many resections had been performed for suspected carcinoma before this entity was recognized. The resected pancreas is usually enlarged. The lesion can be diffuse or focal, but focal lesions are more likely to be resected. The pancreatic lobular structure is relatively well preserved. In addition, peripancreatic adipose tissue is almost always inflamed, and looks like a sheath covering the pancreatic parenchyma (Fig. **1a**). This finding corresponds to the "capsule-like rim" observed radiologically [18]. The pancreatic duct system is open, although it looks stenotic radiologically.

The most characteristic inflammatory pattern is seen in peripancreatic adipose tissue and the interlobular area. It is a mixture of inflammatory cells, spindle-shaped stromal cells, and fibrosis. Inflammatory cells are mainly lymphocytes and plasma cells. Lymphoid follicles are also commonly seen. Eosinophils can be admixed and sometimes numerous, but neutrophils are absent. The degree of fibrosis is inversely proportional to the amount of inflammatory cells. Nodular demarcated foci with cellular inflammatory infiltrates are often seen, where small spindle-shaped cells and a mixture of inflammatory cells often give rise to a swirling pattern called storiform fibrosis (Fig. **1b**). Fibrosis is observed around rather than within such cellular inflammatory foci. When the inflammation is less cellular, such foci merge with the surrounding fibrosis and then become obscure. The regressive lesion may be fibrotic with only scattered inflammatory cells, although lymphoid follicles may remain even in such cases.

The inflammatory process often involves and obliterates veins (Fig. **1c**). This is called obliterative phlebitis, and is seen most prominently in inflamed peripancreatic adipose tissues. According to our preliminary data, obliteration of smaller (<100 μm in diameter) venules with inflammatory cells only or by organized tissue with few or no inflammatory cells is nonspecific and can be seen in various pancreatic diseases. In contrast, veins 100 μm or more in diameter that are obliterated by inflammatory changes similar to those observed in peripancreatic adipose tissue are specific to LPSP. On H&E sections, obliterative phlebitis looks like a nodular demarcated inflammatory focus and is not always easy to identify. Special stains for elastic fibers are helpful for identifying such foci. The splenic vein and even portal vein may also be involved, which makes surgeons suspect that they are dealing with an inoperative carcinoma.

Within the pancreatic parenchyma, characteristic histological findings are observed around the main and interlobular pancreatic ducts (Fig. **1d**). These findings consist of loose inflammatory tissues with numerous lymphocytes and plasma cells that surround the duct epithelium, so that the "duct wall" appears to be thickened by inflammation. Storiform fibrosis is occasionally seen. It is noteworthy, however, that the duct epithelium and lumen are intact. In rare cases with LPSP, the inflammatory process predominantly involves the pancreatic duct system, leaving other intra- and extrapancreatic tissues uninvolved.

In contrast to alcoholic chronic pancreatitis, the lobular contour of the pancreas is relatively well preserved in LPSP, but the inflammatory process does involve pancreatic lobules. Acinar cells are commonly destroyed and are replaced by inflammatory tissue with various amounts of inflammatory cells (Fig. **1e**). Compared to interlobular inflammation, the inflamed lobules look loose rather than fibrotic. Storiform fibrosis may also be seen. The borders of lobules are often blurred, and the inflammation of inter- and intralobular areas becomes continuous. Focally, pancreatic lobules are destroyed completely, and are replaced by the fibroinflammatory process seen in the interlobular area.

Immunohistochemically, numerous IgG4-positive plasma cells are identified in LPSP (Fig. **1f**) [12, 13]. They abound anywhere within the lesion if there are large numbers of plasma cells. The absolute number may be influenced by the number of total plasma cells, and thus the IgG4/immunoglobulin G1 (IgG1) or IgG4/IgG ratio is often evaluated; both are usually elevated in LPSP.

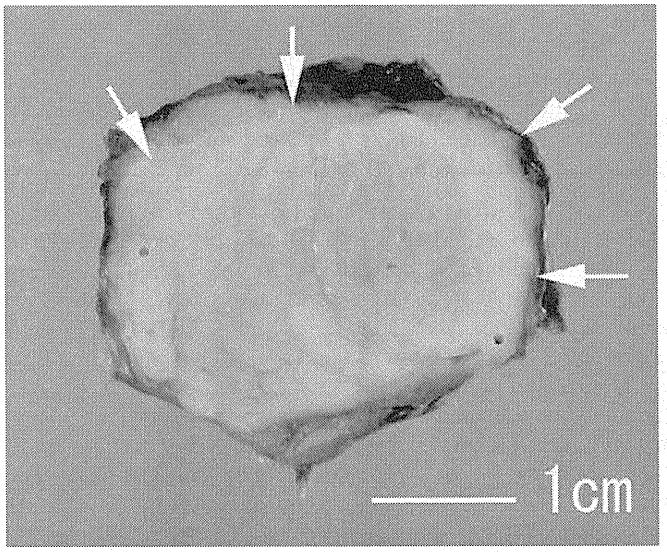
When the lesion becomes regressive, the characteristic histological features remain only focally. The lobules look "empty", lacking the loose inflammatory tissues seen in active LPSP. Often lymphoid follicles are numerous even though other inflammatory components diminish. Focal aggregation of IgG4-positive plasma cells and organized venous obstruction could be a clue toward a diagnosis of regressive LPSP. Unfortunately, there is no consensus so far on making a diagnosis of LPSP when the inflammation is regressive. When the lesion completely resolves, then it would look exactly like other types of chronic pancreatitis. The pathological diagnosis of such cases would be almost impossible. Patients with a regressive form of LPSP often show no serological evidence of AIP/LPSP.

Pathology of Idiopathic Duct-Centric Chronic Pancreatitis

Another pathological group of AIP, designated as IDCP, AIP with GEL, or ductocentric AIP, has been reported by Western authors [6-9]. The inflammation in this group is seen mainly in the main and/or interlobular ducts and is centered on the duct epithelium. Neutrophilic infiltration is characteristic, and is seen within the epithelium and lumen, which is in contrast to the lack of neutrophils and the preservation of normal epithelium in LPSP (Fig. **2**). As a result of the inflammation, duct epithelium reveals destructive and regenerative changes, and the lumen looks stenotic or tortuous. A band of lymphocytes and plasma cells surrounds the lumen but, in contrast to LPSP, it lacks both storiform fibrosis and the appearance of a "thickened wall". Sometimes the entire duct looks as if it is entrapped within an aggregate of inflammatory cells. When the inflammation is severe, pancreatic lobules are also inflamed with neutrophils, lymphocytes, and plasma cells. Microabscesses may be encountered. Although there is fibrosis with the proliferation of fibroblasts around pancreatic lobules, inflammatory cells are scarce within the fibrosis itself, in contrast to LPSP, in which inflammatory cells are often numerous in the fibrotic area. Obliterative phlebitis and dense peripancreatic adipose tissue inflammation are exceptional. IgG4-positive plasma cells are usually few in IDCP [13], and therefore nowadays IDCP is regarded as an entity that is different from LPSP (Table **1**).

(Fig. 1) contd.....

(a)



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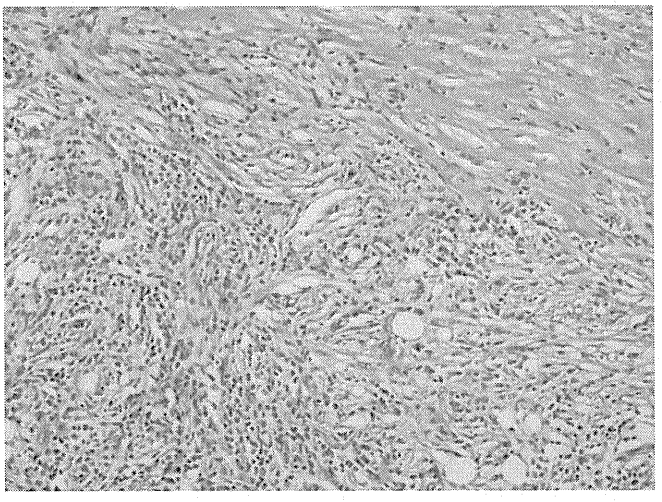

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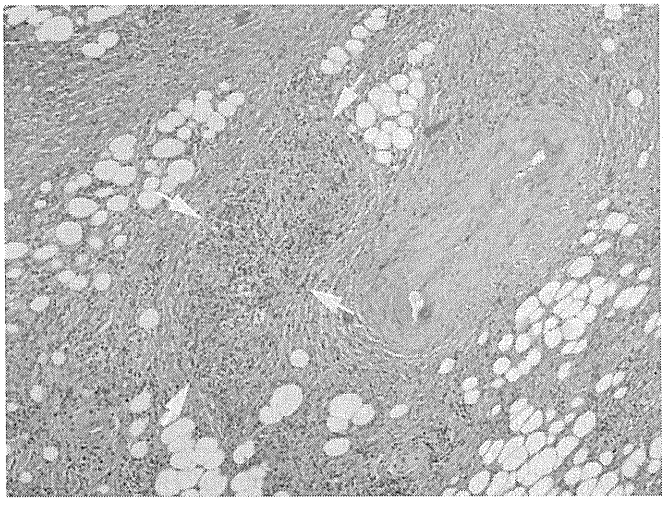

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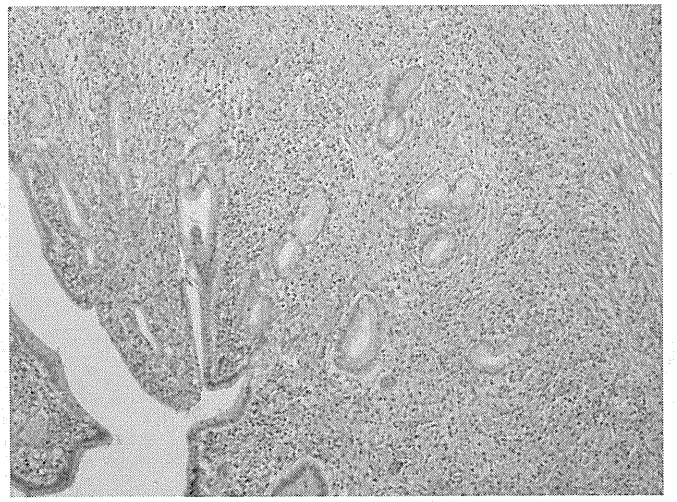

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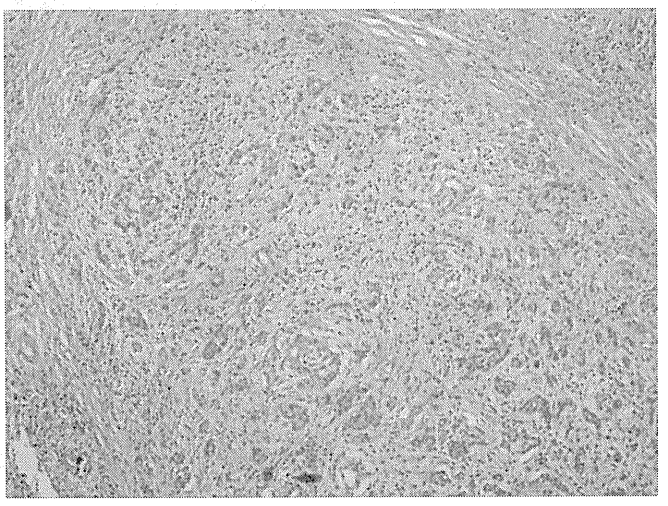

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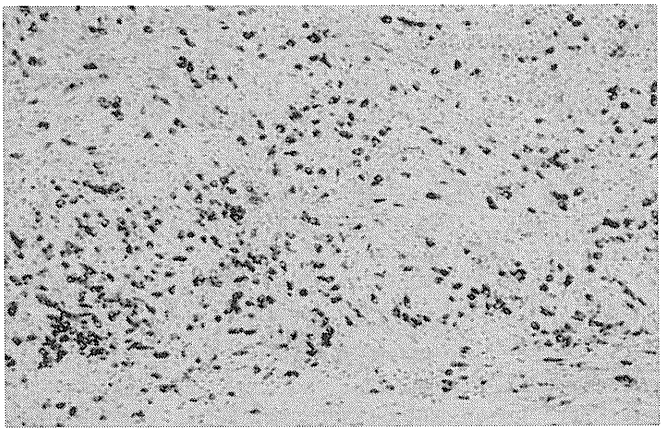


Fig. (1). Lymphoplasmacytic sclerosing pancreatitis (LPSP). (**a**) Macroscopic features with a sheath of inflammatory peripancreatic adipose tissue covering the pancreatic parenchyma (arrow). Representative histology of (**b**) storiform fibrosis, (**c**) obliterative phlebitis (arrow), (**d**) interlobular duct inflammation, (**e**) lobular inflammation, and (**f**) numerous IgG4-positive plasma cells identified with immunostaining.

