommended. However, in our institution, where we have experienced pancreatic surgeons, surgery is performed very infrequently.
Initial and repeat biopsies confirmed the presence of IgG4-negative type 1 AIP. The patient’s response to corticosteroid treatment was confirmed with repeat CT imaging (Figure 4). However, several months later, the patient seroconverted positive for IgG4 with markedly elevated serum levels. Cases such as this one suggest that AIP (both types 1 and 2) is not an isolated disease, but rather part of a syndrome with a unifying autoimmune component.

The conclusive diagnosis of seronegative AIP has been challenging until recently. Historically, AIP was a diagnosis of exclusion. After other causes of pancreatitis were evaluated more easily (gallstones, alcohol, viruses, or medications), these seronegative patients were left with the ambiguous diagnosis of idiopathic pancreatitis. With this vague diagnosis and suspicion for AIP, clinicians were sometimes reluctant to commit patients to a course of corticosteroid treatment, especially when the possibility of a neoplasm had not been completely eliminated.

The precision of AIP diagnosis has greatly improved in recent years, secondary to the concomitant evolution of diagnostic technologies. CT can distinguish autoimmune from other types of pancreatitis, and the use of EUS with fine-needle aspirations and core biopsies has further defined the diagnosis. These techniques are significantly less invasive modes of obtaining definitive histology, thus ruling out carcinoma and confirming a diagnosis of AIP that is otherwise difficult to make, especially in IgG4-negative patients in the West.

Of concern to many clinicians is when the pancreatic histopathology is inconclusive or when tissue biopsy is not possible. In this not-uncommon scenario, one is tempted to refer patients for immediate surgical consultation for a definitive operation for cancer or palliative bypass decompression. However, it is recommended that a short trial of corticosteroid treatment be given first. Such a trial can elucidate the difference between AIP and carcinoma because AIP has a dramatic and lasting response to this therapy. Pancreatic carcinoma may show temporary clinical improvement with corticosteroid treatment; however, rapid recurrence of symptoms and/or radiologic findings is highly suggestive of neoplasm and warrants aggressive surgical intervention.

A correct and timely recognition of AIP prevents unnecessary surgery and reduces patient anxiety, whereas a misdiagnosis of AIP can be very problematic, especially if patients are misdiagnosed with pancreatic cancer. We suspect that the number of AIP patients who mistakenly have undergone surgical resection for suspected carcinoma has altered the epidemiologic data on pancreatic cancer survivorship. We emphasize, however, that early pancreatic cancer detection is paramount to patient survival. We conclude that early, accurate differentiation between AIP and pancreatic carcinoma can reduce patient morbidity.

**Conclusion**

AIP is ubiquitous, presents in several ways, and is associated with other intercurrent medical problems, including IBD and other autoimmune disorders. The classic presentation of AIP can mimic that of pancreatic carcinoma. This presents a conundrum for clinicians in the West because a majority of white patients are IgG4-seronegative, making the definitive diagnosis of AIP nearly impossible without tissue biopsy. In this scenario, rather than immediate invasive surgical intervention, we recommend obtaining tissue for diagnosis via EUS- or CT-guided biopsy and beginning treatment with corticosteroids. The clinical response to corticosteroids is rapid and dramatic in both types of AIP, reassuring the clinician that the decision to start this medication was appropriate. Serial follow-up imaging studies will ultimately justify this decision.

_The authors have no relevant conflicts of interest to disclose._

**References**


