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Histopathologic and Clinical Subtypes of Autoimmune Pancreatitis: The Honolulu Consensus Document

Suresh T. Chari[a] Guenter Kloeppel[b] Lizhi Zhang[a] Kenji Notohara[d] Markus M. Lerch[c] Tooru Shimosegawa[e] for the Autoimmune Pancreatitis International Cooperative Study Group

[a]Mayo Clinic College of Medicine, Rochester, Minn., USA; [b]University of Kiel, Kiel, [c]Klinikum der Ernst-Moritz-Arndt-Universität Greifswald, Greifswald, Germany; [d]Kurashiki Central Hospital, Kurashiki, and [e]Tohoku University Graduate School of Medicine, Sendai, Japan

Key Words
Autoimmune pancreatitis · Lymphoplasmacytic sclerosing pancreatitis · Idiopathic duct-centric pancreatitis · Diagnostic criteria

Abstract
Autoimmune pancreatitis (AIP) has been extensively reported from Japan, Europe and the USA. While the descriptions of AIP from Japan have predominantly been based on the presence of a distinct clinical phenotype, reports from Europe and the USA describe at least 2 histopathologic patterns in patients diagnosed with AIP, namely lymphoplasmacytic sclerosing pancreatitis (LPSP) and idiopathic duct-centric pancreatitis (IDCP) or granulocytic epithelial lesion-positive pancreatitis. While the 2 entities share common histopathologic features (periductal lymphoplasmacytic infiltration and peculiar periductal fibrosis), expert pathologists can accurately distinguish them on the basis of other unique histopathologic features. Clinically, the 2 entities have a similar presentation (obstructive jaundice/pancreatic mass and a dramatic response to steroids), but they differ significantly in their demography, serology, involvement of other organs and disease relapse rate. While LPSP is associated with elevation of titers of nonspecific autoantibodies and serum IgG4 levels, IDCP does not have definitive serologic autoimmune markers. All experts agreed that the clinical phenotypes associated with LPSP and IDCP should be nosologically distinguished; however, their terminology was controversial. While most experts agreed that the entities should be referred to as type 1 and type 2 AIP, respectively, others had concerns regarding use of the term 'autoimmune' to describe IDCP.

Background

A form of idiopathic chronic pancreatitis suspected to be due to an autoimmune process was first described by Sarles et al. [1] in 1961. In 1991, Kawaguchi et al. [2] described 'an unusual lymphoplasmacytic sclerosing inflammatory disease involving the total pancreas, common bile duct, gallbladder, and, in one patient, the lip' in 2 patients who presented with a mass-like enlargement of the pancreatic head. Histopathologic characteristics in-

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Suresh T. Chari, MD
200 First Street SW
Mayo Clinic College of Medicine
Rochester, MN 55905 (USA)
Tel. +1 507 266 4347, Fax +1 507 284 0538, E-Mail chari.suresh@mayo.edu

cluded diffuse lymphoplasmacytic infiltration, marked interstitial fibrosis, acinar atrophy and obliterative phlebitis of the pancreatic and portal veins. They called the condition lymphoplasmacytic sclerosing pancreatitis (LPSP) with cholangitis [2]. In 1995, Yoshida et al. [3] described a 68-year-old woman with steroid-responsive disease presenting with obstructive jaundice, a diffusely enlarged pancreas, an irregularly narrowed pancreatic duct, hypergammaglobulinemia and elevated autoantibody titers. Drawing parallels from the literature on autoimmune hepatitis, the authors coined the term 'autoimmune pancreatitis' (AIP) [3] to describe this clinical entity. In 2002, the Japan Pancreas Society proposed diagnostic criteria for AIP [4] based on the classic imaging and serologic findings; these were revised in 2006 [5].

In 2001, Hamano et al. [6] reported from Japan that elevated serum IgG4 levels were highly specific and sensitive for the diagnosis of AIP. In 2003, Kamisawa et al. [7] suggested that AIP is a systemic disease, based on the findings that there is abundant infiltration of the pancreas and other involved organs with IgG4-positive plasma cells. These features were included in the Korean diagnostic criteria for AIP proposed in 2007 [8]. In 2008, Japanese and Korean societies agreed on Asian consensus criteria for the diagnosis of AIP [9]. Recently, a Japanese study based on a survey of 17 centers in Japan identified 563 patients with AIP in Japan [10].

