International Consensus Diagnostic Criteria for Autoimmune Pancreatitis

Guidelines of the International Association of Pancreatology

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Objectives: To achieve the goal of developing international consensus diagnostic criteria (ICDC) for autoimmune pancreatitis (AIP).

Methods: An international panel of experts met during the 14th Congress of the International Association of Pancreatology held in Fukuoka, Japan, from July 11 through 13, 2010. The proposed criteria represent a consensus opinion of the working group.

Results: Autoimmune pancreatitis was classified into types 1 and 2. The ICDC used 5 cardinal features of AIP, namely, imaging of pancreatic parenchyma and duct, serology, other organ involvement, pancreatic histology, and an optional criterion of response to steroid therapy. Each feature was categorized as level 1 and 2 findings depending on the diagnostic reliability. The diagnosis of type 1 and type 2 AIP can be definitive or probable, and in some cases, the distinction between the subtypes may not be possible (AIP—not otherwise specified).

Conclusions: The ICDC for AIP were developed based on the agreement of an international panel of experts in the hope that they will promote worldwide recognition of AIP. The categorization of AIP into types 1 and 2 should be helpful for further clarification of the clinical features, pathogenesis, and natural history of these diseases.

Key Words: autoimmune pancreatitis, international consensus diagnostic criteria, type 1 AIP, type 2 AIP

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form, whose histological description is called lymphoplasmacytic sclerosing pancreatitis (LPSP) or AIP without granulocyte epithelial lesions (GELs), the pancreatic histopathology shows 4 characteristic features: (1) dense infiltration of plasma cells and lymphocytes, particularly periportal; (2) peculiar storiform fibrosis; (3) venulitis with lymphocytes and plasma cells often leading to obliteration of the affected veins; and (4) abundant (>10 cells per high-power field [HPF]) immunoglobulin (Ig) G4 positive plasma cells. Clinically, this form of AIP seems to be the pancreatic manifestation of an IgG4-related systemic disease characterized by elevated serum IgG4 levels and extrapancreatic lesions (e.g., sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis) associated with infiltration with abundant IgG4-positive plasma cells. This form of AIP presents predominantly with obstructive jaundice in elderly male subjects, and the pancreatic and extrapancreatic manifestations respond to steroid therapy. The clinical diagnosis of LPSP is made by a combination of features previously noted and often can be made without need for histology.

In the United States and Europe, histological examination of resected pancreata of patients with chronic nonalcoholic pancreatitis showed another histopathological pattern of chronic pancreatitis called idiopathic duct-centric pancreatitis (IDCP) or AIP with GEL.5-8 Idiopathic duct-centric pancreatitis and LPSP share some histopathological features, such as periductal lymphoplasmacytic infiltrate and storiform fibrosis. A characteristic feature of IDCP, not seen in LPSP, is the GEL: intraluminal and intrapithelial neutrophils in medium-sized and small ducts as well as in acini, often leading to the destruction and obliteration of the duct lumen. Idiopathic duct-centric pancreatitis usually has none or very few (<10 cells/HPF) IgG4-positive plasma cells, although this can vary. Clinical data from histologically confirmed IDCP cases show that they have distinctly different profile compared with LPSP cases. Idiopathic duct-centric pancreatitis seems not to be a systemic disease; rather, it seems to be a pancreas-specific disorder. It is not associated with either serum IgG4 elevation or with other organ involvement (OOI) typically seen in LPSP. Approximately 30% of reported cases of IDCP have associated inflammatory bowel disease, such as ulcerative colitis. Patients with IDCP are, on average, a decade younger than LPSP patients and do not show a sex predilection. Currently, IDCP lacks a serological biomarker. Because IDCP patients are seronegative and lack other organ involvement, definitive diagnosis requires pancreatic histology.

**AIP Types: Worldwide Distribution**

In a recent worldwide survey of AIP,4 it was noted that whereas most cases of AIP in Asia fit the profile of LPSP, European and American series had a mixture of patients fitting the profiles of both LPSP and IDCP. Because the diagnosis of IDCP requires histological examination of an adequate specimen of the pancreas, which is not frequently available, IDCP cannot be diagnosed easily, and this may explain the fewer cases of IDCP diagnosed worldwide.

