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Review

Diagnosis and classification of autoimmune pancreatitis

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ABSTRACT

Recent studies suggested the existence of two subtypes of autoimmune pancreatitis (AIP): type 1 related with IgG4 as the pancreatic manifestation of IgG4-related disease (IgG4-RD), and type 2 related with a granulocytic epithelial lesion. Apart from type 2 AIP, the characteristic features of type 1 AIP are increased serum IgG4 levels, lymphoplasmacytic sclerosing pancreatitis (abundant infiltration of IgG4+ plasmacytes and lymphocytes, storiform fibrosis, and obliterative phlebitis), extra-pancreatic manifestations of IgG4-RD (e.g. sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis), and steroid responsiveness. Although the way how to diagnose IgG4-RD has not been established yet, the Comprehensive Diagnostic Criteria (CDC) for IgG4-RD for general use, and several organ specific criteria for AIP have been proposed; the International Consensus Diagnostic Criteria (ICDC) and the revised clinical diagnostic criteria in 2011 by Japan Pancreas Society (JPS-2011) for type1 AIP. In cases of probable or possible IgG4-RD diagnosed by the CDC, organ specific diagnostic criteria should be concurrently used according to an algorithm of diagnosis for IgG4-RD with reference to the specialist.

Contents

1. The history of autoimmune pancreatitis (AIP): before and after discovery of IgG4 (Table 1)

In 1961, Sarles et al. [1] observed a case of particular pancreatitis with hypergammaglobulinemia, which is supposed to be a prototype of AIP. In 1995, Yoshida et al. [2] proposed a novel concept of autoimmune pancreatitis (AIP), nowadays recognized as type 1 AIP (IgG4-related pancreatitis), the pancreatic manifestation of IgG4-related disease (IgG4-RD) [3], which has been recognized as a novel clinical entity following the epoch-making evidence of increased serum levels of IgG4 in the history of AIP [4]. The histopathological findings are characterized by the periductal localization of predominantly CD4 positive T-cells,

Abbreviations: AIP, autoimmune pancreatitis; ANA, anti-nuclear antibody; ERCP, endoscopic retrograde cholangio-pancreatography; LPSP, lymphoplasmacytic sclerosing pancreatitis; MD, Mikulicz disease; MOLPS, multiorgan lymphoproliferative disease; SjS, Sjögren's syndrome; PSC, primary sclerosing cholangitis; RF, rheumatoid factor; SIPS, IgG4-systemic plasmacytic syndrome; SLE, systemic lupus erythematosus.

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Table 1
History of autoimmune pancreatitis and IgG4-related disease.

Year	Authors	Ref	Evidences/contents
1892	Mikulicz J. et al.	[12]	Mikulicz's disease (*Z. Chir. Fesrschr*)
1961	Sarles H. et al.	[1]	Hyper-gammaglobulinemia in CP (*Am J Dig Di*)
1967	Comings DE. et al.	[9]	Familial multifocal fibrosclerosis (*Ann Intern Med*)
1972	Kuttner	[13]	Kuttner tumor (*Acta Otolaryngol*)
1991	Kawaguchi K. et al.	[7]	Lymphoplasmacytic sclerosing pancreatitis (*Human Pathol*)
1995	Yoshida et al.	[2]	Autoimmune pancreatitis (*Dig Dis Sci*)
2001	Hamano et al.	[4]	High IgG4 levels in sclerosing pancreatitis (*N Eng J Med*)
2002	Japan Pancreas Society	[43]	Clinical diagnostic criteria for AIP 2002 (*Suizo*)
2006	Okazaki K, et al.	[44]	Clinical diagnostic criteria for AIP 2006 (*J Gastroenterol*)
2006	Chari ST et al.	[47]	Mayo criteria (*Clin Gastroenterol Hepatol*)
2006	Kamisawa T. et al.	[14]	IgG4-related sclerosing disease (*J Gastroenterol*)
2006	Yamamoto M. et al.	[15]	IgG4-related plasmacytic disease (*Mod Rheumatol*)
2008	Masaki Y et al.	[16]	IgG4-multiorgan lymphoproliferative syndrome (MOLPS) (*Ann Rheum Dis*)
2011	Shimosegawa T. et al.	[25]	International Consensus Diagnostic Criteria (ICDC) for AIP (*Pancreas*)
2012	Umehara, Okazaki et al.	[17,18]	Concept and comprehensive Diagnostic Criteria for IgG4-related disease (*Mod Rheumatol*)
2012	Deshpande et al.	[19]	International Pathological Consensus for IgG4-RD (*Mod Pathol*)
2012	Stone, J et al.	[20]	Nomenclatures of individual organ manifestation of IgG4-RD (*Arthritis Rheum*)
2012	Japan Pancreas Society	[43,4444]	Clinical diagnostic criteria for AIP 2011 (*Suizo*)