Meanwhile, reports from Europe and the USA have described unique histologic patterns in resected pancreata of patients with mass-forming, chronic, nonalcoholic pancreatitis, showing clinical and histopathologic features overlapping with those of Japanese patients. In the first European study published in 1997, Ectors et al. [11] described the histologic pattern of 'non-alcoholic duct destructive pancreatitis' in 12 cases of idiopathic chronic pancreatitis, a histologic pattern which was clearly distinguishable from that of alcoholic chronic pancreatitis. The authors noted similarity of the pancreatic histopathologic findings not only with those reported in association with ulcerative colitis by Ball et al. [12] from the Mayo Clinic in 1950, but also with pancreatic involvement seen in sclerosing cholangitis reported from Japan [2], as noted above. Italian diagnostic criteria for AIP were reported in 2003 [13] and were based on the histologic hallmarks outlined in the article by Ectors et al. [11].

In 2003, the Mayo Clinic group in the USA reported 35 cases of 'idiopathic chronic pancreatitis with lymphoplasmacytic infiltration, sometimes called autoimmune pancreatitis' [14]. They observed 2 distinct histologic patterns in these patients: (1) LPSP and (2) idiopathic duct-centric pancreatitis (IDCP). LPSP resembled Japanese descriptions of histology seen in AIP, and IDCP resembled the European descriptions of 'duct-destructive pancreatitis'. The authors noted an overlap between the histologic features of the 2 patterns. They did not speculate on the etiology of IDCP, but wondered if LPSP was of autoimmune etiology. In 2006, Mayo Clinic investigators outlined diagnostic criteria for AIP using clinical data from patients with histologically confirmed LPSP [15].

In 2004, Zamboni et al. [16] described the histology of 62 patients with 'autoimmune pancreatitis' from Europe; the unifying histologic feature in all patients was a periductal lymphoplasmacytic infiltrate with periductal fibrosis without any of the features seen in alcoholic pancreatitis, namely ductal dilatation or irregularity, calculi or pseudocysts. As in the Mayo Clinic series, 2 groups of patients were distinguished on the basis of a histological criterion that was called a 'granulocytic epithelial lesion' (GEL). Interestingly, the 2 groups of patients also differed with regard to features such as gender, mean age and associated immune-related diseases.

Summary: 'AIP' has been extensively described in reports from Japan, Europe and the USA. Large series of 'AIP' reported from Japan have been based on a distinct clinical phenotype, with little emphasis on or need for histology to diagnose the disease. On the other hand, detailed descriptions of at least 2 histopathologic patterns in patients with nonalcoholic idiopathic chronic pancreatitis, namely LPSP or AIP without GELs and IDCP or AIP with GELs, have been reported from Europe and the USA. Both histopathologic patterns have been included under the term 'AIP', based on the presence of features common to both, namely periductal lymphoplasmacytic infiltration and peculiar periductal fibrosis. The European diagnostic criteria for AIP use the presence of GEL as a hallmark of AIP, while criteria from the USA are based on clinical features of LPSP. Not surprisingly, the clinical phenotypes associated with both these histopathologic patterns have been called AIP.

The Honolulu Consensus Conference on AIP

On 4 November, 2009, experts from Japan, Korea, Europe (UK, Germany, Sweden and Italy) and the USA met in Honolulu, Hawaii, to describe the entity of AIP as they recognized it. The experts included gastroenterologists, pathologists, radiologists and surgeons. The goals of the meeting were to (1) agree upon a clinical and histological definition of AIP, (2) determine if the descriptions of the

Table 1. Comparison of the histology of LPSP (fig. 1), IDCP (fig. 5) and alcoholic chronic pancreatitis