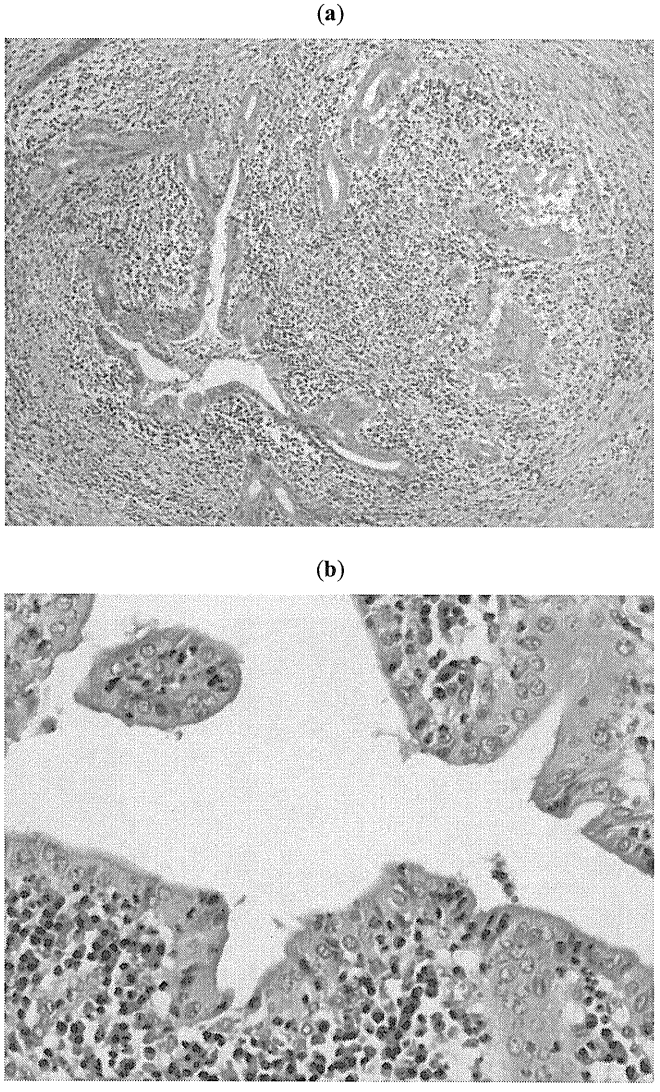


Fig. (2). Idiopathic duct-centric chronic pancreatitis (IDCP). (**a**) Interlobular duct entrapped within an aggregate of inflammatory cells. (**b**) Neutrophilic infiltration in the duct epithelium (granulocytic epithelial lesion).

Clinical Distinction Between LPSP and IDCP

Both LPSP and IDCP share some clinicopathological features. Both reveal pancreatic swelling and narrowing of the main pancreatic duct. From a radiologic standpoint, these two are hard to distinguish.

However, there are some demographic and clinical differences between LPSP and IDCP [6, 14]. LPSP is common in elderly males. In contrast, IDCP patients are younger, on average; many are under 40 years old. There is no gender preponderance. Obstructive jaundice is more common in LPSP than in IDCP. Serologically, LPSP patients often demonstrate hypergammaglobulinemia, elevated IgG level, and the presence of various autoantibodies, such as antinuclear antibody and rheumatoid factor. Elevation of serum IgG4 level is characteristic. IDCP patients usually show negative results for these tests. Unfortunately, there are no serological markers of IDCP and, in most cases, a pathological examination is the only way to correctly diagnose it. The negative serological results, however, do not preclude the diagnosis of LPSP because patients with a regressive form of LPSP may not reveal serological evidence of it. In such cases, the distinction between LPSP and IDCP is clinically difficult. The association of extrapancreatic lesions that belong to IgG4-related disease is a feature of LPSP. Such an association is exceptional in IDCP. In contrast, the association of inflammatory bowel disease (IBD) can be predominantly seen in IDCP [6, 7, 14].

It should be kept in mind that, in some reports the term AIP is used to mean LPSP only [19-22], but, in other reports, it indicates both LPSP and IDCP [23]. In addition, according to a comparative study of surgical cases of AIP (both LPSP and IDCP) between Japan and the US, IDCP was significantly more frequent in the latter [24]. Thus, the differences in demographic and clinical features of AIP between the East and the West, such as younger average age, the absence of gender preponderance, lower frequency of high serum IgG4 level, and more frequent association of IBD in the West, are most likely attributable to the higher frequency of IDCP in the West.

PATHOLOGY OF EXTRAPANCREATIC IGG4-RELATED DISEASE

The histological features and immunohistochemical identification of numerous IgG4-positive plasma cells are unique to LPSP. By using these morphological and immunohistochemical features as a hallmark, numerous IgG4-related lesions in various organs have been reported, such as sclerosing cholangitis and cholecystitis [25-29], duodenal ampullary lesion [30-32], hepatopathy [33], gastrointestinal lesions [34, 35], sclerosing sialadenitis and dacryoadenitis [36-40], pulmonary plasma cell granuloma, and other pleuropulmonary lesions [41-44], mastitis [45, 46], retroperitoneal fibrosis [47], tubulointerstitial nephritis [48, 49], prostatitis [50, 51], inflammatory aortic aneurysm [52, 53], lymphadenopathy [54, 55], infundibulo-hypophysitis [56, 57], pachymeningitis [58], sclerosing mesenteritis [59], sclerosing angiomatoid nodular transformation of the spleen [60, 61], and cutaneous pseudolymphoma [62]. Each of these diseases could occur separately or in various combinations. These lesions are clinically important for two reasons. First, many of them reveal masses of elderly patients that are suspicious for malignant diseases, and IgG4-related disease should be included in the differential diagnosis of a mass in various organs. Second, the proposals of these new concepts triggered a reclassification of preexisting entities of chronic inflammatory diseases. The creation of the new concepts has been justified by the fact that IgG4-related disease is responsive to steroid treatment.

The concept of IgG4-related disease is pathologically similar to that of multifocal fibrosclerosis. Multifocal fibrosclerosis is an idiopathic systemic fibroinflammatory disease that often reveal tumefactive lesions, and includes "primary sclerosing cholangitis" (PSC), retroperitoneal fibrosis, Riedel thyroiditis, and orbital pseudotumor. The association of "pancreatic pseudotumors" has been also reported, which probably represents LPSP [63]. Notably, obliterative phlebitis, one of the unique features of IgG4-related disease, has been reported to occur in multifocal fibrosclerosis [64-67].

Table 1. Clinicopathologic Comparison of LPSP and IDCP

	LPSP	IDCP
Clinical features		
Similarity	Pancreatic swelling Narrowing of the main pancreatic duct Effective corticosteroid treatment	
Differences		
Age and gender	Common in elderly male	Younger average age; no gender preponderance
Obstructive jaundice	More common	Less common
Serological abnormalities	Common (including elevated serum IgG4 level)	Rare
Associated diseases	Extrapancreatic IgG4-related lesions	Inflammatory bowel disease
Pathological features		
Similarity	Diffuse lymphoplasmacytic infiltration Duct-centric inflammation	
Differences		
Storiform fibrosis	Common	Rare
Obliterative phlebitis	Common	Rare
Ductal inflammation	Around the intact epithelium	Neutrophils within the lumen and/or epithelium
Lobular inflammation	Inflammatory swelling; neutrophils absent	Atrophic; neutrophils present (sometimes with abscess)
Involvement of peripancreatic adipose tissue	Deeply involved (corresponding to "capsule-like rim")	Minimal
IgG4-positive plasma cells	Numerous	Usually scarce

Among the family of IgG4-related disease, IgG4-related sclerosing cholangitis (IgG4-SC) is most easily understood to be related to LPSP. These two lesions often coexist in a single patient. IgG4-SC is frequently observed in the common bile duct within resected specimens with LPSP, and is considered to be the main cause of jaundice in AIP patients. The pathological finding of IgG4-SC is the inflammation of the entire wall of the bile duct with lymphoplasmacytic infiltration and fibrosis (Fig. **3**) [25, 27]. Storiform fibrosis and obliterative phlebitis are also common. Biliary epithelium is intact and not inflamed. These features are exactly the same as the pancreatic duct inflammation of LPSP. The inflammatory process often involves peribiliary soft tissue, and gives rise to inflammatory pseudotumor. Historically, IgG4-SC was likely diagnosed as PSC before this entity was recognized. In contrast to IgG4-SC, however, PSC is an inflammation centered on biliary epithelium. The epithelium is often destroyed and numerous inflammatory cells, including neutrophils, are encountered around the affected epithelium. The entire wall inflammation or peribiliary soft tissue involvement is unusual for PSC. From a clinical standpoint, PSC is common in IBD patients, which is a rare association of IgG4-SC. The bile duct system is affected more diffusely in PSC compared to the more localized distribution in IgG4-SC, and the radiological features are also distinct [68]. However, not all lesions with localized biliary strictures are IgG4-SC; some of them histologically resemble PSC, and some are of unknown cause. The distinction of IgG4-SC and PSC is clinically important because corticosteroid treatment is effective for patients with IgG4-SC, whereas there is no such indication for PSC, for which the only treatment is liver transplantation.