IgG4-positive plasma cells, storiform fibrosis with acinar cell atrophy frequently resulting in stenosis of the main pancreatic duct, and obliterative fibrosis [5,6], which is also called lymphoplasmacytic sclerosing pancreatitis (LPSP) [7]. On the other hand, mainly in the western countries, histological analyses using resected pancreatic samples in patients with chronic nonalcoholic pancreatitis demonstrated a different histological pattern of pancreatitis from LPSP, so called idiopathic duct-centric pancreatitis (IDCP) or AIP with GEL. In 2003, Kamisawa et al. [8] first suggested that AIP showing LPSP is a systemic sclerosing disease based on the concept of multifocal fibrosclerosis proposed by Comings et al. [9], because the pancreas and other involved organs have fibrosis with abundant infiltration of IgG4-positive plasma cells. On the other hand, patients with IDCP, extremely rarely observed in Japan, are not associated with either serum IgG4 elevation or with other organ involvement (OOI) typically seen in LPSP. AIP is subclassified according to the International Consensus of Diagnostic Criteria (ICDC) for Autoimmune Pancreatitis as either type 1 (IgG4-related) or type 2 (granulocytic epithelial lesions; GEL) [10]. Different from type 1, type 2 AIP is supposed to be a specific pancreatic disease with occasional coexistence with ulcerative colitis [10,11].

On the other hand, in 1892, Mikulicz first observed a patient with symmetrical swelling of the lachrymal, parotid and submandibular glands, with massive infiltration of mononuclear cells [12]. The condition was called Mikulicz's disease (MD); however, it has since been classified as an atypical type of Sjögren's syndrome, which also presents with bilateral, painless, and symmetrical swelling of the lachrymal, parotid, and submandibular glands. Kuttner reported a tumor-like enlargement of the submandibular gland that was sometimes a result of stones in the Wharton duct [13], which indicated that the underlying cause had not been identified. These patients, lacking anti-SS-A/Ro or anti-SS-B/La antibodies, often show other systemic organ involvement with elevated serum levels of IgG4, infiltration of IgG4-positive plasma cells into the glands, and recovery of secretion with steroid treatment similar to AIP [4–6]. About 60 to 80% of patients with AIP show obstructive jaundice with sclerosing cholangitis (IgG4-related sclerosing cholangitis; IgG4-SC) and other organ involvement (OOI), in which cholangiographic features are similar to those of primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma. The steroid responses and the prognoses of sclerosing cholangitis associated with AIP differ from patients with PSC, which suggests different pathological conditions. In addition to the original concept of multifocal idiopathic fibrosclerosis, recent studies led us to develop a novel concept of a systemic disease such as IgG4-related systemic sclerosing disease [14], systemic IgG4-related plasmacytic syndrome (SIPS) [15], or IgG4-positive multiorgan lymphoproliferative syndrome (IgG4-MOLPS) [16], all of which may refer to the same conditions. Based on these findings, although it is unclear whether the pathogenetic mechanisms in individual organs are same or not [17,18], the comprehensive term "IgG4-related disease IgG4-RD", which was internationally endorsed with the proposal of nomenclatures for individual organ lesions as well as pathological consensus, and diagnostic criteria have been proposed from the Japanese investigators [18].

2. Current concepts of IgG4-RD

Patients with IgG4-RD show diffuse or focal organ enlargement and mass-forming or nodular/thickened lesions in various organs, either synchronously or metachronously. This is due to the prominent infiltration of lymphocytes and plasmacytes with fibrosis [5,14,17]. The causes of the disease are still not clear; however, some abnormal immunological mechanisms are involved. The organs known to be affected include the pancreas, biliary duct, lacrimal/salivary glands, retroperitoneum, central nervous system, thyroid gland, lungs, liver, gastrointestinal tracts, kidneys, prostate gland, and lymph nodes [5,14–20]. These suggest that type 1 AIP related with IgG4 is defined as a pancreatic manifestation and other organ involvements (OOIs) as extrapancreatic of IgG4-RD. IgG4-RD mainly affects middle-aged to elderly men, and clinical symptoms vary depending on the organ in which the lesions are located. Many cases are treated effectively by steroid therapy [5,17,18]; however, the prognosis is not clear. Some patients develop serious complications such as obstructive jaundice due to hepatic, gallbladder, or pancreatic lesions; hydronephrosis due to retroperitoneal fibrosis; or respiratory symptoms due to pulmonary lesions [1–10,13–23]. Although the infiltration of IgG4-positive cells and increased serum levels of IgG4 are characteristic in IgG4-RD, the severity of fibrosis seems to be different among the individual organs involved. These conditions are quite similar to multifocal idiopathic fibrosclerosis [9]. Storiform fibrosis and obliterative phlebitis are characteristic in pancreatic and biliary tract lesions, but the degree varies depending on the individual organs. For example, very seldom do lesions appear in the lachrymal/salivary gland or lymph node. The previous nomenclature of "IgG4-related sclerosing disease" is mainly based on the fibrous swollen organs, whereas those of "IgG4-SIPS" and "IgG4+MOLPS" have been based on lymphoplasmacytic proliferation and swollen lymph nodes without fibrosis [14–17]. Although most patients have multiorgan lesions synchronously or metachronously, about 10 to 20% of the patients do not have confirmed OOI. Therefore, it is unclear whether the pathogenetic mechanism is same among individual organs or not.

