sclerosing inflammation with an infiltration of abundant IgG4-positive plasma cells, and AIP was associated in most cases. Before establishing the concept of AIP, IgG4-SC used to be misdiagnosed as PSC complicating chronic pancreatitis. Therefore, differential diagnosis between IgG4-SC and PSC is important, because the effective treatments and the prognoses are different. Although IgG4-SC is usually associated with pancreatic lesions, a few patients with IgG4-SC have shown little pancreatic change or other organ involvement [25, 26]. The correct diagnosis of such cases is difficult.

In this study, we presented 3 PSC cases with elevated serum IgG4 levels and/or infiltration of abundant IgG4-positive plasma cells in the liver, which usually support the diagnosis of IgG4-SC. In the 3 cases presented, abdominal ultrasound and abdominal CT scan did not show inflammatory swelling of the whole pancreas, and ERCP did not show strictures over one-third of the main pancreatic duct (MPD), which is characteristic of AIP [27]. Cholangiography in these 3 patients showed strictures of the intrahepatic and common bile ducts, and no narrowing of the MPD. After steroid therapy, strictures of the intrahepatic and common bile ducts were not improved on MRCP images. These findings supported the diagnosis of PSC. In these 3 patients, however, there were findings atypical for PSC. First, the serum IgG4 concentrations in cases 2 and 3 were elevated. The Japanese criteria of AIP contain three approaches: pancreatic imaging, laboratory data, and histopathology [18]: (1) Pancreatic image examinations show the narrowing of the main pancreatic duct and enlargement of pancreas which are characteristic of the disease; (2) Laboratory data show the presence of autoantibodies, or elevated levels of serum gammaglobulin, IgG, or IgG4; (3) Histopathological examinations of the pancreas show fibrosis and pronounced infiltration of cells, mainly lymphocytes and plasmacytes. For a diagnosis, criterion (1) must be present, together with criterion (2) and/or (3). However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancers. In the diagnostic criteria of Korea [28] and Asia [29], apparent pancreatic lesions comparable with AIP must be present for a diagnosis of AIP. Two patients (cases 2 and 3) did not fulfill the diagnostic Japanese, Korean, and Asian criteria, because they had no apparent pancreatic lesions comparable with AIP. Secondly, infiltration of abundant IgG4-positive plasma cells in the liver specimens was found in cases 1 and 2. IgG4 immunostaining showing >10 IgG4-positive plasma cells/hpf is suggestive of AIP in the HISORt criteria by the Mayo Clinic [30] and Korean criteria [28]. The presence of IgG4-SC in the HISORt criteria can be diagnosed in patients with effective steroid therapy. Two patients (cases 1 and 2) did not fulfill the HISORt criteria because they had no response to steroid therapy.

The role of IgG4 in patients with PSC has been used to differentiate clinical syndromes of atypical PSC cases. In 1991, Kawaguchi et al. [31] first described clinical and pathological features of variant cases of PSC, which were later known as sclerosing cholangitis complicated with autoimmune pancreatitis (AIP). In 1995, Takikawa et al. [32] analyzed 192 cases of Japanese PSC and found two peaks in the age distribution. Some cases in elderly patients were complicated with chronic pancreatitis, which was regarded as sclerosing cholangitis complicated with autoimmune pancreatitis. The patients in cases 1 and 3 were young, and case 2 was an elderly woman. In 2004, Takikawa et al. [33] analyzed 269 additional cases of Japanese PSC and showed that 7% of these cases had AIP. In a recent study, Mendes et al. [34] have reported that 12 (9%) of 127 PSC patients had elevated serum IgG4 levels. These patients also had significantly higher levels of ALP and total bilirubin, and higher PSC Mayo risk scores. Mendes's study also reveals that IgG4-SC may have been included among PSC cases in the United States. There may possibly be disease entities such as overlap syndrome. In our cases, it is difficult to differentiate IgG4-SC from PSC on cholangiographic and immunohistochemical findings. The findings of elevated serum IgG4 levels and/or an infiltration of abundant IgG4-positive plasma cells in the liver usually support the diagnosis of IgG4-SC. On the other hand, the patients of cases 1 and 3 were younger, and the patient of case 1 was associated with UC. These clinical characteristics may be compatible with PSC. In a recent study, Kawabe et al. have reported an advanced state of biliary cirrhosis and atrophic pancreas but did not reveal typical imaging findings of AIP and AIP-related sclerosing cholangitis [35]. Hamano et al. have reported 3 patients with IgG4-SC who had no apparent pancreatic lesions comparable with AIP [26]. These cases were improved only by steroid therapy or drainage. In this study, however, our 3 patients with sclerosing cholangitis who had no apparent pancreatic lesions comparable with AIP did not respond to steroid therapy. Some AIP patients may develop pancreatic stones and the conventional type of chronic pancreatitis [36, 37]. Though there may be a possibility that far advanced stages of AIP with sclerosing cholangitis who had no pancreatic lesions might not respond to steroid therapy, the long-term untreated prognosis of AIP still remains unclear. Therefore, further studies are necessary. Finally, we diagnosed our 3 patients as PSC according to the commonly used diagnostic criteria for PSC [38]. They did not fulfill all criteria, and histopathological finding of the pancreas in case 1 did not show so-called LPSP. Here, our cases showed elevated serum IgG4 levels and/or an infiltration of abundant IgG4-positive plasma cells in patients with PSC, which do not respond to steroid therapy. Therefore, it is necessary to be aware of the possibility of