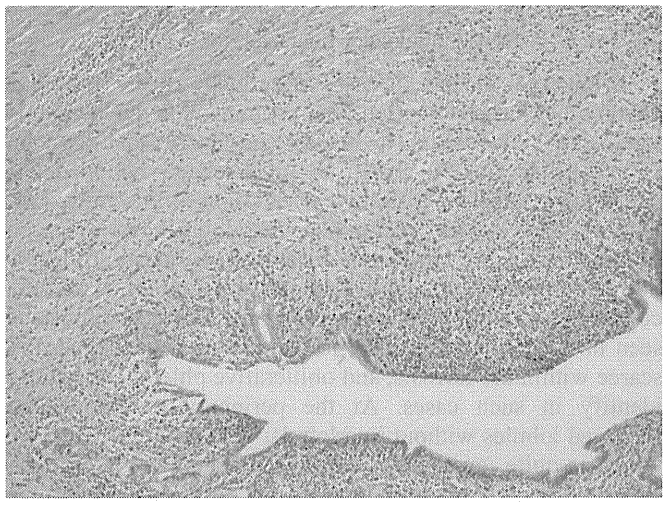


Fig. (3). IgG4-related sclerosing cholangitis. The histological features are similar to those of duct inflammation in LPSP (compare to Fig. **1d**).

Most of the other lesions, including retroperitoneal fibrosis, tubulointerstitial nephritis, inflammatory aortic aneurysm, and inflammatory pseudotumors in the lung and breast, are more like the inflammation of peripancreatic adipose tissue and interlobular area seen in LPSP (Fig. **4**).

According to the pictures presented in the reports as well as our own experience, those lesions reveal dense lymphoplasmacytic infiltration and fibrosis. Storiform fibrosis, eosinophilic infiltration, hyperplastic lymphoid follicles, and obliterative phlebitis are also common. It should be kept in mind, however, that not all of the fibroinflammatory lesions in these organs are IgG4-related. For example, inflammatory aortic aneurysm includes IgG4-unrelated cases, such as atherosclerotic aortic aneurysm [52]. Retroperitoneal fibrosis also includes IgG4-related and unrelated cases [47]. Thus, in cases that belong to IgG4-related disease, we prefer to add a premodifier, "IgG4-related". The distinction from malignant lymphoma may also be a problem. In IgG4-related pulmonary inflammatory pseudotumors, arterial involvement is common, and thus lymphomatoid granulomatosis is a differential diagnosis. Malignant lymphoma may be sclerotic in the retroperitoneum, and it should be distinguished from IgG4-related retroperitoneal fibrosis.

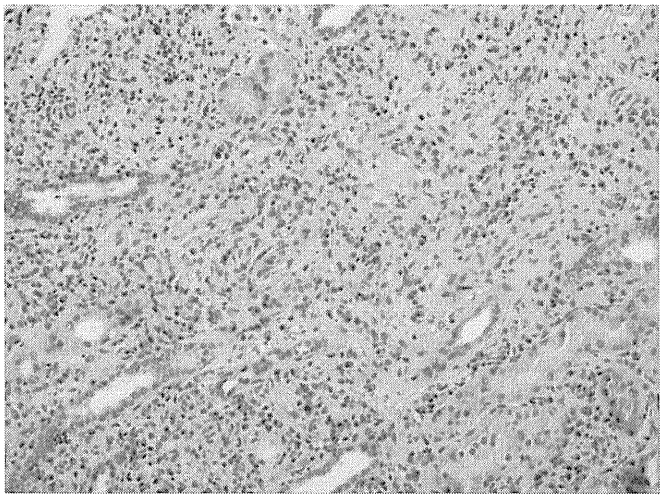
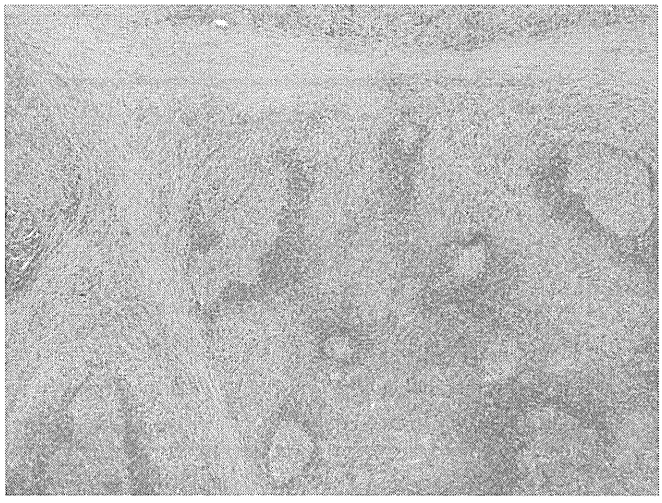


Fig. (4). IgG4-related tubulointerstitial nephritis.

Compared to the diseases described in the previous paragraph, fibrosis is often less prominent in IgG4-related sclerosing sialadenitis (IgG4-SS) and dacryoadenitis than LPSP and is usually absent in IgG4-related lymphadenopathy, suggesting the histological variation of this entity [36, 54, 55]. Instead, the predominant histological features seen in these organs are lymphoplasmacytic hyperplasia. In IgG4-SS, hyperplastic lymphoid follicles and numerous plasma cells are seen within the lobules (Fig. **5**). Although fibrosis is seen in the interlobular area, inflammatory cells are usually scarce within the fibrosis, and obliterative phlebitis is hard to identify in such cases. At the periphery of the lesion, inflamed lobules without interlobular fibrosis are often seen, which is quite unusual for LPSP. Salivary ducts are intact. When the lobular architecture is destroyed, then the inflammation looks similar to LPSP, with storiform fibrosis and obliterative phlebitis. Numerous IgG4-positive plasma cells can be identified in the lobules. They are also identified within the germinal centers. Historically, IgG4-SS was called Küttner tumor or Mikulicz disease, and may have been confused with Sjögren's syndrome [37, 39].

(**a**)



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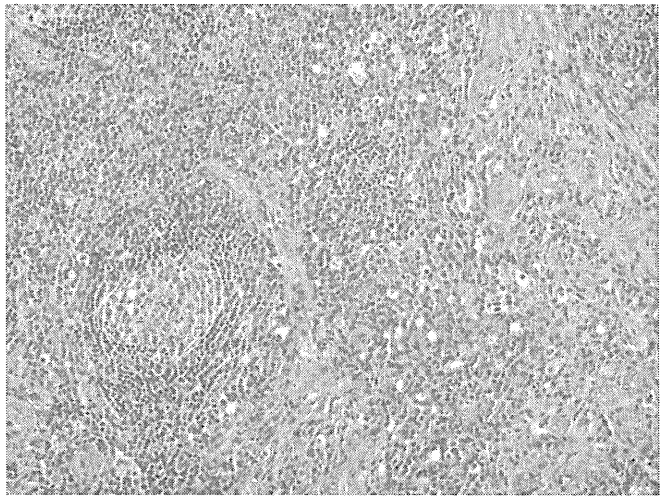

Fig. (5). IgG4-related sclerosing sialadenitis. (**a**, **b**) Numerous lymphoid follicles and plasma cells are seen within the lobules. Inflammatory cells are scarce within the interlobular fibrosis.

HISTOLOGY *VS* IMMUNOSTAINING

From those authors' viewpoint, IgG4-related disease is a distinct entity that shows specific clinicopathological features. Given the full spectrum of characteristics, histological examination alone can be diagnostic for IgG4-related disease. However, the histological features of IgG4-related disease vary depending on the organs and the degree of disease activity. For example, as described earlier, regressing LPSP is hard to diagnose due to its having fewer diagnostic features.

The presence of numerous IgG4-positive plasma cells is one of the main pathological characteristics, and is a useful adjunct for the diagnosis. However, it is not always necessary or sufficient for making a diagnosis of IgG4-related disease; sometimes there are discrepant cases having histological features compatible with IgG4-related disease

but without numerous IgG4-positive plasma cells or vice versa. It can not be emphasized enough that IgG4-immunostaining should be evaluated within the context of compatible histological findings. This is especially true in making a diagnosis on small biopsy samples with a limited amount of information. In the following paragraphs, some important reminders for the evaluation of IgG4-immunostaining are described.

If a lesion morphologically resembles LPSP and has scarce IgG4-positive plasma cells in spite of the presence of numerous plasma cells, it is unlikely that the lesion corresponds to IgG4-related disease. However, a scarcity of IgG4-positive plasma cells does not necessarily exclude the possibility of IgG4-related disease when inflammatory cells are also scarce. It is easily understood that IgG4-positive plasma cells are scarce when the inflammation becomes regressive in IgG4-related disease. Unfortunately, there has been little discussion of the regression of IgG4-related disease, and there is no consensus so far on its diagnosis.

In addition, it should be stressed that numerous IgG4-positive plasma cells are not entirely specific to IgG4-related disease. Suppurative granulation tissue, for example, may contain numerous IgG4-positive cells [69]. This is because the number of IgG4-positive plasma cells increases when the total number of plasma cells increases in the inflammation. In this regard, the IgG4/IgG1 or IgG4/IgG ratio is more specific to IgG4-related disease. Those authors prefer to compare IgG4 and IgG1. In inflammatory lesions that are unrelated to IgG4-related disease, IgG1-positive plasma cells usually predominate, and only a few IgG4-positive cells are identified. In IgG4-related disease, on the other hand, the number of IgG4-positive plasma cells is almost always equal to or more than that of IgG1-positive plasma cells.

Finally, it is also well known that LPSP-like histology and numerous IgG4-positive plasma cells can be seen in association with carcinomas, and some patients with pancreatic carcinoma reveal elevated serum IgG4 [70-73]. It is not clear yet weather these cases are a composition of carcinoma and IgG4-related disease, or if the latter is a reaction against the former.

CONCLUDING REMARKS

The discovery of IgG4-related disease has provoked not only proposals of new disease concepts, but also reclassification of preexisting clinicopathological entities. In addition, the recognition of these new entities is valuable for clinicians as well, because many of these lesions reveal masses of elderly patients that are clinically suspicious for malignant diseases, and nevertheless they are responsive to corticosteroid therapy.

However, the diagnosis of IgG4-related disease should be made with caution because there are morphological mimics and pitfalls in IgG4-immunostaining. At present, the diagnosis should be based on compatible histology as well as on a proliferation and increased ratio of IgG4-positive plasma cells.

ACKNOWLEDGEMENT

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Autoimmune Pancreatitis: Pancreatic Manifestation of IgG4-Related Disease

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Abstract: Autoimmune pancreatitis (AIP) is a unique inflammatory disorder of the pancreas. Two histological types are recognized: lymphoplasmacytic sclerosing pancreatitis and idiopathic duct-centric chronic pancreatitis, with the former representing the pancreatic manifestation of IgG4-related disease. Presented here is a 64-year-old man who was incidentally found to have a mass in the pancreatic tail. The resected specimen revealed typical histological features of lymphoplasmacytic sclerosing pancreatitis, consisting of storiform fibrosis, obliterative phlebitis, and characteristic lobular and ductal inflammation. IgG4-positive plasma cells were numerous, and his serum IgG4 level was elevated (436 mg/dL). He also had systemic lesions, such as hypophysitis, bilateral eyelid lesions and bilateral pleural thickening, that most likely represented IgG4-related disease. Sometimes the distinction of AIP from cancer is clinically difficult, especially in cases with a localized lesion and/or without serological abnormalities; thus, pancreatic resection may be carried out. Pancreas biopsy is attracting attention as a diagnostic tool, and pathologists may play an important role in diagnosing AIP in the future.