3. The clinical diagnostic criteria for IgG4-related disease

The patients with IgG4-related disease show diffuse/focal organ enlargement, mass-forming, or nodular/thickened lesions in various

Table 2
The three major histopathological features associated with IgG4-RD and the minimal criteria in a new organ/site in the international pathological consensus (ref [19]).

1. Dense lymphoplasmacytic infiltrate
2. Fibrosis, arranged at least focally in a storiform pattern
3. Obliterative phlebitis

Other histopathological features associated with IgG4-RD are:
1. Phlebitis without obliteration of the lumen
2. Increased numbers of eosinophils

Minimal Criteria for IgG4-RD in a new Organ/Site
(1) Characteristic histopathological findings with an elevated IgG4t plasma cells and IgG4-to-IgG ratio
(2) High serum IgG4 concentrations
(3) Effective response to glucocorticoid therapy
(4) Reports of other organ involvement that is consistent with IgG4-related disease

organs, synchronously or metachronously, due to the prominent infiltration of lymphocytes and plasmacytes with fibrosis [17–20]; however, the causes of the disease are still not clear. Clinical symptoms vary depending on the organ in which the lesions are located, but many cases are treated effectively by steroid therapy. Although the infiltration of IgG4-positive cells and increased serum levels of IgG4 are characteristic of IgG4-related disease, the severity of fibrosis and infiltration of IgG4-positive cells seem to be different among the individual involved organs (Table 2). Storiform fibrosis and obliterative phlebitis are characteristic in the pancreatic, biliary tract lesions, and retroperitoneal fibrosis, but rare fibrosis and obliterative phlebitis in lacrimal/salivary gland lesions or lymph node lesions. Based on these findings, the comprehensive diagnostic criteria (CDC) for IgG4-RD have been proposed (Table 3) [18]. A diagnosis of IgG4-RD is made as a definitive, probable or possible one, in combination with: (i) organ enlargement, mass or nodular lesions, or organ dysfunction; (ii) a serum IgG4 concentration of 135 mg/dl or higher; and (iii) histopathological findings of greater than 10 IgG4 cells per HPF and an IgG4 + /IgG + cell ratio greater than 40%. Compared with the organ specific diagnostic criteria for AIP, the CDC for IgG4-RD strictly requires the histopathological features of both the ratio of IgG4/IgG higher than 40% and more than 10 IgG4 + cells/HPF, but not storiform fibrosis or obliterative phlebitis. Therefore, the diagnostic sensitivity of the involved organ lesions, in which biopsy samples are hard to be taken such as the pancreas, retroperitoneum, or central nervous system, is low compared with other organ lesions relatively easy to be biopsied such as the salivary/lachrymal gland or kidney. These suggest that the CDC for IgG4-RD is helpful in the diagnosis of OOIs, in which individual organ specific diagnostic criteria have not been proposed yet. For possible or probable cases by the CDC for IgG4-RD, organ-specific criteria for IgG4-RD could be applied, such as those for AIP [25], MD [39], and KD [53] associated with IgG4. Patients who fulfill the organ-specific criteria for IgG4-RD have a definite diagnosis of this disease.

Table 3
Japanese comprehensive clinical diagnostic criteria for IgG4-RD (ref [18]).

1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematological examination shows elevated serum IgG4 concentrations (135 mg/dl)
3. Histopathologic examination shows:
   (1) Marked lymphocyte and plasmacyte infiltration and fibrosis.
   (2) Infiltration of IgG4 + plasma cells: ratio of IgG4 + /IgG + cells > 40% and >10 IgG4 + plasma cells/HPF

Definite: 1) + 2) + 3)
Probable: 1) + 3)
Possible: 1) + 2)
However, it is important to differentiate IgG4-RD from malignant tumors of each organ (e.g. cancer, lymphoma) and similar diseases (e.g. Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, Churg–Strauss syndrome) by additional histopathological examination
Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ specific diagnostic criteria for IgG4RD.

Table 4
Subtypes of autoimmune pancreatitis.