	LPSP (AIP without GELs)	IDCP (AIP with GELs)	Alcoholic chronic pancreatitis
General description	fibroinflammatory process involving pancreatic ducts, lobules, veins and common bile duct, easily recognized on low-power view	fibroinflammatory process involving mainly pancreatic ducts and also the intrapancreatic common bile duct, but less marked in lobules and veins	dilated and irregularly shaped medium-sized and large ducts commonly containing calculi; perilobular and patchy intralobular fibrosis with usually sparse inflammation
Infiltrate	predominantly lymphoplasmacytic infiltration often with eosinophils and rare neutrophils	predominantly lymphoplasmacytic infiltration; neutrophilic infiltration of medium-sized and small ducts and often acini	sparse infiltrates of lymphocytes, plasma cells and macrophages
Pancreatic ducts	dense periductal inflammation without epithelial damage; lumina of the ducts are patent	dense periductal inflammation associated with destruction of the duct epithelium by neutrophilic granulocytes (GEL)	enlarged and distorted ducts, rarely surrounded by an inflammatory infiltrate
Intraductal protein plugs and stones	no	no	frequent
Lobules	lymphoplasmacytic infiltration involving and replacing acinar tissue	patchy lymphoplasmacytic infiltration, commonly admixed with neutrophils	patchy lobular atrophy with fibrosis and sparse mononuclear cell infiltration
Veins	obliterative phlebitis (organized obstruction of veins in association with dense lymphoplasmacytic infiltration)	obliterative phlebitis rarely seen	no obliterative phlebitis
Arteries	intense arterial involvement rarely seen	arterial involvement usually absent	no arterial involvement
Pseudocysts	no	no	yes
Peripancreatic fat	fibroinflammatory process may extend to peripancreatic region	inflammation usually limited to the pancreas	peripancreatic fat necrosis and pseudocysts frequent
IgG4 immunostaining	abundant (>10 cells/high-power field) IgG4-positive cells	scant to no IgG4-positive cells	scant to no IgG4-positive cells

disease from Japan, Europe and USA refer to 1 or more disease entities and (3) arrive at a consensus on diagnostic criteria for AIP. In this review, the deliberations of the expert panel regarding the first 2 questions are detailed. During the deliberations, which were in a question and answer format, the questions shown below were discussed. The document was subsequently revised by the participants.

Definition of AIP

Question: Can AIP Be Distinguished from Other Forms of Chronic Pancreatitis Based on Histologic Features in Resected Pancreata?

At the Honolulu Consensus Conference on AIP, preliminary data were presented from an international concordance study of 40 resected cases of chronic pancreatitis to determine if AIP can be distinguished from alcoholic and obstructive forms of chronic pancreatitis. This study is ongoing. While the interobserver variability was moderate for the group as a whole, data from the 5 most accurate reviewers demonstrated 91.2% sensitivity and 98% specificity. The kappa statistic for the 5 readers was 0.89, reflecting excellent interobserver agreement. These findings suggest the need for additional educational efforts to improve the overall performance among pathologists. Full results of this study will be published shortly.

Summary: The expert panel agreed that AIP has unique histopathologic features which allow it to be distinguished from other forms of chronic pancreatitis.

Question: Is There More than One Histopathologic Subtype of AIP?

In the concordance study noted above, readers were asked to classify the histologic patterns seen in AIP as either LPSP or IDCP. The sensitivity and specificity among the top 5 readers was 84 and 76.4%, respectively, with a kappa of 0.59, reflecting moderate interobserver agreement. Some readers had not previously diagnosed both histologic patterns and chose not to subdivide AIP into LPSP and IDCP, underscoring the need for additional educational efforts to improve the overall performance among pathologists.

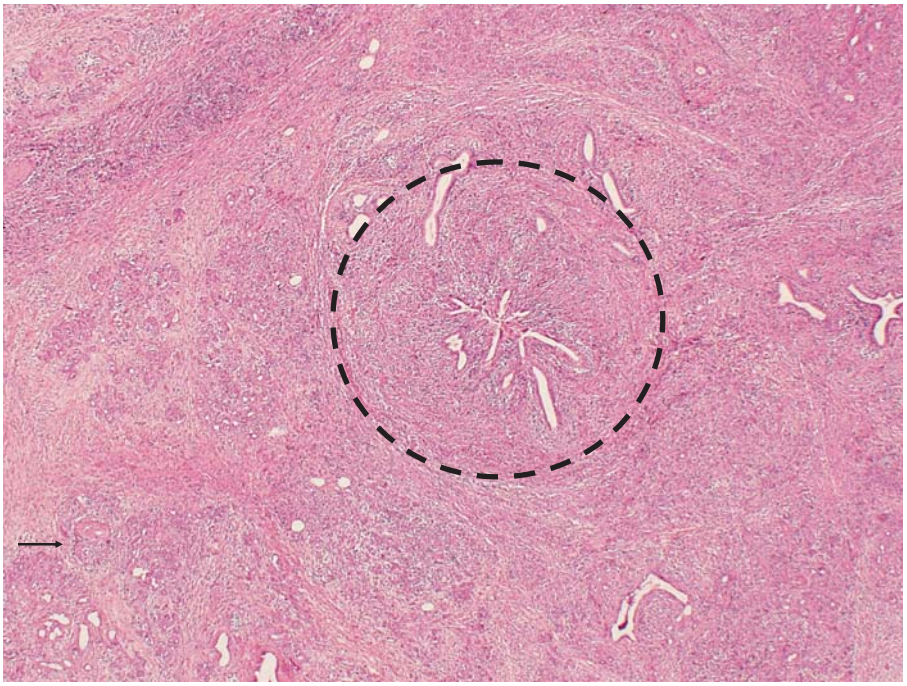

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Fig. 1. LPSP. Low-power view showing periductal lymphoplasmacytic infiltrate (circle), storiform fibrosis with inflammatory cellular stroma and obliterative phlebitis (arrow). Note the intact ductal epithelium without inflammation.