PSC with these findings to correctly differentiate PSC from IgG4-SC. The mechanisms of increased serum IgG4 and the role of the infiltrated IgG4-positive plasma cells in the portal area still remain unclear at this time. Recent studies of immune tolerance and allergy show that high dose antigen exposures cause immune deviation both of Th2 response in favor of Th0/Th1, and in the generation of IL-10- and TGF-β-producing regulatory T cells [39], though our 3 patients were not found to have allergic disease. Additionally, IL-10 induces preferential switching of B cell response in favor of producing IgG4 antibodies, and possibly IgA antibodies under the influence of TGF-β [40]. Our previous data [41] and others [11] showed that IL-10 secreted from increased inducible peripheral regulatory T cells may be involved in switching B cells to produce IgG4-positive cells and increased serum IgG4 in IgG4-related sclerosing pancreatitis (autoimmune pancreatitis) or IgG4-related sclerosing cholangitis, but not in PSC [11]. These findings suggested that increased IgG4 may be reactive and involved in the pathophysiology of IgG4-related diseases, but not in the pathogenesis. Further studies are necessary to clarify the role of IgG4.

In conclusion, some of the patients with PSC show elevated serum IgG4 levels and/or an infiltration of abundant IgG4-positive plasma cells, and do not respond to steroid therapy.

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Review

IgG4-related Diseases Including Mikulicz's Disease and Sclerosing Pancreatitis: Diagnostic Insights

YASUFUMI MASAKI, SUSUMU SUGAI, and HISANORI UMEHARA

ABSTRACT. Since the first report of serum IgG4 elevation in sclerosing pancreatitis in 2001, various systemic disorders have been reported to elevate IgG4, and many names have been proposed from the perspective of the systemic condition. Despite similarities in the organs damaged in IgG4-related Mikulicz's disease and Sjögren's syndrome, there are marked clinical and pathological differences between the 2 entities. The majority of cases diagnosed with autoimmune pancreatitis in Japan are IgG4-related sclerosing pancreatitis, and it should be recognized that this is distinct from the Western type. Diagnosis of IgG4-related disease is defined by both elevated serum IgG4 (> 1.35 g/l) and histopathological features, including lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma cells/IgG+ plasma cells > 50% on a highly magnified slide checked at 5 points). Differential diagnosis from other distinct disorders is necessary: these include sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, cancer, and other existing conditions. The Japanese IgG4 research group has begun multicenter prospective studies to improve diagnostic criteria and treatment strategies. (First Release May 1 2010; J Rheumatol 2010;37:1380–5; doi:10.3899/jrheum.091153)

Key Indexing Terms:
MIKULICZ'S DISEASE SJÖGREN'S SYNDROME AUTOIMMUNE PANCREATITIS
GLUCOCORTICOID IgG4-RELATED DISEASES

Mikulicz's disease (MD) was first described in 1892 in a man with symmetrical swelling of the lacrimal, submandibular, and parotid glands[1]. Morgan, *et al* reported 18 cases of MD and concluded that it was not a distinct clinical and pathological disease entity but merely one manifestation of a more generalized symptom complex known as Sjögren's syndrome (SS)[2]. With the wide acceptance of the conclusions of Morgan, *et al* there have been few reports of MD in Western countries. However, many cases of MD have been reported in Japan, and there has been considerable discussion regarding the differences between MD and SS[3-7]. Patients with MD have been reported to have a point mutation in the *FasL* gene, which may account for their mild sicca symptoms despite massive lymphocytic infiltration[3]. Further, high IgG4 concentrations have been reported in the sera of patients with MD[4], suggesting that MD is an IgG4-related disease.