Subtype of AIP	Type 1	Type 2
Other nomenclatures	AIP without GEL IgG4-related LPSP	AIP with GEL IgG4-unrelated IDCP
Prevalence	Asia > USA, EU	EU > USA > Asia
Age	High aged	Younger
Gender	Male ≫ female	Male = female (NS)
Symptoms		
Obstructive jaundice	Often	Often
Abdominal pain	Rare	Common
Pancreas swelling	Common	Common
Serology	High serum IgG, IgG4, autoAbs (+)	Normal IgG, normalIgG4, autoAbs (−)
Other organ involvement (OOI)	Sclerosing cholangitis Sclerosing sialadenitis Retroperitoneal fibrosis Others	Unrelated with OOI
Ulcerative colitis	Rare	Often
Steroid	Responsive	Responsive
Relapse	High rate	Rare

4. The subtypes of autoimmune pancreatitis (AIP) (Table 4)

4.1. Type 1 AIP (Fig. 1)

Recent studies have suggested that "AIP" manifests two distinct subtypes, type 1 and type 2 AIP [24,25]. Type 1 (IgG4-related) AIP accounts for the great majority of cases in Asia frequently associated with obstructive jaundice in elderly males, and extra-pancreatic manifestations respond to steroid therapy. This condition, once termed lymphoplasmacytic sclerosing pancreatitis (LPSP) (Fig. 2) [7], is characterized histopathologically by i) abundant infiltration of plasma cells (IgG4 + cells; >10/hpf, 40% > IgG4/IgG cells) and lymphocytes, ii) peculiar storiform or swirling fibrosis, and iii) intra/perivenular infiltration of lymphocytes and plasma cells often leading to obliterative phlebitis [17,19,25]. Clinically, type1 AIP is regarded as the pancreatic manifestation of IgG4-RD (IgG4-related pancreatitis), characterized by swelling of the pancreas, elevated serum IgG4 levels and extrapancreatic lesions (e.g., sclerosing cholangitis, sclerosing sialadenitis and retroperitoneal fibrosis) associated with infiltration of abundant IgG4 + plasma cells [18,20].

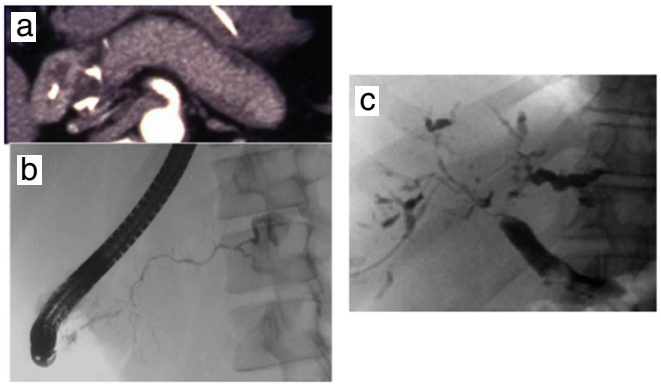

Fig. 1. Type 1 AIP. a. Dynamic CT shows diffuse swelling of the pancreas with late phase enhancement and low-density rim. b. Endoscopic pancreatography shows diffusely irregular narrowing of the main pancreatic duct. c. Endoscopic chorangiography shows beaded like and long stenotic biliary duct similar to primary sclerosing cholangitis.

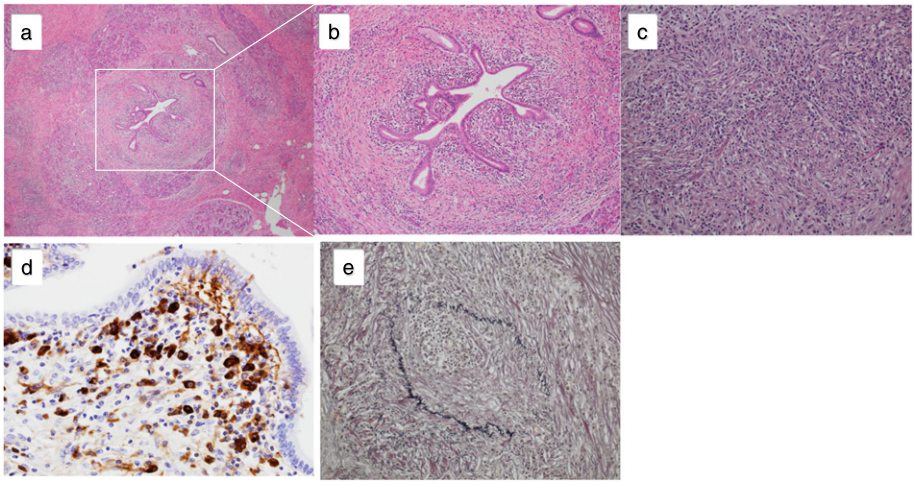

Fig. 2. Lymphoplasmacytic sclerosing pancreatitis (LPSP). a. Abundant infiltration of plasma cells and lymphocytes around the pancreatic duct with fibrosis (H&E, ×40). b. Abundant infiltration of plasma cells and lymphocytes around the pancreatic duct with fibrosis (H&E, ×200). c. Storiform fibrosis (HEx400). d. Abundant infiltration of IgG4 positive plasma cells (anti-IgG4 antibody staining, ×400). e. Obliterative phlebitis (Evans staining, ×400).