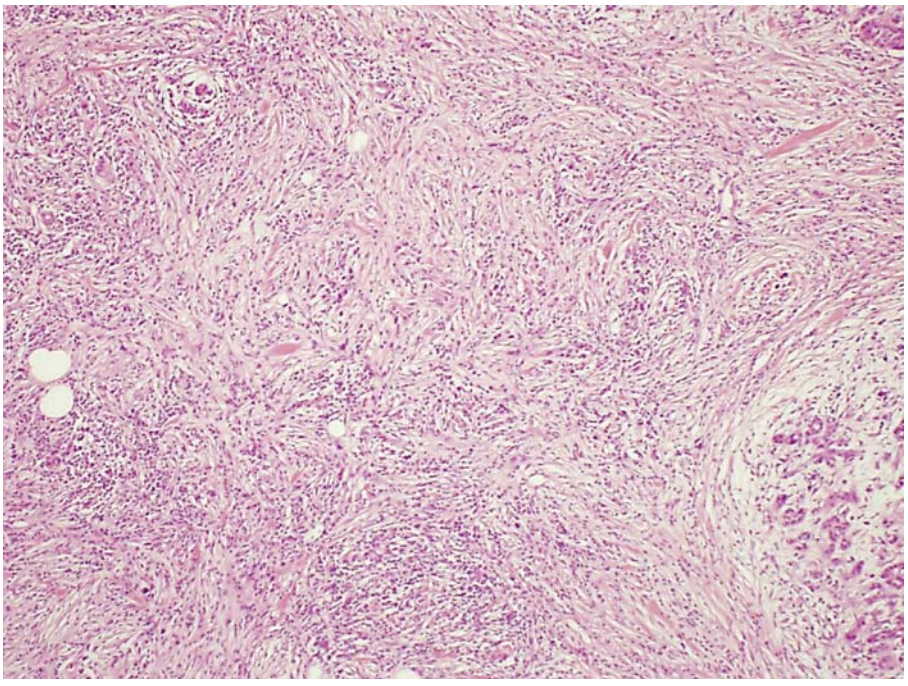

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Fig. 2. Storiform fibrosis showing delicate short collagen bands randomly interlacing in every direction and intermixing with inflammatory cells as well as fibroblasts.

Question: What Are the Histologic Diagnostic Criteria for LPSP and IDCP?

In response to this question, expert pathologists agreed on the following (table 1):

LPSP (AIP without GELs) has 3 essential histologic features (fig. 1) [14, 17]: (1) a lymphoplasmacytic infiltrate surrounding small interlobular pancreatic ducts that does not destroy the pancreatic ductal epithelium; (2) a swirling fibrosis centered around ducts and veins (storiform fibrosis; fig. 2) but most prominent in the peripancreatic adipose tissue, and (3) obliterative phlebitis, wherein the infiltrate surrounds and obliterates pan-