We describe the differences between MD (especially IgG4-related MD) and SS, and refer to other systemic complications of IgG4-related diseases.

Differences between IgG4+ MOLPS and SS. As so-called MD may include various conditions[3-6] and consist of IgG4-related or unrelated subtypes, the IgG4+ multiorgan lymphoproliferative syndrome (MOLPS)/MD research group has established tentative criteria for IgG4+ MD (Table 1).

MATERIALS AND METHODS

We collected data on 64 patients with IgG4+ MOLPS including MD and performed retrospective analysis to clarify the differences between IgG4+ MOLPS and definite SS (Table 2)[7]. Despite similarities in the involved organs, there are marked differences between IgG4+ MOLPS and SS. For example, their sex distributions were quite different. Men with SS were very rare (2 of 31), while almost half (31 of 64) the patients with IgG4+ MOLPS were men.

RESULTS

Significantly fewer patients with IgG4+ MOLPS than with SS showed symptoms of xerostomia, xerophthalmia, and arthralgia. Patients with IgG4+ MOLPS showed significantly lower incidences of rheumatoid factor (RF), antinuclear

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Table 1. Diagnostic criteria of IgG4+ Mikulicz's disease (Japanese Sjögren's Syndrome Society, 2008). Differential diagnosis is necessary from other distinct disorders, including sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer. The diagnostic criteria for Sjögren's syndrome (SS) may also include some patients with IgG4+ Mikulicz's disease; however, the clinicopathological conditions of patients with typical SS and IgG4+ Mikulicz's disease are different.

1. Symmetrical swelling of at least 2 pairs of the lacrimal, parotid, or submandibular glands continuing for more than 3 months.

AND

2. Elevated serum IgG4 (> 135 mg/dl), OR
3. Histopathological features including lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma cells/IgG+ plasma cells > 50%) with typical tissue fibrosis or sclerosis.

Table 2. Comparison of symptoms, complaints, and laboratory findings in IgG4+ MOLPS and typical SS. Data are percentage (number) unless stated otherwise. Incidence rates (numbers of positive patients) are shown for xerophthalmia, xerostomia, arthralgia, allergic rhinitis, bronchial asthma, sclerosing pancreatitis, interstitial nephritis, interstitial pneumonitis, RF, ANA, A-SSA, A-SSB, and low CH50. Masaki Y, *et al*[7]. Ann Rheum Dis 2009; 68:1310-5. Adapted with permission.

Feature	IgG4+ MOLPS	Typical SS	Japanese, %	p
No. of Patients	64	31		
Xerophthalmia	32.8 (21)	93.5 (29)		< 0.001
Xerostomia	37.5 (24)	87.1 (27)		< 0.001
Arthralgia	15.6 (10)	48.4 (15)		0.001
Allergic rhinitis	40.6 (26)	6.5 (2)	5–10	0.001
Bronchial asthma	14.1 (9)	3.2 (1)	3–5	0.158
Sclerosing pancreatitis	17.2 (11)	0 (0)	< 0.001	0.014
Interstitial nephritis	17.2 (11)	6.5 (2)	< 0.005	0.210
Interstitial pneumonitis	9.4 (6)	32.3 (10)	< 0.005	0.008
RF	26.6 (17)	87.1 (27)		< 0.001
ANA	23.4 (15)	90.3 (28)		< 0.001
A-SSA	1.6 (1)	100 (31)		< 0.001
A-SSB	0 (0)	100 (31)		< 0.001
Low CH50	57.8 (37)	48.4 (15)		0.510
IgG, mg/dl	2960.1 (1.7)	2473.4 (1.4)	870–1700	0.042
IgG1, mg/dl	1155.3 (1.6)	1437.1 (1.5)	320–748	0.039
IgG2, mg/dl	786.5 (1.5)	566.6 (1.6)	208–754	0.001
IgG3, mg/dl	57.6 (2.8)	81.9 (1.8)	6.6–88.3	0.047
IgG4, mg/dl	697.7 (2.6)	23.5 (2.1)	4.8–105	< 0.001
IgA, mg/dl	194.7 (1.80)	389.7 (1.7)	110–410	< 0.001
IgM, mg/dl	63.0 (2.0)	147.3 (1.7)	35–220	< 0.001
IgE, IU/ml	307.4 (4.0)	15.3 (1.4)	< 173	0.005