**AIP Types: Nomenclature**

The terms LPSP (AIP without GELs) and IDCP (AIP with GELs) refer to pancreatic histological patterns in AIP. Because pancreatic histology often is not available, the terms type 1 and type 2 AIP have been introduced to describe the clinical profiles associated with LPSP and IDCP, respectively, while recognizing the similarities between the 2 entities.9 Whether type 2 is an autoimmune process has been debated10; however, its clinical presentation with obstructive jaundice, overlap in histological features with type 1, and anecdotal but yet unconfirmed response to steroids leads to a clinical diagnosis of AIP in patients with type 2. Additionally, clinically important diagnostic and therapeutic considerations, that is, need to accurately distinguish it from pancreatic cancer and treatment with steroids, are similar in the 2 types of AIP. The consensus opinion was that the term type 1 and type 2 should be used to describe the clinical profiles associated with LPSP and IDCP, respectively.4

**International Consensus Diagnostic Criteria for AIP**

The goals of the ICDC for AIP are to develop criteria that can be applied worldwide, taking into consideration marked differences in clinical practice patterns, to safely diagnose AIP and avoid misdiagnosis of pancreatic cancer as AIP (Tables 1–5, Figs. 1–3). The ICDC for AIP were developed after review of existing criteria, including JPS (2002, 2006),4,11 HISORt (2006, 2009),12 Korean (2007),13 Asian (2008),13 Mannheim (2009),14 and Italian (2003, 2009).15

**DIAGNOSIS OF AIP: BACKGROUND CONSIDERATIONS**

**Clinical Presentation**

**Acute Presentation**

The most frequent acute presentation of AIP is with obstructive jaundice and/or pancreatic mass. Whereas most patients have pancreatic swelling (diffuse or focal), a few patients may have a low-density pancreatic mass, and rarely, no abnormality may be seen on cross-sectional imaging. The proposed criteria are meant to be used to diagnose AIP in this setting.

**Late Presentation**

Pancreatic atrophy, calcification, ductal dilation, and other features of advanced painless chronic pancreatitis may be seen on follow-up of patients with typical acute presentation of AIP. These patients do not complain of pain or recurrent pancreatitis.

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**TABLE 1. Diagnosis of Definitive and Probable Type 1 AIP Using ICDC**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Primary Basis for Diagnosis</th>
<th>Imaging Evidence</th>
<th>Collateral Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive type 1 AIP</td>
<td>Histology Typical/indeterminate</td>
<td>Imaging Typical Indeterminate</td>
<td>Histologically confirmed LPSP (level 1 H) Any non-D level 1/level 2 Two or more from level 1 (+level 2 D*)</td>
</tr>
<tr>
<td>Response to steroid</td>
<td>Indeterminate</td>
<td>Level 1 S/OOI + Rt or level 1 D + level 2 S/OOI/H + Rt</td>
<td></td>
</tr>
<tr>
<td>Probable type 1 AIP</td>
<td>Indeterminate</td>
<td>Level 2 S/OOI/H + Rt</td>
<td></td>
</tr>
</tbody>
</table>

*Level 2 D is counted as level 1 in this setting.*
Diagnosis of AIP in the burnt out stage is not easy and is not within the scope of these diagnostic criteria.

**Presentations Not Suggestive of AIP**

Marked cachexia, inability to eat, and narcotic requiring pain are more suggestive of cancer and are rarely seen in AIP. Although patients with typical acute presentation may concomitantly meet criteria for pancreatitis (2 of the following 3: 3-fold elevated pancreatic enzymes, abdominal pain, or computed tomography (CT) evidence of pancreatic swelling), typical idiopathic pancreatitis or painful chronic pancreatitis are not commonly seen in histologically confirmed AIP.

**Cardinal Features of AIP**

As previously noted, AIP and its subtypes have a histopathological pattern that is diagnostic. However, histology is not usually available. Therefore, the diagnosis of AIP requires a
combination of features. The existing diagnostic criteria have used a combination of 1 or more of 5 cardinal features of AIP: 1. imaging features of the following: (a) pancreatic parenchyma (on CT/magnetic resonance imaging [MRI]) and (b) pancreatic duct (endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography), 2. serology (IgG4, IgG, and antinuclear antibody), 3. OOI, 4. histopathology of the pancreas, and 5. response to steroid therapy.

**Distinguishing Type 1 From Type 2 Using Diagnostic Criteria**

1. Based on our current knowledge, it does not seem that imaging and response to steroids can distinguish type 1 from type 2 (Tables 1–5).
2. Typical serological abnormalities and OOI are seen only in type 1. Inflammatory bowel disease seems to be associated with both forms, more so with type 2.
3. Absence of serological abnormalities or lack of OOI in patients with “AIP” does not necessarily imply the diagnosis of type 2, as type 1 also can be seronegative and without OOI.
4. For the purposes of the development of criteria, “definitive type 1” can be diagnosed with surrogate criteria for AIP not including histology. However, definite IDCPC requires histological confirmation.