Key Words: autoimmune pancreatitis, IgG4-related disease, IgG4

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Autoimmune pancreatitis (AIP) is a unique inflammatory condition that is clinicopathologically distinct from other chronic inflammatory disorders of the pancreas, such as alcoholic chronic pancreatitis.[1] Histologically, it consists of dense lymphoplasmacytic infiltration and fibrosis, and it had been reported under various pathological designations before the concept of AIP was proposed.[2–5] From the clinical standpoint, AIP patients reveal various serological abnormalities such as hypergammaglobulinemia, elevated IgG level, and the presence of autoantibodies (antinuclear antibody, rheumatoid factor, etc) and respond to corticosteroid treatment well. These findings suggest that a certain autoimmune cause may be involved in the disease process.

Although it is rare for pathologists to handle surgical specimens of pancreatitis, AIP is an exception. Because AIP induces pancreatic swelling and irregular narrowing of the main pancreatic duct and even the common bile duct, distinction from pancreatic carcinoma based on imaging is clinically difficult. Many unnecessary resections had been performed before the concept of AIP was recognized, and even today, some cases are difficult to diagnose without histological examination. As a result, biopsy diagnosis of AIP is recently attracting attention as a diagnostic tool for AIP. This trend has been driven by advances in the technology of endoscopic ultrasonography (EUS)–guided fine-needle aspiration (FNA) or trucut biopsy (TCB).

Elevated serum levels of IgG4 were reported in AIP patients by Hamano et al[6] in 2001. Serum IgG4 is now regarded as a useful tool for diagnosing AIP. In addition, the same group also identified numerous IgG4-positive plasma cells in the affected tissues of AIP[7]; nowadays, immunostaining for IgG4 is a valuable diagnostic adjunct for pathologists. More importantly, their findings also contributed to the identification of various IgG4-related lesions outside the pancreas.[8–11] They correspond to a previously known entity called multifocal fibrosclerosis, now collectively called IgG4-related disease.[12,13] Autoimmune pancreatitis is therefore regarded as a pancreatic manifestation of this systemic disease, but it should be also kept in mind that there is another pathological group unrelated to IgG4 among cases reported as AIP.

CASE REPORT

A 64-year-old man who had been experiencing organized pneumonia for 4 years and had been on steroid treatment (1 mg/d) was referred because of abnormal liver function test results and suspicion of steatohepatitis. He also had a history of central diabetes insipidus and dry mouth. He had no abdominal symptoms. Results of the physical examinations were unremarkable. Chemical blood examinations revealed hyperproteinemia (8.5 mg/dL) and mild elevation of aspartate aminotransferase (46 IU/L) and alanine aminotransferase (52 IU/L) levels. Biliary and pancreatic enzymes (alkaline phosphatase, γ-glutamyl transferase, amylase, lipase, and elastase 1) and tumor markers (carcinoembryonic antigen, CA-19-9, and neuron-specific enolase) were within reference limits. Serum gastrin level was elevated (550 pg/mL).

Contrast-enhanced computed tomography and magnetic resonance imaging of the abdomen (Fig. 1) demonstrated a mass in the pancreatic tail, 2 cm in diameter, which was enhanced in a fashion similar to the pancreas. The whole-body 18 F-fluorodeoxyglucose (FDG)–positron emission tomography/computed tomography showed abnormally increased FDG uptake in the mass in the pancreatic tail. In addition, increased uptake was seen in bilateral pleural thickening and bilateral eyelids. On brain magnetic resonance imaging, the pituitary stalk was thickened, and the "bright spot" of the posterior gland had disappeared.

He was suspected to have malignant mesothelioma, but percutaneous needle biopsy of the pleura revealed fibrous tissue with only scattered inflammatory cells and no evidence of malignancy. The pancreatic mass was suspicious for neoplasm, especially an endocrine neoplasm, given the fact that the serum gastrin level was elevated. A distal pancreatectomy was performed.

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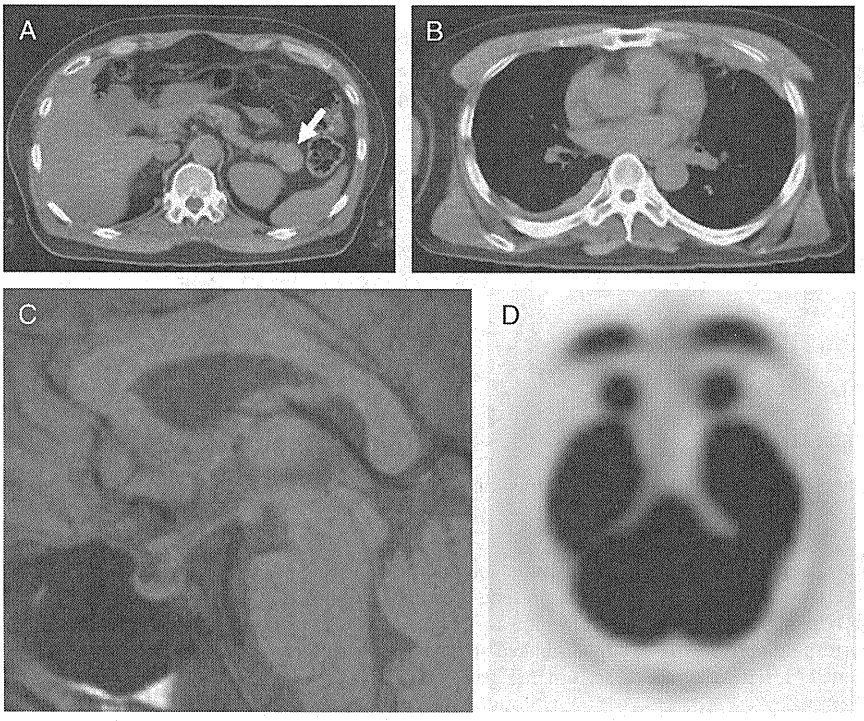

FIGURE 1. A and B, Computed tomographic images demonstrating a mass (arrow) in the pancreatic tail (A) and irregular pleural thickening on both sides (B). C, Magnetic resonance image (T1-weighted) demonstrating thickened pituitary stalk. The high signal intensity, which is normally seen in the posterior lobe, has disappeared. D, Positron emission tomographic/computed tomographic image showing diffusely increased FDG uptake in both eyelids.

A 33 × 30 × 20-mm-sized, vaguely circumscribed mass was identified in the resected pancreas. Histologically, the lesion was an inflammatory mass that involved the peripancreatic adipose tissue and a portion of the pancreatic parenchyma and comprised dense lymphoplasmacytic infiltration and fibrosis. Eosinophils were scattered, but neutrophils were absent. In the peripancreatic adipose tissue, prominent storiform fibrosis (Fig. 2A), a swirling pattern of inflammation with an admixture of small spindle-shaped cells, inflammatory cells, and various amounts of collagen was seen, and obliterative phlebitis (Fig. 2A), where small veins were obliterated with the inflammatory process, was also evident. The parenchymal lesion resulted from the destruction of acinar cells and replacement by inflammatory lymphoplasmacytic infiltration. The lobular architecture, however, was vaguely preserved (Fig. 2B). Interlobular areas were fibrotic and contained various amounts of inflammatory cells, which were continuous with peripancreatic inflammation. Lymphoplasmacytic infiltration surrounded by fibrosis was seen around the epithelium of interlobular pancreatic ducts (Fig. 2C), but the duct epithelium was intact and no neutrophils were seen.

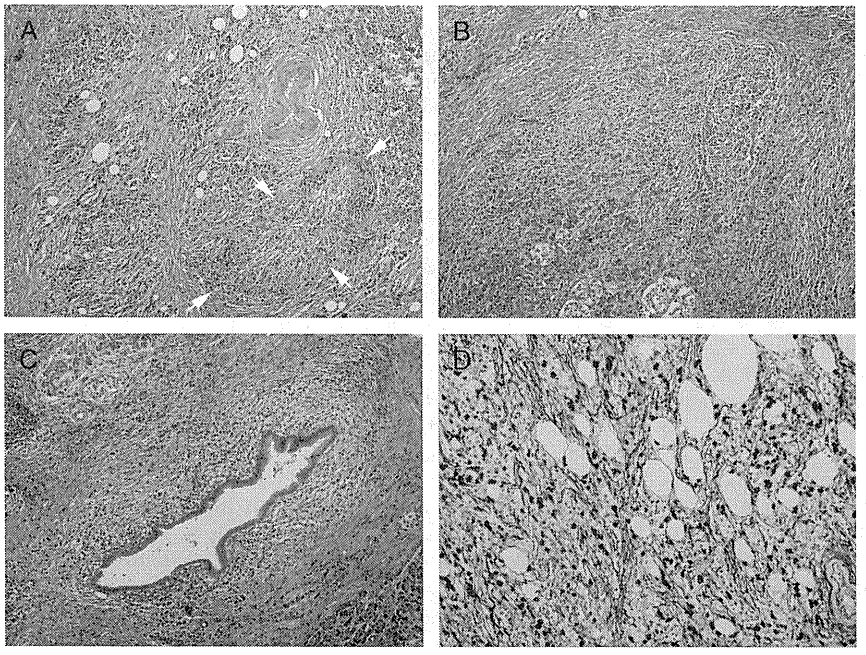

FIGURE 2. A, Inflammation in the peripancreatic adipose tissue showing storiform fibrosis and obliterative phlebitis (arrow). B, Lobular inflammation with lymphoplasmacytic infiltration. Note that the lobular architecture is vaguely preserved. C, Ductal inflammation. D, Numerous IgG4-positive plasma cells.

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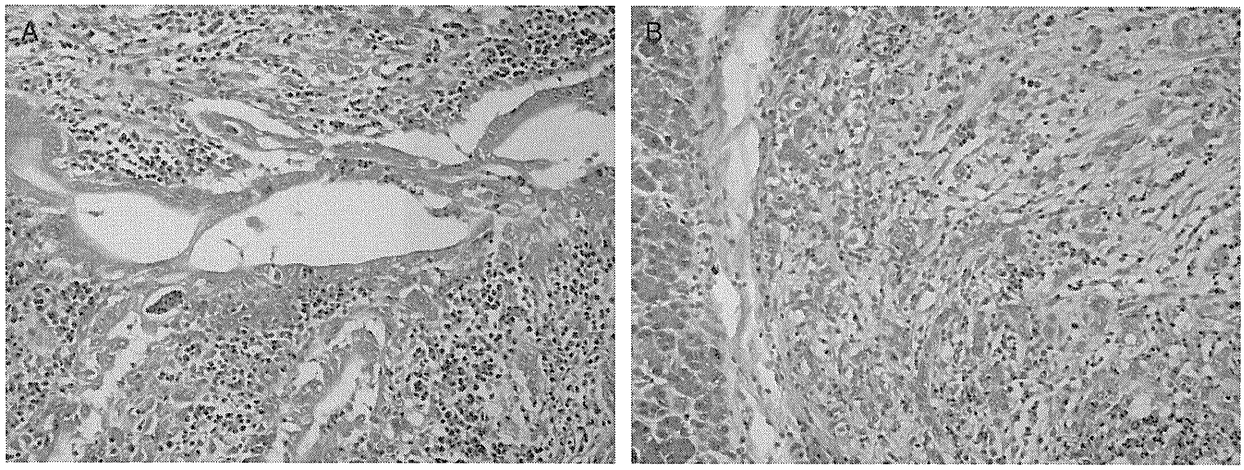

FIGURE 3. Idiopathic duct-centric chronic pancreatitis. A, Neutrophils are seen within the duct lumen. B, Inflammatory cells are also seen in the lobular stroma.