5. Other organ involvements (OOIs)

A variety of extrapancreatic lesions in patients with type 1 AIP have been noted, including lachrymal and salivary gland lesions [26], pulmonary lesions including hilar lymphadenopathy [27], sclerosing cholangitis [28,29], retroperitoneal fibrosis [30], and tubulointerstitial nephritis [31,32]. Associations were also reported with hypophysitis [33], chronic thyroiditis [34], and prostatitis [35]. Other OOIs have been reported in a few cases [36–38]. Though it is not certain that all of them have a relation with AIP, OOIs are prevalent in the systemic organs as IgG4-RD [26–38]. The OOIs appear synchronously or metachronously with the pancreatic lesion(s), share the same pathological conditions, and show favorable response to steroid therapy. The lesions are usually detected by imaging and blood tests (CT, MRI, gallium scintigraphy, FDG-PET, and IgG4); however, these should be confirmed by histological findings. Extrapancreatic lesions sometimes mimic, or are misdiagnosed as, primary lesions of the corresponding organs: lachrymal and salivary gland lesions for Sjögren's syndrome, respiratory lesions for sarcoidosis, and sclerosing cholangitis for primary sclerosing cholangitis (PSC). Therefore, it is necessary to differentiate between IgG4-related diseases and inherent diseases of the corresponding organs. The patients with IgG4-related sialodacryoadenitis, synonymous with IgG4-related Mikulicz's disease [12,39], have usually symmetrical enlargement of salivary and lacrimal glands. The IgG4-related central nervous system lesions include infundibulohypophysitis, hypertrophic pachymeningitis, intracranial inflammatory pseudotumor, and orbital pseudotumor [36–38].

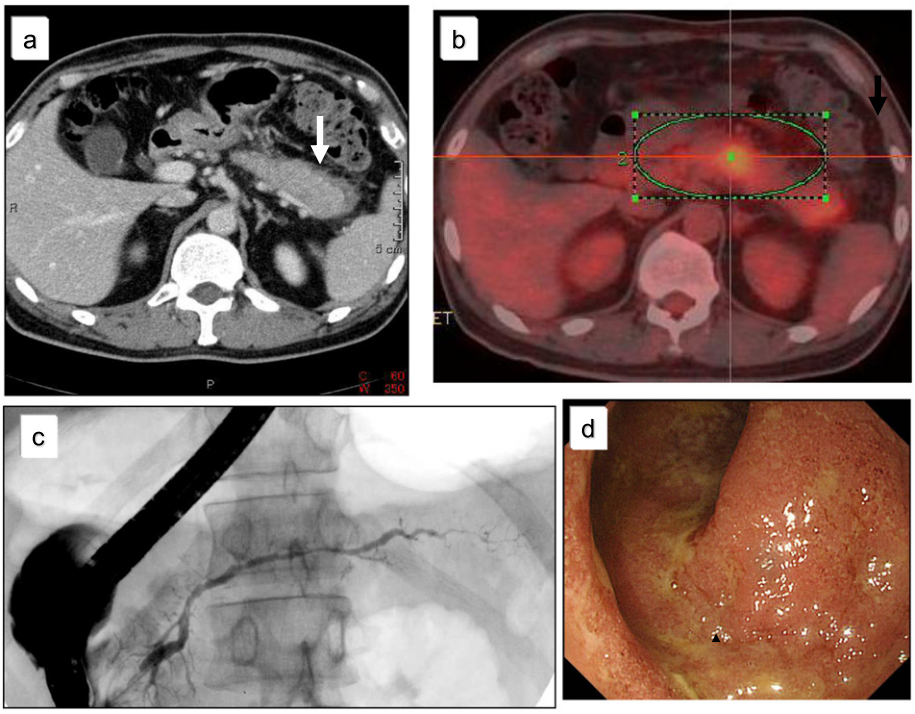

Fig. 3. Type 2 AIP. a. Dynamic CT shows diffuse swelling of the pancreas with late phase enhancement and low-density rim (arrow) similar to type 1 AIP. b. PET-CT shows diffusely abnormal accumulation of FDG. c. Endoscopic pancreatography shows irregular narrowing of the main pancreatic duct. d. Colonoscopy shows proctitis type of ulcerative colitis.

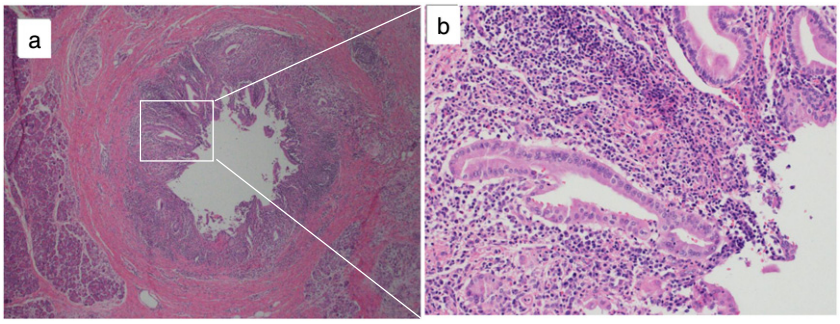

Fig. 4. Granulocytic epithelial lesion. a. Abundant infiltration of granulocytes into and around medium-sized pancreatic duct with destruction of epithelia (H&E, ×40). b. Abundant infiltration of granulocytes into and around medium-sized pancreatic duct with destruction of epithelia (H&E, ×200).