**TABLE 4. Diagnosis of AIP—Not Otherwise Specified Using ICDC**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Imaging Evidence</th>
<th>Collateral Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP—not otherwise specified</td>
<td>Typical/indeterminate</td>
<td>D1/2 + Rt</td>
</tr>
</tbody>
</table>

**TABLE 5. Level 1 and Level 2 Criteria for Type 2 AIP**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Level 1</th>
<th>Level 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>P Parenchymal imaging</td>
<td>Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)</td>
<td>Indeterminate (including atypical)</td>
</tr>
<tr>
<td>D Ductal imaging (ERP)</td>
<td>Long (&gt;1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation</td>
<td>Segmental/focal narrowing without marked upstream dilatation (duct size, &lt;5 mm)</td>
</tr>
<tr>
<td>OOI Other organ involvement</td>
<td></td>
<td>Clinically diagnosed inflammatory bowel disease</td>
</tr>
</tbody>
</table>

**Histology of the pancreas (core biopsy/resection)**

IDCP: Both of the following:
1. Granulocytic infiltration of duct wall (GEL) with or without granulocytic acinar inflammation
2. Absent or scant (0–10 cells/HPF) IgG4-positive cells

Response to steroid (Rt)*

*Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats (see text) only after negative workup for cancer including endoscopic ultrasound-guided fine needle aspiration.

†Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilatation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP, and a thorough workup for cancer is negative (see algorithm).

5. Autoimmune pancreatitis that does not meet these criteria, including histologically unconfirmed but clinically suspected type 2, is categorized as “probable AIP.”

**Imaging: Probability of AIP Versus Pancreatic Cancer Varies Depending on Pancreatic Imaging Findings on CT/MRI**

Pancreatic findings on abdominal CT or MRI often are the first clues that raise the suspicion of pancreatic cancer or AIP (Tables 2 and 5). However, AIP is uncommon compared with pancreatic cancer. Before AIP was recognized as a clinical entity, only 2% to 3% of patients undergoing resection for suspected pancreatic cancer had AIP. However, the probability of AIP versus pancreatic cancer in patients with obstructive jaundice can be predicted based on CT/MRI findings:

1. Patients with obstructive jaundice with a diffusely enlarged pancreas (especially with a capsule-like rim) without pancreatic ductal dilatation/cutoff or pancreatic low density mass on CT/MRI are highly likely to have AIP. In such patients, presence of less collateral evidence is required to make the diagnosis of AIP.
2. Subjects with findings typical of pancreatic cancer (low density mass on contrast-enhanced CT, pancreatic ductal dilatation/cutoff with or without pancreatic atrophy) should be considered as having pancreatic cancer unless the workup for cancer is negative and there is strong collateral evidence of AIP.
3. Subjects without features typical of AIP or pancreatic cancer should first be investigated for pancreatic cancer, and AIP should be considered only if workup for cancer is negative and there is strong collateral evidence of AIP.

**Pancreatographic Findings**

When expert physicians read pancreatograms, they can distinguish AIP from pancreatic cancer, with some features...
being more helpful than others (Tables 2 and 5). Thus, a combination of typical imaging and pancreatographic findings is highly suspicious for AIP. However, in the West, diagnostic pancreatograms are rarely performed in the setting of obstructive jaundice. Therefore, in the West, a diagnostic pancreatogram may assume the role of collateral evidence when

![Algorithm to diagnose type 1 AIP in subjects presenting with obstructive jaundice and/or pancreatic enlargement](image1)

**FIGURE 1.** Algorithm to diagnose type 1 AIP in subjects presenting with obstructive jaundice and/or pancreatic enlargement. This schematic drawing shows a flow to diagnose type 1 AIP with typical diffuse enlargement of the pancreas on CT/MRI (level 1 parenchymal findings).

![Algorithm to diagnose type 1 AIP in subjects presenting with obstructive jaundice and/or pancreatic enlargement/mass](image2)

**FIGURE 2.** Algorithm to diagnose type 1 AIP in subjects presenting with obstructive jaundice and/or pancreatic mass. This schematic drawing shows a flow to diagnose type 1 AIP with indeterminate or atypical findings of the pancreas on CT/MRI (level 2 parenchymal findings).
imaging findings are not typical or in seronegative patients without OOI.