Immunostaining revealed numerous IgG4-positive plasma cells (Fig. 2D) in the lesion, outnumbering the IgG1-positive plasma cells. All of these features were diagnostic for lymphoplasmacytic sclerosing pancreatitis (LPSP), clinically corresponding to AIP. The postoperative serum IgG4 level was elevated (436 mg/dL).

DISCUSSION

Pathology of AIP

Lymphoplasmacytic sclerosing pancreatitis is a peculiar inflammatory condition of the pancreas reported by Kawaguchi et al.[3,14,15] It is generally accepted as a prototype of AIP. In fact, most of the AIP cases reported from Japan and Korea, including the original report from Japan,[1] are considered to represent LPSP. However, among the reports of AIP, especially from the West, there is another histological type called idiopathic duct-centric chronic pancreatitis (IDCP).[15] Autoimmune pancreatitis with granulocytic epithelial lesion[16,17] is synonymous with IDCP.

Lymphoplasmacytic sclerosing pancreatitis typically reveals diffuse pancreatic swelling but may form a localized mass. Histologically, LPSP consists of dense lymphoplasmacytic infiltration and fibrosis. Eosinophils are often encountered, but neutrophils are rare. The storiform fibrosis, obliterative phlebitis, and ductal inflammation found in the present case are considered to be diagnostic for LPSP. Immunohistochemically, numerous IgG4-positive plasma cells are seen; thus, LPSP is now regarded as the pancreatic manifestation of IgG4-related disease.[18,19]

Storiform fibrosis and obliterative phlebitis are notable in peripancreatic adipose tissue, which is accompanied by the inflammatory process in most cases. Obliterative phlebitis is seen as a nodular inflammation, with a diameter of 100 μm or larger, adjacent to small arteries. Elastic stains may help identify such foci. Sometimes, larger veins, such as the splenic vein or even the portal vein, may be involved, in which case only a portion of the venous wall is replaced by the inflammation.

Ductal inflammation comprises lymphoplasmacytic infiltration around the epithelium with a variable degree of surrounding fibrosis. This change causes the characteristic irregular narrowing of the main pancreatic duct seen radiographically. Storiform fibrosis may be prominent in the ductal inflammation, giving rise to an appearance as if the "duct wall" is thickened with the inflammation. Notably, the duct epithelium is typically intact and, in contrast to IDCP, neutrophils are scarce. When present, the common bile duct is often inflamed in a similar fashion to the pancreatic duct. This finding corresponds to IgG4-related sclerosing cholangitis[8] and is the cause of jaundice seen in AIP patients.

Although not emphasized in the previous reports, features seen in pancreatic lobules are also characteristic for LPSP. Although acinar cells are destroyed and replaced in the inflammatory process by lymphoplasmacytic infiltration, the size of the lobules is normal or even larger rather than atrophic, and the lobular architecture is vaguely preserved in most cases. When heavily inflamed, storiform fibrosis may be also seen within the lobules. Fibrosis with various numbers of inflammatory cells is seen between the lobules and is continuous with the inflammation in peripancreatic adipose tissue.

Histological features of IDCP are different from those of LPSP, with some similarities. Idiopathic duct-centric chronic pancreatitis can show diffuse or focal lesions. The characteristic histological feature of IDCP is duct epithelium–centered inflammation, most notably seen in interlobular ducts (Fig. 3). In addition to lymphoplasmacytic infiltration, neutrophils are seen within the duct epithelium and/or in the duct lumens, which is called granulocytic epithelial lesion. The duct epithelium shows regenerative changes, but such a finding is unusual in LPSP. When the inflammation is severe, intralobular stroma may be inflamed with neutrophils, lymphocytes, and plasma cells, and even microabscesses can be encountered. Interlobular areas are fibrotic, but inflammatory cells are scarce there. Storiform fibrosis or obliterative phlebitis is rarely seen, and IgG4-positive plasma cells are scarce.[19] Idiopathic duct-centric chronic pancreatitis is thus different from LPSP and should not be included in IgG4-related disease.

Clinical Features of AIP

On the one hand, LPSP and IDCP share some clinical features. Radiologically, both of them reveal diffuse or focal pancreatic swelling and irregular narrowing of the main pancreatic duct, making their distinction from pancreatic cancer difficult. Abdominal symptoms are usually mild, and the severe abdominal pain seen in patients with acute or chronic pancreatitis is rare. Corticosteroid treatment is effective in both types. On the other hand, however, there are some demographic and clinical differences between the two.

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Lymphoplasmacytic sclerosing pancreatitis is common in elderly males.[20,21] Jaundice is a common symptom. Interestingly, some LPSP cases are accompanied by recent onset of diabetes mellitus. Some patients are asymptomatic and visit a hospital with abnormalities found in medical checkup. Serological abnormalities such as hypergammaglobulinemia, elevated IgG level, and the presence of autoantibodies (antinuclear antibody, rheumatoid factor) are common. Notably, the serum IgG4 level is often elevated in LPSP patients. Extrapancreatic lesions that are included in IgG4-related disease are often seen synchronously or metachronously in LPSP patients.[22] Lymphoplasmacytic sclerosing pancreatitis often recurs after corticosteroid treatment.

The mean age of IDCP patients is younger than that of LPSP.[15,21] This is because IDCP is seen in a wide range of ages, equally among the 2 sexes. No serological markers that are useful for diagnosing IDCP have been discovered, and IgG4 is not elevated. Thus, confirmation of IDCP diagnosis is difficult without histological examination. Idiopathic duct-centric chronic pancreatitis is known to occur in patients with inflammatory bowel disease,[15,21] although extrapancreatic manifestations that belong to IgG4-related disease are not seen. Compared with LPSP, obstructive jaundice is rarer, and the recurrence rate is lower.

In the past, there was a debate about whether LPSP and IDCP are 2 different entities or just 2 ends of the spectrum of a single disease, but based on the different clinicopathological features between the two, a consensus has been built among specialists that they are clinicopathologically different. Considering the fact that LPSP and IDCP have different recurrence rates and different patterns of extrapancreatic complications, pathologists are advised to establish a case as either LPSP or IDCP rather than just simply use the encompassing term, AIP.

Nowadays, many AIP patients are diagnosed clinically and are treated with corticosteroids. In addition to more and more awareness of AIP among clinicians, various diagnostic criteria and guidelines proposed from different groups have contributed to this trend.[23–28] However, it should be acknowledged that each set of criteria reflects a particular stance in the inclusion of IDCP in AIP. Those from Japan, Korea, and Asia depend on the perspective that only LPSP represents AIP, but there are different criteria that regard both LPSP and IDCP as AIP.

Biopsy Diagnosis of AIP

As described in the previous section, typical cases of AIP are diagnosed clinically today. However, in some situations, AIP diagnosis is hard to achieve based on clinical information. Autoimmune pancreatitis is easily diagnosed when the pancreas shows diffuse swelling; however, when the lesion reveals a localized mass in the pancreas, as in the present case, the distinction from pancreatic cancer is difficult. In addition, there are no serological markers known for IDCP, and even LPSP patients could be seronegative when the inflammation regresses. Thus, in cases with a localized mass with irregular narrowing of the main pancreatic duct and without any serological abnormalities, the distinction among LPSP, IDCP, and pancreatic cancer might be very difficult. Pancreatic biopsies are therefore attracting attention for their ability to render a proper diagnosis. This trend has been driven by an advance in the technology of EUS-guided FNA or TCB. Diagnosing LPSP with EUS-TCB is promising and is reported to be effective in about half of LPSP patients.[29,30] Unfortunately, however, this procedure is not currently available in most institutes. Compared with TCB, the more conventional EUS-FNA biopsy is seldom valuable for diagnosing LPSP because of the smaller amount of tissue obtained.[29,30]

The histological features of LPSP are so characteristic that the diagnosis of LPSP can be easily rendered with resected specimens. However, biopsy diagnosis of LPSP is challenging because diagnostic hallmarks are rarely obtained or hard to identify in tiny biopsy samples. According to our preliminary study, interobserver concordance among pathologists who were familiar with diagnosing LPSP was only moderate, even if immunostaining for IgG4 was taken into consideration. In the biopsy diagnosis, immunostaining for IgG4 is mandatory. The presence of more than 10 positive plasma cells in a high-power field is a rough standard for diagnosing LPSP, although this is not always specific. Numerous IgG4-positive cells may be seen in suppurative inflammation if numerous plasma cells are present.[31] In this sense, the IgG4/IgG ratio (>0.5) or IgG4/IgG1 ratio (>1) is more specific for LPSP. It should be kept in mind that IgG4-positive plasma cells may be numerous in and around pancreatic cancer,[19] and these patients may show elevated serum levels of IgG4.[32,33] Moreover, pancreatic cancer can be seen in association with LPSP.[34,35]

So far, FNA cytology is believed to be unsatisfactory in diagnosing AIP. However, it is a sensitive and specific test to diagnose pancreatic cancer and is an effective tool for excluding pancreatic cancer. Moreover, there is a report suggesting that the presence of stromal fragments rich in lymphocytic infiltration is useful in rendering an AIP diagnosis.[36] Future studies may increase the diagnostic value of FNA cytology.

IgG4-Related Disease

Patients with AIP/LPSP are known to have various extrapancreatic lesions. Pulmonary hilar lymphadenopathy, bile duct lesions (sclerosing cholangitis), lachrymal and salivary gland lesions (sclerosing dacryoadenitis/sialadenitis), hypothyroidism, and retroperitoneal fibrosis are reported to be common.[22] All of these lesions histologically resemble LPSP and possess numerous IgG4-positive plasma cells in the affected tissues, suggesting that they are pathogenetically related.[12,13] At present, they are collectively called IgG4-related disease, and the constituent diseases belonging to this family are still increasing in number.[37] Lesions in the pituitary gland,[38,39] eyelid,[40] and pleura[41] seen in the present case have been reported in the literature and are considered to be IgG4-related. In some organs, recognition of a new concept has drastically changed preexisting entities. For example, IgG4-related sclerosing cholangitis was probably originally included in the concept of primary sclerosing cholangitis, but for therapeutic purposes, those 2 should be distinguished because corticosteroid treatment is effective only for the former.[8] Historically, IgG4-related disease was likely reported as multifocal fibrosclerosis.[3,12] In fact, obliterative phlebitis has also been reported in the latter.[42,43]

Biopsy materials from extrapancreatic organs such as lip, duodenal papilla, and liver (in cases with sclerosing cholangitis) of patients who are suspected to have AIP may be submitted and sometimes contribute to the diagnosis of IgG4-related disease. Although it is not common to see typical LPSP-like features in these biopsy tissues, numerous (>10 in a high-power field) IgG4-positive plasma cells may be identified. Biopsy of duodenal papilla is useful in approximately 60% of AIP patients; this is especially true in cases with a swollen duodenal papilla.[44–46] Compared with the duodenal papilla, biopsy of the bile duct is less informative.[44,47] IgG4-related sclerosing cholangitis is a localized disease at the hepatic hilum or extrahepatic bile duct; therefore, liver biopsies obtained from the periphery of the liver are useful in only about half the cases.[44] Usually, focal accumulation of lymphocytes and plasma cells is a histological feature of liver biopsy.