P values are for comparisons of all IgG4+ MOLPS with typical SS. MOLPS: multiorgan lymphoproliferative syndrome; SS: Sjögren's syndrome; RF: rheumatoid factor; ANA: antinuclear antibody. Japanese: Incidence rates of the entire Japanese study population for allergic rhinitis, bronchial asthma, sclerosing pancreatitis, interstitial nephritis, interstitial pneumonitis, and ranges of normal laboratory values of total IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE. IgE was measured in 50 patients (not all), and IgG1, IgG2, and IgG3 were measured in 58 patients (not all), with IgG4+ MOLPS. Geometric means (geometric SD) are shown for IgG, IgG1, IgG2, IgG3, IgG4, IgE, IgA, and IgM concentrations. Patients with typical SS fulfilled both Japanese[8] and European[9] SS criteria, and were positive for both anti-SSA/Ro and anti-SSB/La antibodies.

antibody (ANA), anti-SSA/Ro antibody, and anti-SSB/La antibody than patients with SS. We found that not only IgG4 but also total IgG, IgG2, and IgE concentrations were significantly higher in patients with IgG4+ MOLPS than in patients with SS[7]. Almost half of patients with IgG4+ MOLPS demonstrated low CH50, which apparently correlated with hyper-IgG (especially IgG1 and IgG2).

Histological specimens from patients with IgG4+ MOLPS showed marked IgG4+ plasma cell infiltration with occasional lymphocyte follicular formation, but without lymphoepithelial lesions (Figure 1)[7]. This may explain the marked glandular swelling without severe dryness in patients with IgG4+ MOLPS. Importantly, treatment with glucocorticoids resulted in marked clinical improvements in almost all patients with IgG4+ MOLPS, while the effects of glucocorticoids on SS were not so dramatic[10].