5.1. Type 2 AIP (Fig. 3)

On the other hand, type 2 AIP was proposed from histological examination of the resected pancreas of patients with chronic non-alcoholic pancreatitis by American and European pathologists, who reported another histopathological pattern named as idiopathic duct-centric pancreatitis (IDCP) or AIP with granulocytic epithelial lesion (GEL) [40,41]. The most characteristic feature of type 2 AIP is the granulocytic epithelial lesion (GEL) often with destruction and obliteration of the pancreatic duct (Fig. 4). Type 2 AIP has swelling of the pancreas, but none or very few IgG4-positive plasma cells, and clinical features show a distinctly different profile associated with no serum IgG4, IgG elevation, presence of autoantibodies, or other organ involvement except for inflammatory bowel disease (approximately 30%). Different from type 1 AIP, the patients with type 2 AIP seem to have no serological biomarkers, but deposition of C3c and IgG at the basement membrane of pancreatic ducts and acini suggests immune complex-mediated destruction of ducts and acini in type2 AIP as well as type 1 AIP [42]. Although, it is still in debate as to whether both types can be classified as one clinical entity of AIP or not, these two subtypes and diagnostic criteria were internationally consented because of unknown etiology and similar pancreas images to pancreatic cancer [25].

6. Diagnosis of AIP

Several kinds of organ specific diagnostic criteria for AIP such as the International Consensus of Diagnostic Criteria (ICDC) [25], JPS-2002 [43], JPS-2006 [44], JPS-2011 [45,46], HISORTs [47,48], Korean [49], Asian [50], Italian [51], and Manheim's criteria [52], have been proposed in addition to the CDC [18]. These organ specific criteria contain steroid effects as a diagnostic criterion, but the CDC for IgG4-RD does not. Although the ICDC for AIP is somewhat complicated for general use, it is

Table 5
Level 1 and level 2 criteria for type 1 AIP in International Consensus of Diagnostic Criteria (ICDC) (ref [25]).

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim like enhancement)	Indeterminate (including Atypical[a]): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the mpd) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size < 5 mm)
S	Serology	IgG4 > 2 × upper limit of normal value	IgG4 1–2 × upper limit of normal value
OOI	Other organ involvement	a or b	a or b
		a. Histology of extrapancreatic organs	a. Histology of extrapancreatic organs including endoscopic biopsies of bile duct[b]
		Any three of the following	Both of the following
		i. Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration	i. Marked lymphoplasmacytic infiltration without granulocytic infiltration
		ii. Storiform fibrosis	ii. Abundant (>10 cells/hpf) IgG4 positive cells
		iii. Obliterative phlebitis	
		iv. Abundant (>10 cells/hpf) IgG4 positive cells	
		b. Typical radiological evidence	b. Physical or radiological evidence
		At least one	At least one
		i. Segmental/multiple proximal (hilar/intra hepatic) or proximal and distal bile duct stricture	i. Symmetrically enlarged salivary/lacrimal glands
		ii. Retroperitoneal fibrosis	ii. Radiologic evidence of renal involvement described in association with AIP
H	Histology of the pancreas	LPSP (core biopsy/resection)	LPSP (core biopsy)
		At least 3 of the following	Any 2 of the following
		i. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration	i. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration
		ii. Obliterative phlebitis	ii. Obliterative phlebitis
		iii. Storiform fibrosis	iii. Storiform fibrosis
		iv. Abundant (>10 cells/hpf) IgG4 positive cells	iv. Abundant (>10 cells/hpf) IgG4 positive cells
Diagnostic steroid trial			
Response to steroid (Rt)[c]		Rapid (≦2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extra-pancreatic manifestations	

[a] 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 work-up for cancer is negative (see algorithm).
[b] Endoscopic biopsy of duodenal papilla is a useful adjunctive method because ampulla is often involved pathologically in AIP.
[c] Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats (see text) only after negative work-up for cancer including EUS-FNA.

Table 6
Diagnosis of definitive and probable type 1 AIP using International Consensus Diagnostic Criteria (ICDC) (ref [25]).

Diagnosis	Primary basis for diagnosis	Imaging evidence	Collateral evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (Level 1 H)
	Imaging	Typical	Any non-D Level 1/Level 2
		Indeterminate	Two or more from Level 1 (+Level 2 D[a])
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or Level 1 D + Level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H + Rt

[a] Level 2 D is counted as Level 1 in this setting.

the most sensitive with differential diagnosis between type 1 and type 2 AIP. Herein, as the most recently diagnostic criteria for AIP after proposal of two subtypes, the ICDC, JPS-2011 and CDC for IgG4-RD are compared.