**Serology**

1. Elevation in any one or more IgG, IgG4, and antinuclear antibody titers is commonly seen in AIP. However, false-positive elevation of each of these markers has been seen in pancreatic cancer and other disorders. When all markers are measured, the false positivity of the panel can be significantly high (up to 40%) (Table 2).
2. Serum IgG4 elevation is the single best marker of AIP. Therefore, in the ICDC for AIP, only serum IgG4 is recommended as a serological marker. Because the upper limits of normal IgG4 vary between laboratories, only fold elevation above normal rather than absolute value is used in the ICDC.
3. Marked elevation of serum IgG4 (>2 times upper limit of normal) is strongly suggestive of AIP in the setting of obstructive jaundice/pancreatic mass.
4. Elevation in serological markers is not sufficient to make a diagnosis of AIP unless seen in the setting of typical imaging finding.

**Other Organ Involvement**

1. Other organ involvement noted here is part of the manifestation of IgG4-related systemic disease. Other unrelated autoimmune disorders (eg, rheumatoid arthritis, psoriatic arthropathy, true seropositive Sjögren) are not typically associated with AIP and should not be included as OOI (Tables 2 and 5).
2. Other organ involvement may be diagnosed by histological evaluation of tissue, by imaging (proximal bile duct structure, retroperitoneal fibrosis) or by clinical examination (salivary gland enlargement).

**Histology of the Pancreas: Role in the Diagnosis of AIP**

1. As mentioned earlier, type 1 often can be diagnosed without histology, but type 2 requires an adequate histological specimen to make a definitive diagnosis (Tables 2 and 5).
2. Autoimmune pancreatitis can be diagnosed on resection or biopsy specimen, provided the specimen displays the characteristic features.
3. Biopsy showing some but not all features of LPSP or IDC (lymphoplasmacytic infiltrate with storiform fibrosis) can be used as supportive evidence for diagnosis of AIP.

**Response to Steroids**

1. A steroid trial involves use of prednisone 0.6 to 1 mg/kg with reassessment of imaging and Ca 19-9 after 2 weeks of treatment (Tables 2 and 5). The panel agreed on 2 weeks for duration of steroid trial based on the study by Moon et al. the only study which has examined this issue. In AIP, one would expect a definitive improvement in imaging abnormalities, including biliary strictures and pancreatic enlargement. In the study by Moon et al, no patient with pancreatic cancer showed “response” to steroids. In AIP, CA 19-9 levels drop with treatment, and a rising CA 19-9 suggests that the diagnosis of AIP is incorrect. Resolution of imaging abnormalities may take weeks to months and, in some, is associated with atrophy of gland.
2. In patients with appropriate collateral evidence of AIP, response to steroids can confirm a strong suspicion of AIP. However, steroid trial as a means to diagnose AIP is to be used sparingly and should not be used as a substitute for a thorough search for an etiology.
3. The strategy that “if steroids work, it must be AIP” is fraught with problems when there is no collateral evidence to support the diagnosis.
4. Symptomatic improvement and a sense of well-being occur nonspecifically in response to steroids and can be seen even in pancreatic cancer patients. Therefore, these parameters should not be used to assess response.

5. Steroid therapy leads to reduction in IgG4 levels in AIP. However, falsely elevated IgG4 in pancreatic cancer and other non-AIP states also can decrease with steroid therapy. Therefore, a “response” of IgG4 to steroid treatment cannot be used to diagnose AIP.

6. Spontaneous radiological improvement in pancreatic cancer-induced pancreatitis can be mistaken for steroid response.

The consensus diagnostic criteria (Tables 1–5) and diagnostic algorithms (Figs. 1–3) are an effort of Eastern and Western experts to find common bases for diagnosis of AIP worldwide. They are inclusive of practice patterns in different countries. They can be tailored for use in individual institutions depending on local expertise.

These diagnostic criteria are meant to recognize the spectrum of AIP as we know it today. The panel recognizes that the spectrum of AIP may extend beyond our current understanding of the disease (after all, it has rapidly expanded in the past 10 years). However, future “extensions” of the spectrum of AIP or better allocation into the 2 groups will have to be based on histologically confirmed cases and determination of novel serum markers5,18 rather than response to steroids.

CONCLUSIONS

This ICDC for AIP was developed by a panel of experts during the International Association of Pancreatologists held in Fukuoka, Japan. This consensus guidelines was based on the recognition that AIP has 2 distinct histopathology and clinical subtypes, previously agreed upon by the consensus meeting held in Honolulu during the joint meeting of the Japan Pancreas Society and the American Pancreatic Association.4 We look forward to the further input by the health care providers and professional groups in using these guidelines in the clinical management of AIP and for further updating these guidelines.

REFERENCES