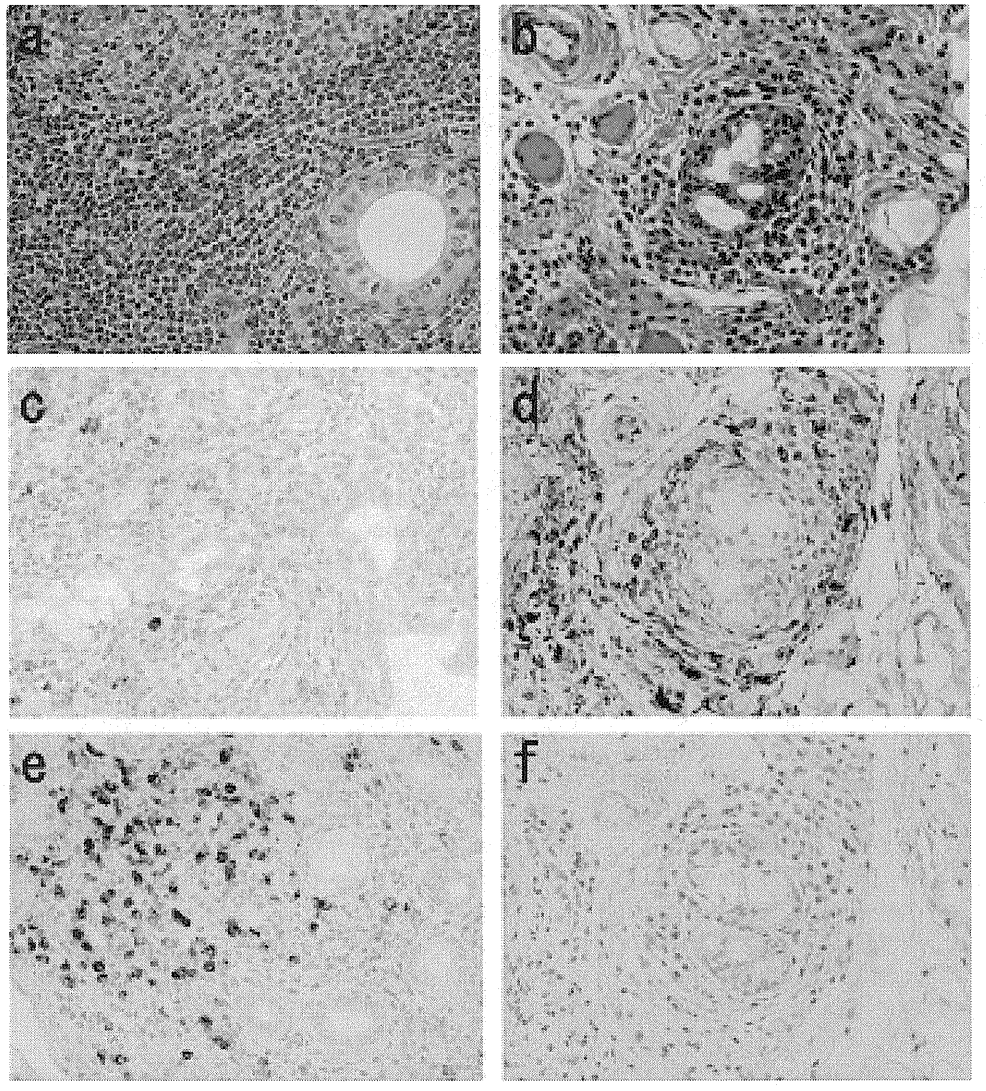

Figure 1. Histopathological findings of labial minor salivary gland biopsy in patients with IgG4+ MOLPS/Mikulicz's disease (a, c, e) and Sjögren's syndrome (b, d, f). (a, b) Hematoxylin and eosin staining; (c, d) IgG immunostaining; (e, f) IgG4 immunostaining. (a) Massive lymphocyte and plasmacyte infiltration and lymphoid follicle formation were seen in IgG4+ MOLPS. The ducts remained clear without lymphocytic infiltration. Both IgG+ and IgG4+ plasma cells were scattered in the periphery of the follicles (c, e). In contrast, there were few or no IgG4+ cells in typical SS (d, f), not even in patients with severe lymphocytic infiltration (b).

Autoimmune pancreatitis and IgG4. Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis, first described by Sarles, *et al* in 1961[11] and characterized by infrequent attacks of abdominal pain, jaundice, irregular narrowing of the pancreatic duct, and swelling of the pancreatic parenchyma[11-22]. Kawaguchi, *et al* described cases complicated with similar pathological features in the common bile duct, gall bladder, and minor salivary glands, suggesting a systemic disorder[12]. Yoshida, *et al* described the typical features of AIP as hyper-γ-globulinemia, the presence of autoantibodies (RF and ANA), lymphocytic infiltration of pancreas tissue, coexistence of other manifestations such as sicca complex, and good responsiveness to glucocorticoids[13]. AIP is now known to be associated with types of sialadenitis and cholangitis distinct from SS and primary sclerosing cholangitis.

In 2001, Hamano, *et al* first reported high serum IgG4 concentrations in patients with sclerosing pancreatitis[14]. Further, massive IgG4+ plasmacytic infiltration in the pancreatic tissue was reported[15]. There have been many recent reports of AIP in Asia[12-19] and in Western countries[20,21].

Various diagnostic criteria for AIP have been proposed in Japan[23], Korea[17], and the United States (Mayo Clinic)[21]. In 2008, the Japan-Korea Symposium on AIP proposed Asian diagnostic criteria[19]. Further international criteria are currently under discussion.

IgG4 and other clinical conditions (Figure 2). Hyper-IgG4-γ-globulinemia and IgG4+ plasma cell infiltration with sclerotic lesions, although first reported in patients with sclerosing pancreatitis, have also been reported in patients with many other disorders, including sclerosing cholangitis[15,16]; inflammatory pseudotumors of the lung[24], liver[16], and breast[16,25]; retroperitoneal or mediastinal fibrosis[26]; interstitial nephritis[27]; hypophysitis[5]; sclerosing dacryoadenitis[28]; sialadenitis (MD and Küttner's tumor)[4,5,29]; inflammatory aortic aneurysm[30,31]; tumorous lesions of the coronary artery[31]; lymphadenopathy[32]; and many other inflammatory conditions in multiple organs.

In addition, various systemic involvements have been reported in each disorder. Kawaguchi, *et al*[12] noted the same etiology between autoimmune pancreatitis and multifocal idiopathic fibrosclerosis (MIF) reported by Comings, *et al*[33] because both conditions include occlusive phlebitis and sclerotic lesions.