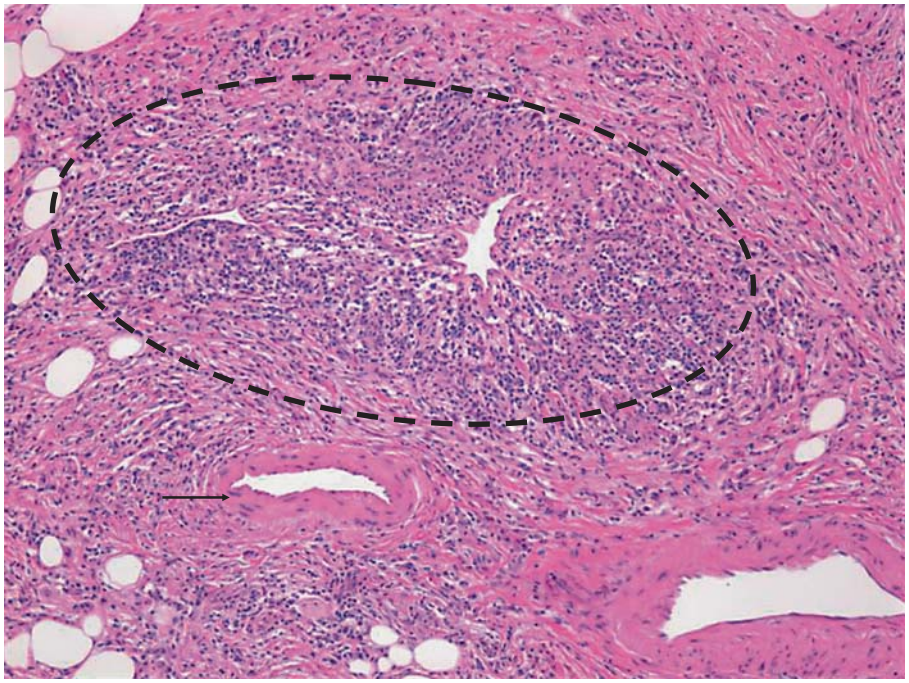

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Fig. 3. Obliterative phlebitis (oval). Dense peri- and intravenular inflammatory infiltrate with fibrosis destroying the endothelium and obliterating the lumen. Note that the neighboring artery (arrow) is spared.

creatic veins (fig. 3). Destructive changes in the ducts and acini caused by infiltrating granulocytes are typically absent. Immunostaining reveals abundant (>10 cells/high-power field) IgG4-positive cells (fig. 4) [18, 19].

IDCP (AIP with GELs) has a histologic pattern distinct from LPSP [2, 14, 17], though it also shares some features with LPSP. Periductal lymphoplasmacytic infiltrate is seen in both forms of AIP. Diffuse inflammation and diffuse storiform fibrosis as well as obliterative phlebitis, which are characteristic of LPSP, are less prominent in IDCP (fig. 5). The most distinctive feature of IDCP is the presence of GELs, seen in medium-sized and small ducts and also often in the acini (fig. 6), changes that may lead to the destruction and obliteration of the duct lumen [14, 17]. The other distinctive feature is the scanty presence (<10 cells/high-power field) or complete absence of IgG4-positive plasma cells on immunostaining.

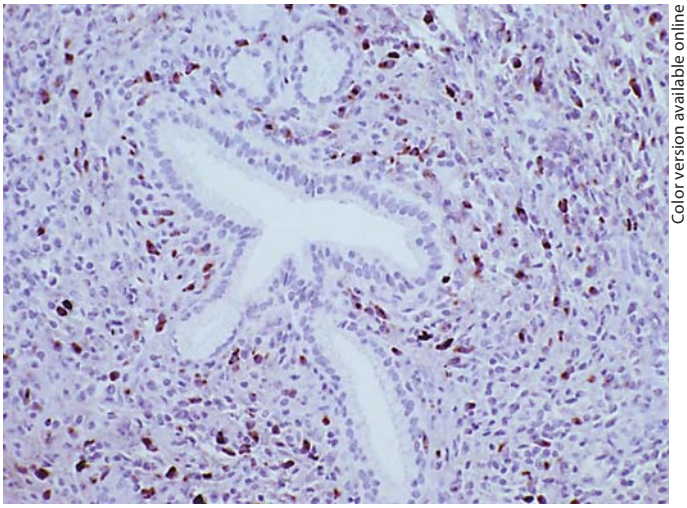

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Fig. 4. IgG4 immunostain in LPSP shows markedly increased (>30/high-power field) periductal IgG4+ plasma cell infiltrate.

Question: Do LPSP and IDCP Have Distinct Clinical Profiles?

Data were presented from Europe and the USA, based on histologically confirmed cases of LPSP and IDCP, highlighting differences in the demography, clinical presentation, serology, involvement of other organs and disease relapse (table 2).

Summary: The participants agreed that patients currently diagnosed with 'AIP' have 2 histopathologically distinct types of disease that are associated with distinct clinical profiles. Thus, it is possible that LPSP (AIP without GELs) and IDCP (AIP with GELs) are histopathologic correlates of 2 distinct forms of AIP.