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CONCLUSIONS

The case presented here is typical for LPSP. The extrapancreatic lesions seen in this case, hypophysitis, bilateral eyelid lesions, and pleuritis, are probably IgG4-related. Sometimes the distinction of AIP from cancer is clinically difficult, especially in cases with a localized lesion, and thus the resected pancreas may be submitted for histological examination. Pancreas biopsy is attracting attention as a diagnostic tool, and pathologists may need to play an important role in diagnosing AIP in the future.

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Review Article

IgG4-related disease: Historical overview and pathology of hematological disorders

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IgG4-related diseases comprise a recently recognized systemic syndrome characterized by mass-forming lesions in mainly exocrine tissue that consist of lymphoplasmacytic infiltrates and sclerosis. There are numerous IgG4-positive plasma cells in the affected tissues, and the serum IgG4 level is increased in these patients. The present study describes the history, autoimmune pancreatitis (AIP), IgG4-related lymphadenopathy and lymphomagenesis based upon ocular adnexal IgG4-related disease. Lymphoplasmacytic sclerosing pancreatitis, a prototypal histological type of AIP, is now recognized as a systemic IgG4-related disease. Lymph node lesions can be subdivided into at least five histological subtypes, and systemic IgG4-related lymphadenopathy should be distinguished from multicentric Castleman's disease. Interleukin-6 and CRP levels are abnormally high in multicentric Castleman's disease, but are normal in the majority of systemic IgG4-related lymphadenopathy. Ocular adnexal IgG4-related disease frequently involves bilateral lacrimal glands swelling, and obliterative phlebitis is rare. Moreover, some malignant lymphomas, especially mucosa-associated lymphoid tissue lymphoma, arise from ocular adnexal IgG4-related disease. In addition, IgG4-producing lymphoma also exists.

Key words: autoimmune pancreatitis, IgG4, lymph node, mucosa-associated lymphoid tissue lymphoma, ocular adnexa

IgG4 is a minor component of the four subclasses of IgG in serum. Sporadic examples, such as IgG4 autoantibodies present in patients with autoimmune bullous skin diseases[1–3] and deposition of IgG4 seen in membranous nephropathy,[4] had indicated that IgG4 might be pathogenetically related to some diseases. But little attention has been paid to this minor component of IgG since Hamano *et al.* found elevated serum IgG4 level in patients with autoimmune pancreatitis (AIP).[5] This was the beginning of the use of IgG4 as a serological marker for a specific disease, and nowadays serum IgG4 is acknowledged as an important serological test for making a diagnosis of AIP and other related diseases. The same group also reported that numerous IgG4-positive plasma cells were characteristically observed in pancreatic tissues with AIP.[6] This perception facilitated the identification of numerous extrapancreatic diseases that were potentially related to AIP pathogenetically, and more importantly triggered a reclassification of pre-existing entities. These diseases are now grouped together and called IgG4-related diseases, and the number of constituents in this category is still increasing.

This review article first focuses on how the concept of IgG4-related diseases emerged by reviewing the history, and debates the pathology of AIP, with special references to the lymph nodal lesion and lymphomagenesis of the ocular adnexal region.

HISTORICAL PERSPECTIVES OF AUTOIMMUNE PANCREATITIS AND IgG4-RELATED DISEASES

Pathology of AIP and its relationship to IgG4

The concept of AIP was proposed by Yoshida *et al.* in 1995.[7] According to their description and other reports mainly from Japan, AIP is common in elderly men. The chief complaint is usually mild abdominal symptoms or obstructive jaundice. Diabetes mellitus is commonly associated with this. Some patients are asymptomatic. Severe abdominal pain is exceptional. Radiologically, the affected pancreas has diffuse or focal swelling and irregular narrowing of the main pancreatic

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duct. Thus from the clinical standpoint, it is difficult to distinguish AIP from pancreatic carcinoma, and many resections had been performed for suspected carcinoma before this entity was recognized. Serology often indicated hypergammaglobulinemia, elevated IgG level and the presence of various autoantibodies, such as antinuclear antibody and rheumatoid factor. Characteristically, serum IgG4 level is often elevated. Notably, corticosteroid treatment is effective, and its effect is usually evident in a few weeks. From these observations, autoimmune mechanism has been considered to play a role in this condition, which led to the term AIP.

The histological feature of AIP is diffuse lymphoplasmacytic infiltration and fibrosis. It is pathologically so peculiar among inflammatory conditions of the pancreas that, indeed, there had been some sporadic reports on pathology dealing with this topic even before the concept of AIP was proposed, such as chronic inflammatory sclerosis of the pancreas,[8] lymphoplasmacytic sclerosing pancreatitis (LPSP),[9] non-alcoholic duct destructive chronic pancreatitis[10] and inflammatory pseudotumor.[11] As the concept of AIP had been gradually accepted among clinicians, and it has become recognized that lymphoplasmacytic infiltration with fibrosis was a histological characteristic of AIP, these pathological concepts were regarded as equivalent to AIP. It should be noted, however, that there are some differences among these reports. For example, patients with chronic inflammatory sclerosis complained of severe abdominal pain and died of cachexia, which is unusual for the current concept of AIP.[8] According to studies of non-alcoholic duct destructive chronic pancreatitis, neutrophilic infiltration in interlobular ducts was common, although this is not a feature of LPSP.[5,10]

After 2000, some groups argued that what was clinically diagnosed as AIP was not pathologically a single entity, but consisted of at least two different groups. A group from Mayo Clinic conducted a retrospective study with resected pancreata with a diagnosis of pancreatitis, and concluded that, in addition to a group that corresponded to LPSP, there was a group designated as idiopathic duct-centric chronic pancreatitis (IDCP).[12] A similar observation was also reported from Europe and Massachusetts General Hospital.[13–15]

LPSP is a histologically unique lesion that was proposed by Kawaguchi *et al.* in 1991.[9] It consists of diffuse lymphoplasmacytic infiltration and fibrosis that focally gives rise to a swirling pattern (storiform fibrosis; Fig. 1a). Eosinophils can be observed, but neutrophils are absent. Pancreatic lobules are relatively well preserved compared to alcoholic chronic pancreatitis, but focal destruction of pancreatic acini and replacement with fibrosis are commonly seen. The same inflammatory process is characteristically observed around the main and interlobular ducts, leaving the duct epithelium and lumen intact (Fig. 1b). It appears as if the duct wall is thickened with inflammation. Veins are almost always obliterated by the same inflammatory process (obliterative phlebitis; Fig. 1c). Splenic vein and even portal vein may be involved, which makes surgeons suspect that they are dealing with an inoperative carcinoma. The common bile duct is also often inflamed. This is the main cause of jaundice seen in patients with AIP. Numerous IgG4-positive plasma cells are identified in LPSP (Fig. 1d).[16,17]

Another group, designated as IDCP, is characterized by inflammation centered on the duct epithelium.[12,13,15] Neutrophilic infiltration in the main and/or interlobular ducts is characteristic, and is seen within the epithelium and lumen (Fig. 2). This finding is called 'granulocytic epithelial lesion' by the European group.[13] Duct epithelium shows destructive and regenerative changes, and, due to the inflammation, the lumen looks stenotic or tortuous. A band of lymphocytes and plasma cells surrounds the lumen but, in contrast to LPSP, the ductal lesion lacks the appearance of a thickened wall. Sometimes the entire duct appears to be entrapped within an aggregate of inflammatory cells (Fig. 2a). When the inflammation is severe, pancreatic lobules are also inflamed with neutrophils, lymphocytes and plasma cells. Microabscesses may be encountered. Although there is fibrosis around pancreatic lobules, inflammatory cells are scarce within fibrosis itself, in contrast to LPSP, in which inflammatory cells are numerous within fibrosis. Obliterative phlebitis is rare, and inflammation of the common bile duct is less common compared to LPSP. IgG4-positive plasma cells are usually few in IDCP.[17]

The clinical features of LPSP are concordant with those of AIP reported from Japan, described previously.[12] Serum IgG4 is elevated in 80% of AIP patients in Japan, which correlates well with numerous IgG4-positive plasma cells seen in LPSP. In contrast, patients with IDCP are younger than LPSP patients, and many of them are younger than 40 years.[12] There is no gender preponderance. Obstructive jaundice is less common in IDCP than in LPSP. The association of inflammatory bowel disease (IBD) is found in IDCP, but extrapancreatic manifestations seen in LPSP, which are described in the following section, are rare. Notably, IDCP is rare in Japan.[18]

Both LPSP and IDCP share some clinicopathological features. There has been a debate therefore on whether these two pathological groups are different manifestations of a single entity of AIP, or whether they are different clinicopathological entities. The controversy is due to the variety of AIP diagnostic criteria proposed by different groups. The diagnostic criteria from Japan,[19] Korea,[20] Asia[21] and Mayo Clinic[22] define LPSP as the pathological entity of AIP, but other groups include both LPSP and IDCP in AIP.[13,15,23] Considering the demographic and clinical differences as well as different immunoreactivity for IgG4, however, the idea that LPSP and IDCP are different is gradually gaining acceptance. Recently, new terms, type 1 and type 2 AIP, which correspond to LPSP and IDCP, respectively, have been proposed from the West.[24] It is important to note that, among these two groups, only

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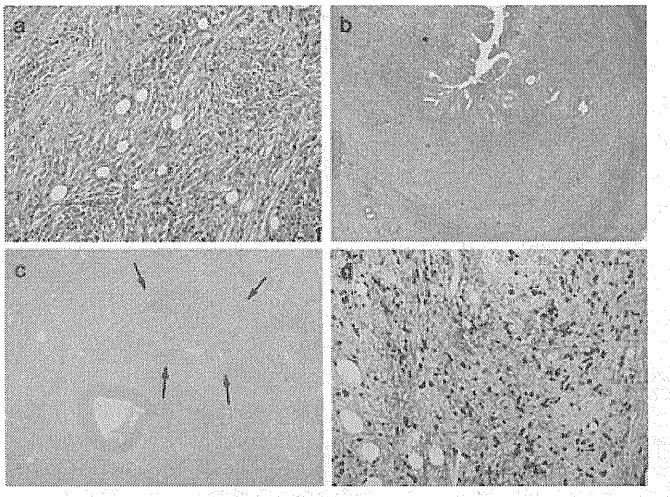

Figure 1 Lymphoplasmacytic sclerosing pancreatitis. (**a**) Lymphoplasmacytic infiltration and fibrosis giving rise to storiform fibrosis. (**b**) Ductal inflammation around the intact epithelium. The duct wall appears to be thickened with the inflammation. (**c**) Obliterative phlebitis (arrow). (**d**) Numerous IgG4-positive plasma cells are identified on immunostaining.