DISCUSSION

Proposal of a new clinical entity, IgG4+ MOLPS, as a more generalized disorder. In addition to the term "IgG4+ MOLPS," there are many synonyms, such as MIF, IgG4-related autoimmune disease[15], IgG4-related plasmacytic disease[6], and IgG4-related sclerosing disease[18], all of which may refer to the same conditions.

Although various other disorders have been associated with hyper-IgG4-γ-globulinemia, including multicentric Castleman's disease[34], Wegener's granulomatosis[35], lymphoma[36,37], and cancer[38], IgG4+ MOLPS should be defined as a distinct clinicopathological entity, characterized by sclerosing sialadenitis and dacryoadenitis, AIP, sclerosing cholangitis, and other clinical conditions with good response to glucocorticoids.

Hypothetical mechanism of IgG4+ MOLPS. At present, the pathogenesis of IgG4+ MOLPS is not clear. Although some patients are positive for RF and ANA, these incidences are significantly lower than in SS, suggesting that RF and ANA positivity may be due to nonspecific immunoglobulin binding. Although IgG4+ MOLPS is accompanied by various immunological disorders, including AIP, there is little evidence that IgG4+ MOLPS is an autoimmune disorder because of the lack of disease-specific autoantibodies.

The role of IgG4 in IgG4+ MOLPS is still unknown. IgG4 represents the smallest population among IgG subclasses in the sera of normal subjects (3%–6% of total IgG), and is unique among the IgG subclasses in its inability to bind with the C1q complement[39]. IgG4 is associated with the pathogenicity of a small number of disorders, such as atopic dermatitis, parasitic disease, pemphigus vulgaris, and pemphigus foliaceus.

In clonality analysis, most tissue-infiltrating and circulating IgG4-positive cells are polyclonal[40]. These findings have suggested that IgG4 does not play a major pathological role in IgG4+ MOLPS, and that there may be other upstream regulators in its pathogenesis.

Zen, *et al* reported that the pathogenesis of IgG4-related AIP was characterized by the infiltration of T helper 2 and regulatory T cells (Treg), which secrete various cytokines such as interleukin 10 (IL-10) and tumor growth factor-ß (TGF-ß)[41]. Moreover, the level of Foxp3 messenger RNA expression was significantly increased in patients with AIP, and immunohistochemical staining revealed increases in the numbers of CD4+ CD25+ Foxp3+ cells. Treg may be

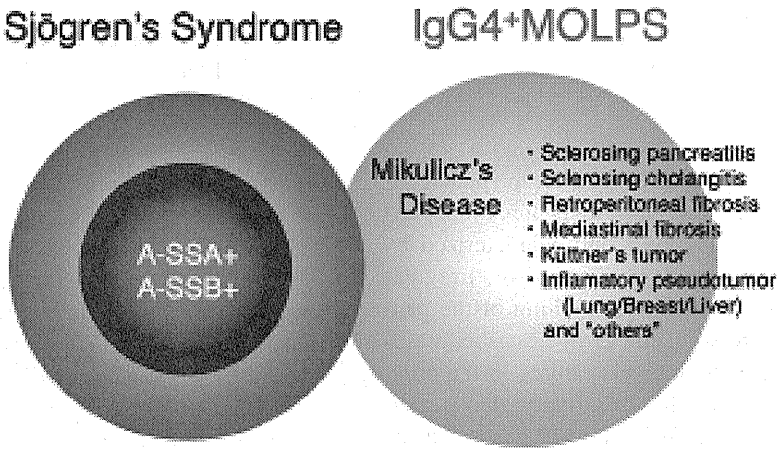

Figure 2. IgG4+ MOLPS should be defined as a distinct clinicopathological entity that includes Mikulicz's disease (MD), autoimmune pancreatitis (AIP), sclerosing cholangitis, and other clinical conditions with good response to glucocorticoids. Although the diagnostic criteria of SS may include some patients with IgG4+ MOLPS/MD, typical SS and IgG4+ MOLPS/MD are different clinical conditions.

involved in the *in situ* production of IL-10 and TGF-ß, which could be followed by IgG4 class switching and fibroplasia[41].