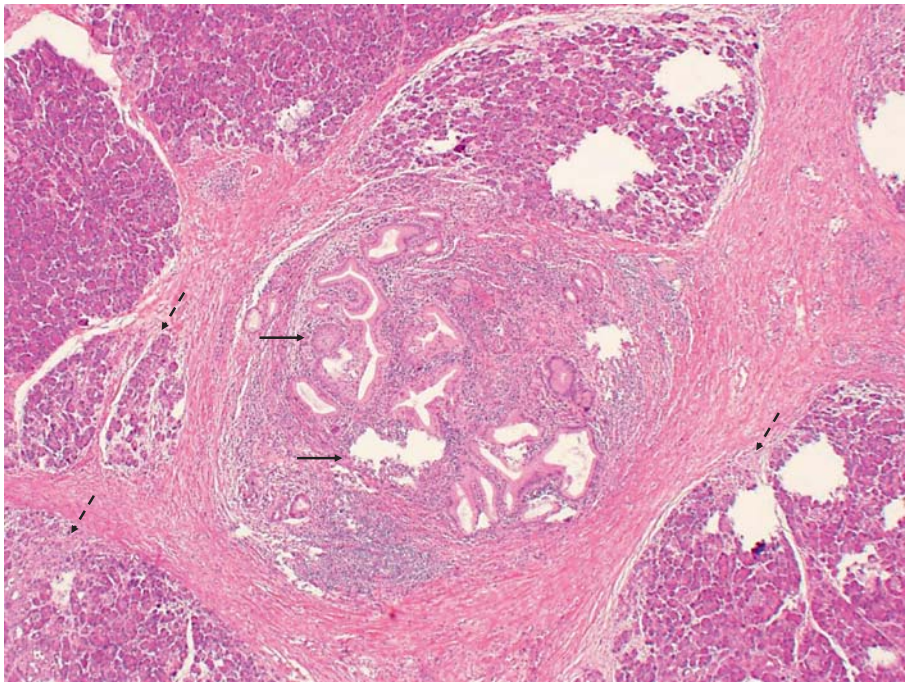

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Fig. 5. GEL-positive AIP or IDCP. Low-power view showing periductal lymphoplasmacytic and neutrophilic infiltrate with intraepithelial inflammation and destruction of small ducts and ductal epithelium (solid arrows), as well as lobular lymphoplasmacytic and neutrophilic infiltrate (dashed arrows). Note that the storiform fibrosis is not as prominent as that in LPSP.

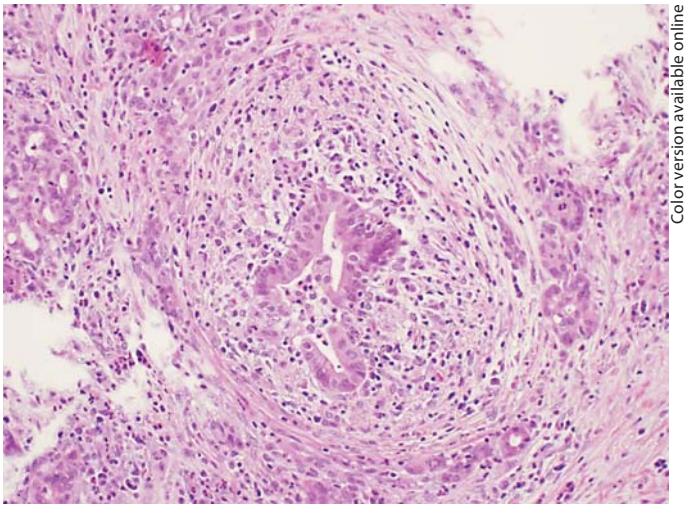

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Fig. 6. GEL in IDCP. Periductal and intraepithelial neutrophilic infiltrate destroying the ductal epithelium, often with intraluminal microabscesses.

Question: Are There Geographic Differences in the Proportion of AIP Cases Identified as LPSP or IDCP?

The diagnosis of LPSP and IDCP requires histopathologic examination, which is not frequently available. Based on data presented at the meeting, there are only a very small number of histologically confirmed IDCP cases in Japan. Over 500 cases of AIP with a clinical profile resembling that seen in subjects with LPSP have been reported from Japan. In contrast, in the USA and in most centers in Europe (Germany, Sweden, Italy), both types of AIP, i.e. LPSP (AIP without GELs) and IDCP (AIP with GELs), are observed. Reports from London, UK, suggest a predominantly LPSP-like profile of AIP. A Mayo Clinic series had 78 patients with an LPSP-like clinical profile and 19 with an IDCP-like clinical profile. A series of 88 patients from Germany, Italy and Belgium who were treated by pancreatic resection showed a predominance of LPSP (60%) over IDCP (40%).

Summary: The proportion of LPSP versus IDCP among patients diagnosed with AIP varies substantially among centers across the world. Whether this reflects a true geographic difference in the incidence of these 2 forms of AIP is not yet clear.