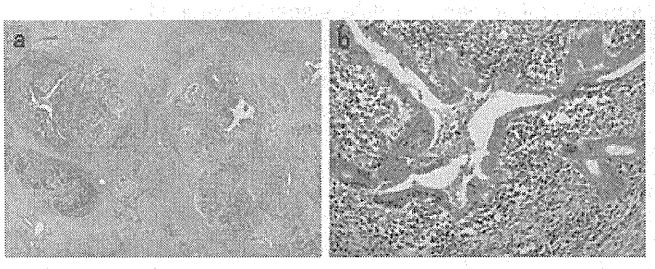

Figure 2 Idiopathic duct-centric chronic pancreatitis. (**a**) Duct-centric inflammation. Two ducts shown here are entrapped within an aggregate of inflammatory cells. (**b**) Neutrophilic infiltration in the duct lumen.

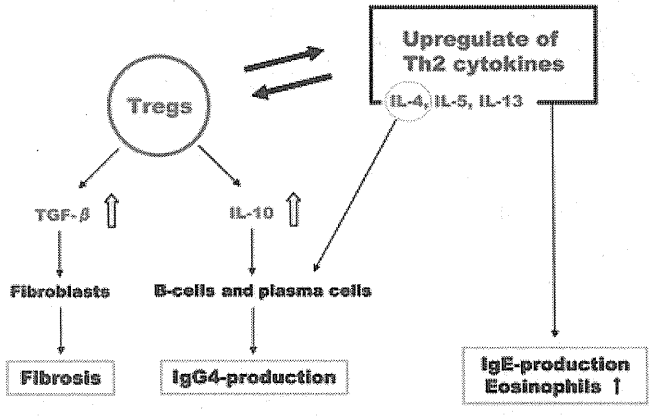

Figure 3 IgG4-related disease: hypothesis of the pathogenesis. The expression of T-helper cell 2 (Th2) cytokines (interleukin (IL)-4, IL-5, and IL-13) and regulatory cytokines (IL-10 and transforming growth factor (TGF)-β) was upregulated in the affected tissues of patients with IgG4-related diseases, suggesting that this disease might reflect an allergic mechanism in its pathogenesis. Tregs, regulatory T cell.

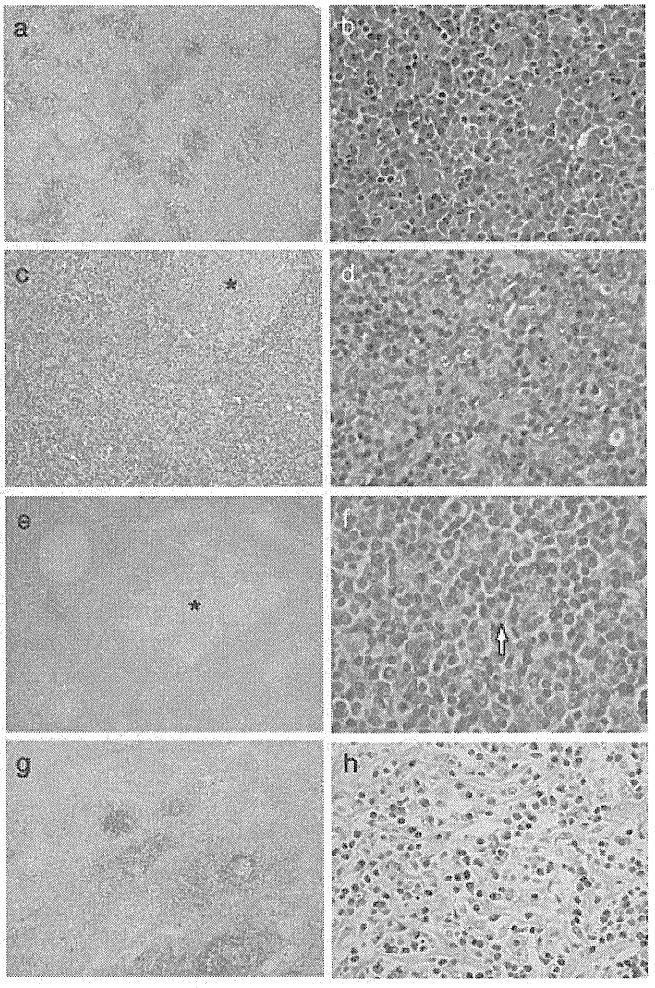

Figure 4 (**a**) Type I lesion. On low-power field, the lymph node demonstrated numerous lymphoid follicles with active germinal centers and distinct mantle zone and expansion of the interfollicular area. The interfollicular area contained a moderate number of capillaries. (**b**) Type I lesion. On high-power field, the interfollicular area was heavily infiltrated by mature plasma cells, plasmacytoid cells and small lymphocytes. Scattered medium-sized lymphocytes, transformed lymphocytes including immunoblasts and eosinophils were also present. (**c**) Type III lesion. On medium-power field, the lymph node demonstrated an active germinal center (*) with a distinct mantle zone, and expansion of the interfollicular area containing moderate vascularization. (**d**) Type III lesion. On high-power field, the paracortical area contained numerous mature plasma cells, plasmacytoid cells, immunoblasts, small and medium-sized lymphocytes and histiocytes. Note an eosinophil. (**e**) Type IV lesion. On low-power field a large early stage progressive transformation of germinal center (*) is surrounded by secondary lymphoid follicles. (**f**) Type IV lesion. On high-power field, a relatively large number of residual centrocytes, centroblasts and immunoblasts are present, in addition to the small mantle zone lymphocytes. Note a few mature plasma cells (arrow). (**g**) Type V lesion. On low-power field, the majority of the lymph nodes were occupied by the hyalinized tissue, and a few residual lymphoid follicles and a focally dense lymphoid infiltrate were observed. (**h**) Type V lesion. On high-power field, mature plasma cells, small lymphocytes and eosinophils focally infiltrated in the sclerosing tissue.

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LPSP should be regarded as the pancreatic manifestation of IgG4-related diseases.

Concept of IgG4-related disease

Kawaguchi *et al.* suggested that LPSP was a systemic disease.[9] In addition to the pancreas, their patients had involvements in the extrahepatic bile duct, gallbladder and labial gland, and all lesions showed histological similarity to LPSP. They further noted that LPSP histologically resembled multifocal fibrosclerosis. Multifocal fibrosclerosis is an entity that includes systemic diseases, such as 'primary sclerosing cholangitis' (PSC), retroperitoneal fibrosis, Riedel thyroiditis and orbital pseudotumor. Association of 'pancreatic pseudotumors' has also been reported.[25] Notably, obliterative phlebitis, one of the unique features of LPSP, has been reported to occur in multifocal fibrosclerosis.[26–29] Ever since AIP was recognized as an entity, it has become well realized among clinicians that extrapancreatic lesions are common in AIP patients. According to a recent report, pulmonary hilar lymphadenopathy, bile duct lesions, lacrymal and salivary gland lesions, hypothyroidism and retroperitoneal fibrosis are commonly seen in Japanese patients with AIP,[30] suggesting the analogy of LPSP and multifocal fibrosclerosis. Curiously, an association with Riedel thyroiditis has been rarely reported in AIP, but the reason is not known.

On immunohistochemistry, Hamano *et al.* identified numerous IgG4-positive plasma cells in the retroperitoneal fibrosis seen in AIP patients.[6] Kamisawa *et al.* extended the observation, and reported that IgG4-positive plasma cells are increased systemically in patients with AIP.[31] They concluded that AIP patients have a systemic disease, and proposed the entity 'IgG4-related sclerosing disease'.[32] More recent entities, such as IgG4-related plasmacytic exorinopathy[33] and IgG4-positive multiorgan lymphoproliferative syndrome,[34] are synonymous.

The histological features and numerous IgG4-positive cells are unique to LPSP. Using these morphological and immunohistochemical features as a hallmark, Zen *et al.* proposed new concepts of IgG4-related diseases in various organs.[35–40] This is not merely a proposal of new concepts, but a reclassification of pre-existing entities. In addition, the recognition of these new entities is important from the clinical standpoint as well, because many of these lesions involve a mass that is clinically suspicious for malignant diseases, and nevertheless they are responsive to corticosteroid therapy. For example, IgG4-related sclerosing cholangitis had been diagnosed as PSC before this entity was recognized,[35] but the histological finding is different from classic PSC.[35] IgG4-related sclerosing cholangitis produces changes that are histologically similar to LPSP including numerous IgG4-positive plasma cells, while in classic PSC, the inflammation is centered on the bile duct epithelium, and IgG4-positive plasma cells are usually few. Importantly, IgG4-related sclerosing cholangitis is common in elderly men, in a similar fashion to LPSP. Classic PSC is well known to be associated with IBD, but such an association is rare in IgG4-related sclerosing cholangitis. The radiological features of the two are also different.[41] Corticosteroid treatment is effective for patients with IgG4-related sclerosing cholangitis, while there is no such indication for classic PSC, for which the only treatment option is liver transplantation.

Table 1 Previous reports of IgG4-related diseases

• Pachymeningitis	• Autoimmune pancreatitis
• Hypophysitis	• Hepatitis
• Lacrimal gland lesion (Mikulicz's disease)	• Sclerosing cholangitis
	• Retroperitoneal fibrosis
• Sclerosing sialadenitis (Küttner tumor)	• Prostatitis
	• Inflammatory aortic aneurysm
• Thyroid gland	• Tubulointerstitial nephritis
• Pulmonary lesions	• Lymphadenopathy
• Mastitis	• Skin Lesion

Since then, many entities that are related to IgG4 have been described from all over the world (Table 1), especially in Western countries, as well as in Japan.[36–57] They include sclerosing sialadenitis,[36] pulmonary plasma cell granuloma and other pulmonary lesions,[38,47,48] mastitis,[37,49] hepatitis,[39] tubulointerstitial nephritis,[50] prostatitis,[51]inflammatory aortic aneurysm,[40,43,44,52] lymphadenopathy,[53,54] pachymeningitis[55] and skin lesion.[54,56] Each of these diseases could occur separately, or in various combinations. It should be stressed, however, that the occurrence of numerous IgG4-positive plasma cells is not entirely specific for IgG4-related diseases. Suppurative granulation tissue, for example, may contain numerous IgG4-positive cells.[57] It is also well known that LPSP-like histology and numerous IgG4-positive plasma cells can be seen in association with pancreatic carcinomas, and some patients with pancreatic carcinoma have elevated serum IgG4.[58–60] A cautious approach is thus mandatory for pathologists to determine if each condition or each case is truly related to IgG4-related diseases.

The etiology of IgG4-related diseases is not well understood. The overall immune response seems to be mediated by T-helper cell 2 (Th2) reaction, and involvement of regulatory T cells is suggested (Fig. 3)[61]

Kawa *et al.* reported that the human leukocyte antigen DRB1*0405-DQB1*0401 haplotype is common among Japanese patients with AIP,[62] suggesting that a certain genetic preponderance is involved in the disease. IgG4 autoantibodies to various tissues have been found in the patients' sera,[63] and dense deposits have been identified ultrastructurally.[15] But IgG4 cannot activate the classic complement pathway, and it is unclear how IgG4 deposition can lead to tissue damage. Another unique feature of IgG4 is its ability to bind

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other immunoglobulins through its Fc (Fragment, crystallizable),[64] but its relationship to IgG4-related diseases is still unknown.