The concentrations of IgG2, IgG4, and IgE have been shown to be significantly higher in patients with IgG4+ MOLPS than in those with typical SS, while the concentrations of IgG1, IgG3, IgA, and IgM were significantly higher in patients with typical SS than in those with IgG4+ MOLPS[7]. The immunoglobulin gene fragments Cμ, Cδ, Cγ3, Cγ1, Cα1, Cγ2, Cγ4, Cε, and Cα2, which encode IgM, IgD, IgG3, IgG1, IgA1, IgG2, IgG4, IgE, and IgA2, respectively, are arranged linearly in this order from upstream to downstream. Gene linkage and different class-switch mechanisms may cause the hyperproduction of the different immunoglobulin subclasses observed in these 2 diseases, which may contribute to the pathophysiology of IgG4+ MOLPS.

Future perspectives. Although IgG4+ MOLPS may be distributed worldwide, this disease entity has not been well recognized to date. Most reports on IgG4-related diseases have been from Japan, while many reports on AIP have come from Western countries, especially the Mayo Clinic[21] in the United States. Therefore, we believe that an international consensus regarding IgG4-related diseases as new clinical entities is required.

In this regard, the Japanese IgG4 research group (Research Committee of Intractable Diseases, Health and Labor Sciences Research Grants, Ministry of Health, Labor and Welfare, Japan) has begun multicenter prospective clinical studies (UMIN: R000002820, R000002823) to formulate better diagnostic criteria, to identify novel diagnostic and prognostic factors, and to design better treatment strategies.

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We thank all participants in the IgG4+ MOLPS/Mikulicz's Disease Research Group and the researchers of the Autoimmune Pancreatitis Group for critical discussion.

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Differentiation of Autoimmune Pancreatitis From Pancreatic Cancer by Diffusion-Weighted MRI

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OBJECTIVES: **We sought to clarify the clinical utility of diffusion-weighted magnetic resonance imaging (DWI) for differentiating autoimmune pancreatitis (AIP) from pancreatic cancer.**

METHODS: **Thirteen AIP patients underwent DWI before therapy, and six of them underwent DWI after steroid therapy. The extent and shape of high-intensity areas were compared with those of 40 pancreatic cancer patients. Apparent diffusion coefficient (ADC) values were calculated in the AIP area before and after steroid therapy in pancreatic cancer patients and in a normal pancreatic body.**

RESULTS: **On DWI, AIP and pancreatic cancer were detected as high-signal intensity areas. The high-intensity areas were diffuse ($n=4$), solitary ($n=6$), and multiple ($n=3$) in AIP patients, but all pancreatic cancer patients showed solitary areas ($P<0.001$). A nodular shape was significantly more frequent in pancreatic cancer, and a longitudinal shape was more frequently found in AIP ($P=0.005$). ADC values were significantly lower in AIP ($1.012\pm0.112\times10^{-3}$ mm^2/s) than in pancreatic cancer ($1.249\pm0.113\times10^{-3}$ mm^2/s) and normal pancreas ($1.491\pm0.162\times10^{-3}$ mm^2/s) ($P<0.001$). Receiver operating characteristic analysis yielded an optimal ADC cutoff value of 1.075×10^{-3} mm^2/s to distinguish AIP from pancreatic cancer. After steroid therapy, high-intensity areas on DWI disappeared or were markedly decreased, and the ADC values of the reduced pancreatic lesions increased almost to the values of normal pancreas.**

CONCLUSIONS: **DWI is useful for detecting AIP and for evaluating the effect of steroid therapy. ADC values were significantly lower in AIP than in pancreatic cancer. An ADC cutoff value may be useful for distinguishing AIP from pancreatic cancer.**

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INTRODUCTION

Autoimmune pancreatitis (AIP) is a type of pancreatitis with a presumed autoimmune etiology. AIP is characterized radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct, serologically by elevation of serum IgG4 levels, histopathologically by fibrosis with dense infiltration of T lymphocytes and IgG4-positive plasma cells in the peripancreatic and interlobular area of the pancreas, and clinically by a preponderance of elderly men and good responsiveness to steroid therapy (1–4). As AIP patients often present with painless jaundice in the setting of a pancreatic mass, they are sometimes misdiagnosed as having pancreatic cancer and undergo pancreatic resection (5). In North America, about 2.5% of pancreatoduodenectomies were performed for AIP because of a mistaken diagnosis of pancreatic cancer (6). As AIP responds dramatically to steroid therapy, to avoid unnecessary surgery, an accurate differential diagnosis between AIP and pancreatic cancer is required. As it is usually difficult to take adequate biopsy specimens from the pancreas, AIP is currently diagnosed on the basis of a combination of clinical, laboratory, and imaging studies (1–4). Recently, fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has been used to diagnose pancreatic cancer; however, it cannot definitively differentiate AIP from pancreatic cancer, as inflammatory foci in the pancreas also accumulate FDG (7).