Question: Should the Clinical Phenotypes Associated with LPSP and IDCP Be Referred to as Type 1 and Type 2 AIP?

This question sparked a vigorous debate. The center of the controversy related to the use of the term 'autoimmune' for IDCP. The Japanese experts contended that there is strong evidence to suggest that LPSP is an autoimmune disorder [hypergammaglobulinemia, prevalence of autoantibodies (albeit nonspecific) and a steroid-

Table 2. Clinical profiles of LPSP (AIP without GELs) and IDCP (AIP with GELs)

Clinical feature	German series		USA (Mayo Clinic) series [22]	
	GEL –ve (n = 55)	GEL +ve (n = 33)	LPSP (n = 78)	IDCP (n = 19)
Mean age, years	62	48	61.8 ± 14.2	47.7 ± 18.8
Male, %	61	48	77	74
Serum IgG4			47/59 (80%)	1/6 (17%)
Other organ involvement	sialadenitis, retroperitoneal fibrosis, interstitial nephritis	none	proximal biliary stenosis, sialadenitis, retroperitoneal fibrosis, interstitial nephritis	none
Inflammatory bowel disease	absent	present	5 (6%)	3 (16%)
Relapse	biliary	present	55% (biliary, retroperitoneum most common)	none

responsive lymphoplasmacytic infiltrate], while IDCP lacks such evidence. They believed that because of the relative paucity of data concerning IDCP, it was premature to label it as an autoimmune disorder. They further noted that unlike LPSP, which is commonly associated with extrapancreatic manifestations, IDCP appears to occur in isolation, except for a potential association with inflammatory bowel disease, particularly ulcerative colitis.

Others contended that the 2 diseases had many similarities. The most common clinical presentation of both diseases is obstructive jaundice with a pancreatic enlargement/mass. However, in the AIP patients with LPSP (unlike in IDCP), obstructive jaundice is caused by the specific pathologic change, i.e. sclerosing cholangitis with similar pathological features to LPSP. The few pancreatograms from IDCP cases that were shown during the meeting were not distinguishable from those seen in LPSP. Also, IDCP is also associated with a periductal lymphoplasmacytic infiltrate and storiform fibrosis, though to a lesser extent than LPSP. In fact, in the concordance study, many pathologists could not distinguish LPSP from IDCP. Finally, IDCP is also steroid responsive. Many experts believed therefore that IDCP may be an organ (pancreas)-specific autoimmune disorder. However, the occurrence of neutrophils infiltrating some ducts and acini so far remains unexplained by an autoimmune mechanism.

At least some experts believe that the overlap between the 2 forms of AIP is further confounded by the fact that IDCP and LPSP may not always be distinguishable using current diagnostic criteria. For example, both can fulfill Japanese and Asian diagnostic criteria for AIP based on imaging criteria and biopsy showing lymphoplasmacytic infiltrate with fibrosis, histologic features common to both LPSP and IDCP. Similarly, with the Italian criteria such patients would fulfill the criteria for AIP if they responded to steroids, as both forms of the disease do. Similarly, clinicians have used a steroid trial for the diagnosis of AIP using HISORt (histology, imaging features, serology, other organ involvement and response to steroid treatment) criteria, though collateral evidence of AIP in the form of raised serum IgG4 or other organ involvement (features of LPSP) is necessary before steroids are given. A case of AIP from Japan was presented which resembled IDCP with regard to the clinical profile (young, seronegative and associated with inflammatory bowel disease) but met the Japanese/Asian diagnostic criteria noted above. A histologically confirmed case of IDCP from Korea was presented whose imaging features resembled those seen in LPSP and which responded dramatically to steroids with normalization of imaging abnormalities.

The expert panel acknowledged that the current practice is to refer to both disease entities as AIP due to the inability to differentiate LPSP from IDCP without histology and review by an experienced pathologist. Therefore, there is a clear need to distinguish these entities nosologically to avoid continued confusion between them, to help provide prognostic information and to guide patient care. This would also provide the framework for future research in the field, including identification of specific biomarkers for both entities.

The European and American experts favored the continued inclusion of IDCP as a unique type of AIP due to

the similar clinical presentations, overlapping diagnostic criteria (including histology) and similar response to steroid administration. The terms type 1 and type 2 AIP have recently been introduced into the literature to refer to the clinical profiles associated with LPSP and IDCP, respectively, [20–22]. Most, but not all present at the meeting agreed that this terminology best reflected our current state of knowledge. All agreed that as we learn more about both entities, the terminology would surely change.