IgG4-RELATED LYMPHADENOPATHY

Pathology and clinical findings of IgG4-related lymphadenopathy.

Concomitant lymphadenopathy is common in IgG4-related diseases.[39,53] Recently, several reports dealing with the morphological and immunohistological findings of the lymph nodal lesion have been published.[53,54,65,66] It appears that histomorphological findings of IgG4-related lymphadenopathy showed histological diversity.[53,54,65,66] Moreover, clinically, IgG4-related lymphadenopathy occasionally showed systemic lymphadenopathy, polyclonal hyperimmunoglobulinemia, especially elevation of IgG and IgE, and positivity of various autoantibodies.[53,54,65] Although some cases of lymphadenopathy were previously designated as atypical lymphoproliferative disorders,[67] mimicking malignant lymphomas, these cases lack immunoglobulin gene monoclonality, and are thought to be non-neoplastic.

We considered that there are five histological subtypes in IgG4-related lymphadenopathy (Table 2).

Type I: Castleman's disease- like morphology

The lymph node architecture is preserved. The lesion contains numerous lymphoid follicles (Fig. 4a). Cheuk *et al.* noted that the lymphoid follicles had a variable degree of regressive changes in the germinal centers, with decreased centroblasts, tingible body macrophages, and mitotic figures in some cases.[53] Hyalinized blood vessels frequently penetrate into the germinal centers. In some lymphoid follicles concentric files of small lymphocytes produced an onion skin pattern in the mantle zone. Other authors, however, reported that the lymphoid follicles had normal germinal centers with distinct mantle zone (Fig. 4a).[54,65,66] The interfollicular area contained mild–moderate increased vascular proliferation and moderate–large numbers of mature plasma cells with a few plasmacytoid cells and large transformed cells (immunoblasts) (Fig. 4b).[54,65,66] Occasionally, eosinophilic infiltration is observed in the interfollicular area (Fig. 4b). Immunohistology showed polytypic immunoglobulin in the plasma cells, and there was no human herpes virus type-8 (HHV-8) positive cells in 11 cases examined.[53,54,66]

Table 2 Histological subtypes and distribution pattern of IgG4-positive cells in IgG4-related lymphadenopathy

	Histological subtype	Distribution pattern of IgG4-positive cells
Pattern I	Castleman's disease-like morphology	Interfollicular
Pattern II	Reactive follicular hyperplasia	Interfollicular
Pattern III	Interfollicular plasmacytosis and immunoblastosis	Interfollicular
Pattern IV	Progressive transformation of germinal center-like	Intra-germinal center
Pattern V	Inflammatory pseudotumor-like morphology	Interfollicular

Type II: Reactive follicular hyperplasia

The lymph node shows reactive follicular hyperplasia, and small–moderate numbers of mature plasma cells in the interfollicular area.[53]

Type III: Interfollicular plasmacytosis and immunoblastosis

On low-power field, the lesion has paracortical hyperplasia with small vessel proliferation, and various numbers of lymphoid follicles with minimal sinuses (Fig. 4c).[53,54] The germinal centers were usually hyperplastic, although a few were atrophic. On high-power field, the paracortical area was diffusely infiltrated by a polymorphous population consisting of numerous mature plasma cells, plasmacytoid cells, large basophilic transformed lymphocytes (immunoblasts), eosinophils, small to medium-sized lymphocytes and histiocytes (Fig. 4d).[53,54] Immunostain demonstrates the mixed T- and B-cell nature of immunoblasts. The T cells in the interfollicular area were negative for CD10 and there was no extrafollicular proliferation of follicular dendritic cells using the anti-follicular dendritic cell antibodies, which are usually observed in angioimmunoblastic T-cell lymphomas (AITL). On immunohistochemistry, light chain immunoglobulin of the interfollicular plasma cells, plasmacytoid cells and B-immunoblasts is bi-modal and non-neoplastic.

Type IV: Progressive transformation of germinal center like

Progressive transformation of germinal center (PTGC) is characterized by the presence of large nodules of lymphocytes, often threefold to fourfold the size of other normal reactive germinal centers (Fig. 4e).[68] In PTGC, small lymphocytes migrate into the germinal center in a multifocal fashion, progressively accumulate and expand there, and then disrupt germinal centers.[68] In the early stage, germinal centers develop an unusual shape or break up without clear demarcation of the germinal center and mantle zone (Fig. 4e). These germinal center cell clusters contain centroblasts and centrocytes. Mitotic figures and tingible body macrophages are usually evident in the germinal center. In the late stage, PTGC are composed of large nodules with numerous small lymphocytes and centroblasts and centrocytes. In IgG4-related lymphadenopathy, early PTGC and normal

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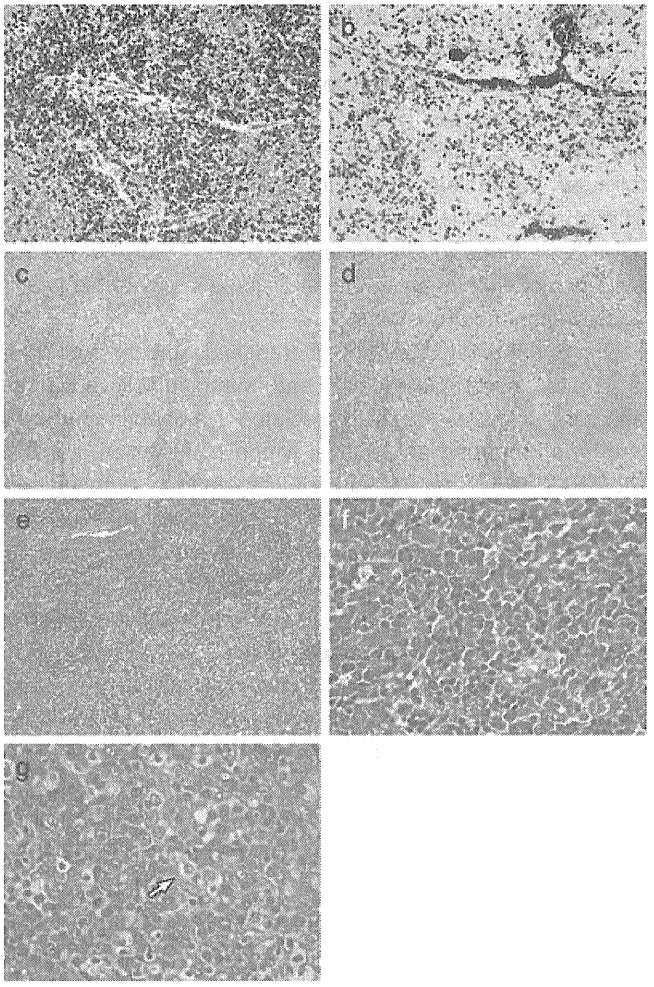

Figure 5 (**a**) Immunostaining for IgG and (**b**) IgG4. A large number of IgG4-positive cells infiltrated the type III lesion. (**c**) Immunostaining for IgG and (**d**) IgG4. IgG4-positive cells mainly infiltrated the type IV lesion of PTGC. (**e**) ALPIB. On low-power field, the lesion contained diffuse paracortical hyperplasia with small vessel proliferation and two small germinal centers. (**f**) ALPIB. On high-power field, the paracortical area contained numerous mature plasma cells, plasmacytoid cells, immunoblasts, small and medium-sized lymphocytes and histiocytes. (**g**) Angioimmunoblastic T-cell lymphoma. On high-power field, the lesion contained numerous plasma cells. Note scattered clear cells (arrow).

reactive germinal centers had scattered mature plasma cells (Fig. 4f) in the germinal centers.[54]

Type V: Inflammatory pseudotumor like

Inflammatory pseudotumor (IPT) of the lymph node develops in stages:[68,69] stage I, small nodules with partial involvement of the lymph node; stage II, inflammatory infiltrate and fibroblastic proliferation cause marked distortion of the connective tissue framework of the lymph node including hilum, trabeculae and capsule with secondary spread into the lymph node parenchyma and extranodal adipose tissue; and stage

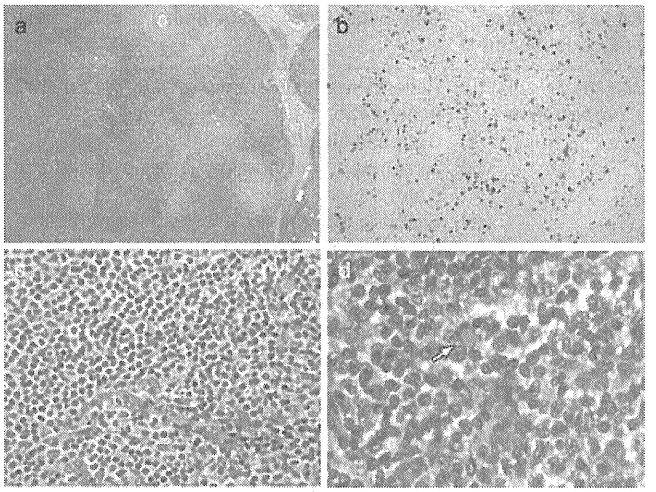

Figure 6 Ocular adnexal IgG4-related mucosa-associated lymphoid tissue lymphoma. (**a**) Diffuse dense infiltrate of lymphoid cells with lymphoid follicles and fibrosis band in lacrimal gland. (**b**) Numerous IgG4-positive plasma cells are identified (IgG4/IgG-positive cell ratio ≥ 50%). (**c**) The infiltrate consists of monocytoid B-cell-like cells, centrocytic cells and eosinophils. (**d**) Eosinophil infiltration and a few lymphoid cells exhibit Dutcher body (arrow).

III, areas of dense sclerosis of the lymph node with minimal inflammation. IgG4-related lymphadenopathy has similar histological findings to those of stage III of IPT (YS and MK, pers. comm., 2009). Histologically, the majority of the lymph nodes were occupied by the hyalinized tissue, and a few residual lymphoid follicles and focally dense lymphoid infiltrate were observed in the lymph node (Fig. 4g). Mature plasma cells, small lymphocytes and eosinophils focally infiltrate the sclerosing tissue (Fig. 4h).

The proportion of IgG4/IgG-positive plasma cells ranged from 40% to 99% in the literature.[53,54,66] We recognized two types of distribution pattern of IgG4-positive plasma cells, namely interfollicular and intra-germinal center type (Table 2).[54] In the interfollicular pattern, the majority of IgG4-positive plasma cells are located in the interfollicular area (Fig. 5a,b), whereas IgG4-positive plasma cells were observed more frequently in the lymphoid follicles in the intragerminal center type (Fig. 5c,d). Patterns I, II, III and V usually involved an interfollicular distribution, but pattern IV involved an intragerminal center distribution.

Clinically, three types of lymphadenopathy are recognized.[53] Group A involves enlarged regional and group B involves non-regional lymph node of organs affected by IgG4-related disease. Cases of unexplained lymphadenopathy were designated as group C. The characteristic clinical presentation of group B and C patients can be summarized as follows (Table 3):[53,54] (i) the patients are middle-aged to elderly with marked male predominance; (ii) usually systemic lymphadenopathy; (iii) the lymph nodes are not very large (usually up to 2 cm); (iv) the exocrine or extranodal lesions

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