7. International Consensus of Diagnostic Criteria (ICDC) for AIP

The ICDC for AIP [25] first enabled us to make an independent clinical diagnosis for type 1 and type 2 AIP. The diagnosis of type 1 AIP by ICDC requires a combination of five primary cardinal features (Tables 5, 6): i) imaging features of a) pancreatic parenchyma (on CT/MRI) and b) pancreatic duct (ERCP or MRCP); ii) serology (IgG4); iii) other organ involvement; iv) histopathology of the pancreas; and v) response to steroid therapy. On the other hand, the diagnosis of type 2 AIP is made in a combination of four primary cardinal features same as type 1 except for serology (Tables 6, 7): i) imaging features of a) pancreatic parenchyma (on CT/MRI) and b) pancreatic duct (ERCP or MRCP); ii) ulcerative colitis as other organ involvement; iii) histopathology of the pancreas; and iv) response to steroid therapy. Each criterion, except for steroid responsiveness, is classified as either level 1 or level 2 collateral criteria.

Patients with obstructive jaundice and 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. However, subjects with typical findings of pancreatic cancer (e.g., low density mass on contrast-enhanced CT, pancreatic ductal dilatation/cutoff with or without pancreatic atrophy) should be considered as having pancreatic cancer. Subjects without features typical of AIP or pancreatic cancer should first be investigated for pancreatic cancer. AIP should be considered only after negative work-up of malignancy. 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.

8. Clinical diagnostic criteria for type 1 AIP by Japan Pancreas Society in 2011 (JPS-2011)

JPS-2011 [43,44] (Table 7) took basic concepts from both the previous Japanese criteria [51,52] and the CDC for type 1 AIP [41]. These include ensuring that the criteria are i) simple for general physicians'

Table 7
Clinical diagnostic criteria for autoimmune pancreatitis in 2011 by Japan Pancreas Society (JPS-2011) (ref [43,44]).

A. Diagnostic criterion	
I. Enlargement of the pancreas:	
a. Diffuse enlargement	
b. Segmental/focal enlargement	
II. ERP (endoscopic retrograde pancreatography) shows irregular narrowing of the main pancreatic duct	
III. Serological findings	
Elevated levels of serum IgG4 (≥135 mg/dl)	
IV. Pathological findings: among i)–iv) listed below,	
a. three or more are observed	
b. two are observed	
i) Prominent infiltration and fibrosis of lymphocytes and plasmacytes	
ii) Ten or more diffuse IgG4-positive plasmacytes per high-power microscope field	
iii) Storiform fibrosis	
iv) Obliterative phlebitis	
V. Other organ involvement (OOI): sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis, retroperitoneal fibrosis	
a. Clinical lesions	
Extra-pancreatic sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis (Mikulicz disease), or retroperitoneal fibrosis can be diagnosed with clinical and image findings.	
b. Pathological lesions	
Pathological examination shows characteristic features of sclerosing cholangitis, sclerosing dacryoadenitis/sialoadenitis, or retroperitoneal fibrosis.	
<Option> Effectiveness of steroid therapy	
A specialized facility may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or bile duct cancers have been ruled out. When it is difficult to differentiate from malignant conditions, it is desirable to perform cytological examination using an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). Facile therapeutic diagnosis by steroids should be avoided unless the possibility of malignant tumor has been ruled out by pathological diagnosis.	
B. Diagnosis	
I. Definite diagnosis	
① Diffuse type	I a + <III/IVb/V(a/b)>
② Segmental/focal type	I b + II + two or more of <III/IV b/V (a/b)>
	I b + II + <III/IV b/V (a/b)> + Option
③ Definite diagnosis by histopathological study	IV a
II. Probable diagnosis	
Segmental/focal type:	I b + II + <III/IV b/V (a/b)>
III. Possible diagnosis*	
Diffuse type:	I a + II + Option
Segmental/focal type:	I b + II + Option
When a patient with a focal/segmental image of AIP on CT/MRI without ERCP findings fulfill more than one of III, IVb and V(a/b) criteria, he/she can be diagnosed as possible AIP only after the negative workup for malignancy by EUS-FNA, and confirmed as probable one by an optional steroid response.	
Possible diagnosis*: A case may be possibly type 2, although it is extremely rare in Japan. "+" refers to "and", and "/" refers to "or".	

Table 8
Comparison of diagnostic criteria among pathological, comprehensive and pancreatic manifestation for IgG4-RD.