Summary: (1) Diagnostic criteria for AIP should recognize that there are 2 forms of the disease. This will allow further study of these entities and identification of specific markers for both forms of AIP.

(2) Currently, the disease associated with IDCP can be definitively diagnosed only by histologic examination. Use of a steroid trial does not distinguish the disease associated with LPSP from IDCP.

(3) While uniform consensus was not achieved, the majority of experts agreed that the clinical phenotypes associated with the histopathologic patterns of LPSP (AIP without GELs) and IDCP (AIP with GELs) should be referred to as type 1 and type 2 AIP, respectively.

Acknowledgement

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Appendix

Names, specialties and affiliations of the Autoimmune Pancreatitis International Cooperative Study Group members (in alphabetical order)

Name	Specialty	Affiliation
Suresh T. Chari, MD	Internal Medicine/Gastroenterology	Mayo Clinic College of Medicine, Rochester, Minn., USA
Carlos Fernandez del Castillo, MD	Surgery	Massachusetts General Hospital, Boston, Mass., USA
Vikram Deshpande, MD	Pathology	Massachusetts General Hospital, Boston, Mass., USA
Martin L. Freeman, MD	Internal Medicine/Gastroenterology	University of Minnesota, Minn., USA
Luca Frulloni, MD, PhD	Internal Medicine/Gastroenterology	University of Verona, Verona, Italy
Timothy B. Gardner, MD	Internal Medicine/Gastroenterology	Dartmouth Medical School, Lebanon, N.H., USA
Vay Liang William Go, MD	Internal Medicine/Gastroenterology	University of California Los Angeles, Los Angeles, Calif., USA
Atsushi Irisawa, MD, PhD	Internal Medicine/Gastroenterology	Fukushima Medical University School of Medicine, Fukushima, Japan
Tetsuhide Ito, MD, PhD	Internal Medicine/Gastroenterology	Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
Terumi Kamisawa, MD, PhD	Internal Medicine/Gastroenterology	Tokyo Metropolitan Komagome Hospital, Tokyo, Japan
Shegiyuki Kawa, MD, PhD	Internal Medicine/Gastroenterology	Shinshu University, Japan
Okazaki Kazuichi, MD, PhD	Internal Medicine/Gastroenterology	Kansai Medical University, Osaka, Japan
Myung-Hwan Kim, MD, PhD	Internal Medicine/Gastroenterology	University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea
Guenter Kloeppel, MD	Pathology	University of Kiel, Kiel, Germany
Motohiro Kojima, MD	Pathology	National Cancer Center Hospital, Chiba, Japan
Markus M. Lerch, MD	Internal Medicine/Gastroenterology	Klinikum der Ernst-Moritz-Arndt-Universität Greifswald, Greifswald, Germany
Michael J. Levy, MD	Internal Medicine/Gastroenterology	Mayo Clinic College of Medicine, Rochester, Minn., USA
Matthias Lohr, MD	Internal Medicine/Gastroenterology	Karolinska Institute, Stockholm, Sweden
Daniel S. Longnecker, MD	Pathology	Dartmouth Medical School, Lebanon, N.H., USA
Mari Mino-Kenudson, MD	Pathology	Massachusetts General Hospital, Boston, Mass., USA
Nobumasa Mizuno, MD	Pathology	Aichi Cancer Center Hospital, Nagoya, Japan
Kenji Notohara, MD, PhD	Pathology	Kurashiki Central Hospital, Kurashiki, Japan
Manuel Rodriguez-Justo, MD	Pathology	University College London Hospitals, London, UK
Tooru Shimosegawa, MD, PhD	Internal Medicine/Gastroenterology	Tohoku University Graduate School of Medicine, Sendai, Japan
Thomas C. Smyrk, MD	Pathology	Mayo Clinic College of Medicine, Rochester, Minn., USA
Amitabh Srivastava, MD	Pathology	Dartmouth Medical School, Lebanon, N.H., USA
Aravind Sugumar, MD	Internal Medicine/Gastroenterology	Mayo Clinic College of Medicine, Rochester, Minn., USA
Naoki Takahashi, MD	Radiology	Mayo Clinic College of Medicine, Rochester, Minn., USA
George Webster, MD, FRCP	Internal Medicine/Gastroenterology	University College London Hospitals, London, UK
Giuseppe Zamboni, MD	Pathology	University of Verona, Verona, Italy
Yoh Zen, MD	Pathology	King's College Hospital, London, UK
Lizhi Zhang, MD	Pathology	Mayo Clinic College of Medicine, Rochester, Minn., USA

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