Diagnostic criteria [ref]	Clinical findings/images	Serology (serum IgG4)	Histology	OOI	Efficacy of steroid
Minimal Criteria by the International Pathological Consensus [19]	ND	High	Characteristic histopathological findings with an elevated IgG4t plasma cells and IgG4-to-IgG ratio	Reports of OOI consistent with IgG-RD	Yes
Comprehensive Diagnostic Criteria (CDC) for IgG4-RD [18]	Diffuse/localized swelling or masses in single or multiple organs	≤135 mg/dl	(i) Marked lymphocyte and plasmacyte infiltration and fibrosis. (ii) Ratio of IgG4+/IgG+ cells > 40% and >10 IgG4+ plasma cells/HPF	ND	No
ICDC for type1 AIP [25]	(i) Parenchymal image on CT/MRI (ii) Duct image on ERP		LPSP (i) Lymphoplasmacyte infiltrate (ii) >10 IgG4+ cells (/hpf) (iii) Storiform fibrosis (iv) Obliterative phlebitis	a. Histology of OOI b. Radiological evidence	Yes
Level 1	Diffuse	>2 × ULN	More than 3 (i–iv)	a. Any three (i–iv); b. typical one	
Level 2	Segmental/focal	1–2 × ULN	Any 2	a. Two (i + ii); b or physical	
JPS-2011 [43,44]	Enlarged pancreas on CT/MRI Diffuse enlargement Segmental/focal enlargement Irregular narrowing of the MPD on ERP	≥135 mg/dl	(i) Lymphoplasmacyte infiltrate (ii) >10 IgG4+ cells (/hpf) (iii) Storiform fibrosis (iv) Obliterative phlebitis	Sclerosing cholangitis, Dacryoadenitis/sialoadenitis Retroperitoneal fibrosis (a) Clinical lesions (b) Pathological lesions	

use; ii) rely on diffuse/segmental/focal classification of pancreatic imaging; iii) use IgG4 alone as a serological marker; iv) identify OOIs such as sclerosing cholangitis; sclerosing sialadenitis and retroperitoneal fibrosis; v) have no classifications of level1/2 in serum IgG4 and OOI; and vi) apply optional steroid trial only after determining non-malignancy using EUS-FNA. Different from the previous Japanese criteria, with JPS-2011, patients are diagnosed as having definitive, probable, or possible AIP by a combination of the criteria described. This is similar to the concept of the ICDC.

Although the JPS-2011 is focused on type 1 AIP, some patients with type 2 AIP, which is extremely rare in Japan, may be diagnosed as possible AIP using these criteria. As ERCP is more commonly performed to diagnose AIP or pancreatic cancer than EUS-FNA in Japan, ERCP is essentially required in the diagnosis of the focal/segmental type of AIP. However, to follow the concept of the ICDC as much as possible, the following exceptional case can be deemed acceptable only by an expert: when a patient with a focal/segmental image of AIP on CT/MRI without ERCP findings fulfills more than one of III (serum IgG4), IVb (two of pathological findings) and V(a/b) (OOI), he can be diagnosed as possible AIP only after the negative workup for malignancy by EUS-FNA and AIP is confirmed as probable by an optional steroid response. Comparison of each diagnostic criteria applicable for AIP is shown in Table 8.

9. Treatment

Even after diagnosis, it is important to recognize the possibility of misdiagnosing pancreatic cancer as AIP, and vice versa. As relief of swelling pancreatic parenchyma or narrowing of the MPD with steroid administration can be observed as early as 2 weeks after steroid therapy in AIP cases, which does not occur in pancreatic cancer cases, the Korean investigators advocate a short trial of steroid therapy to differentiate AIP from pancreatic cancer [23]. Before induction of remission by an initial steroid therapy, jaundice and blood glucose levels should be managed by biliary drainage in patients with obstructive jaundice and diabetes mellitus, respectively. For the initial oral prednisolone dose for induction of remission, 0.6–1.0 mg/kg/day is usually used and gradually tapered during 2–3 months [23]. An alternative administration with steroid mini-pulse treatment may be more useful for induction of remission in refractory cases [54]. However, it is still under debate whether the steroid maintenance therapy provides beneficial outcomes after remission or not, although type1 AIP relapsed in 18%–32% of cases treated with maintenance therapy [55–57] and in 53% of cases without maintenance therapy [58]. Although usefulness of steroid as an initial treatment is consented, there is no gold standard for retreatment in relapsing cases, in which re-administration or dose-up of steroid [23], immune-modulators such as thiopurine or mycophenolate [58], or rituximab [59,60] is used in the local expertise.

10. Conclusion

Recent advances support the concept of IgG4-RD, a unique clinical entity as a systemic disease, and classification of two distinctive subtypes of AIP, in which type 1 AIP is supposed as a pancreatic manifestation of IgG4-RD and type 2 AIP is associated with granulocytic epithelial lesion and inflammatory bowel disease. Although the comprehensive diagnostic criteria (CDC) for IgG4-RD is useful for diagnosis of the involved organs easy to be biopsied, AIP can be clinically diagnosed by the organ specific diagnostic criteria such as the ICDC or the JPS-2011 because of difficulty in taking biopsy samples. To improve the diagnostic criteria, novel biomarkers specific for each subtype of AIP should be established in the near future.

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