Recent technical developments make diffusion-weighted magnetic resonance imaging (DWI) of the body feasible, and DWI has been increasingly used to evaluate diseases involving abdominal organs. DWI is a technique in which phase-defocusing and -refocusing

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gradients are used to evaluate the rate of microscopic water diffusion within tissues (8,9). Quantitative measurements of the diffusivity of water are described by the apparent diffusion coefficient (ADC). ADC represents microcirculation of blood perfusion, as well as molecular diffusion of water. The ability to measure the rate of water diffusion within the tissue is important, as water diffusion is frequently altered in various disease processes and may reflect physiological and morphological characteristics, such as cell density and tissue viability. Decreased ADC values correlate with increased tumor cellularity and the total nuclear area, which restrict water diffusion (10–12). In general, malignant tumors have a higher cellularity than benign lesions; therefore, ADC values assist in differentiating between malignant and benign lesions (10–13). It has been reported that ADC values are lower in pancreatic cancer than in the normal pancreas (14–16). This study aimed at clarifying the clinical utility of DWI for differentiating AIP from pancreatic cancer.

METHODS

This study was approved by our institutional review board, and all subjects gave their written informed consent.

Study subjects

Between January 2008 and December 2009, 13 AIP patients (eight men, five women; mean age±s.d. 58.6±16.4 years; age range 25–83 years) who prospectively underwent DWI were enrolled in this study. The diagnosis of AIP was based on the revised diagnostic criteria for AIP (4) as follows: enlargement of the pancreas (diffuse ($n=5$) or segmental (body and tail ($n=2$), body ($n=3$), and tail ($n=3$))); irregular narrowing of the main pancreatic duct (diffuse ($n=6$) or segmental ($n=7$)); elevation of serum IgG4 ($n=11$); presence of autoantibodies ($n=7$); and histological findings of lymphoplasmacytic sclerosing pancreatitis with abundant infiltration of IgG4-positive plasma cells in endoscopic ultrasonography-guided fine needle aspiration specimens with a 19-gauge needle ($n=3$) and sclerosing sialadenitis with abundant infiltration of IgG4-positive plasma cells in surgically biopsied submandibular glands ($n=4$). Seven patients underwent steroid therapy and responded well. The other six patients with segmental AIP lesions were asymptomatic, and were followed-up conservatively. All patients also fulfilled the HISORt criteria for AIP (17).

The patients underwent DWI before any therapy, and six patients who were treated with steroids underwent DWI again about 2 months after steroid therapy. During the same period, 40 patients (23 men, 17 women; mean age±s.d. 59.8±16.8 years) with pancreatic cancer, histologically confirmed as ductal adenocarcinoma, also underwent DWI. The main locations of pancreatic cancer were the head ($n=10$), body ($n=20$), and tail ($n=10$). Tumor category classified according to the International Union Against Cancer TNM system (18) was T2 ($n=4$), T3 ($n=19$), and T4 ($n=17$). All tumors were radiologically solid without a cystic component. Surgical resection was performed in 10 patients (pylorus preserving pancreatoduodenectomy ($n=5$) and distal pancreatectomy ($n=5$)), and the other patients were treated with chemotherapy or conservatively. The imaging results of the pancreatic body of 30 patients (20 men, 10 women; mean age±s.d. 59.8±14.7 years) with hepatic tumors who underwent DWI were used as normal controls. There were no differences in age and sex ratio between AIP patients and pancreatic cancer patients or normal controls. There were no differences in body mass index between AIP patients (21.5±3.0 kg/m^2) and pancreatic cancer patients (20.9±3.1 kg/m^2) or normal controls (21.2±2.8 kg/m^2).

Magnetic resonance imaging

All magnetic resonance imaging (MRI) examinations were performed on a clinical 1.5-T MRI scanner (MAGNETOM Avant, Siemens Medical Solutions, Erlangen, Germany). All MR images, including T1-weighted images (T1WI), T2-weighted images (T2WI), and DWI, were obtained during the same examination. DWI was obtained using a single-shot echo-planar imaging sequence. For respiratory triggering, prospective acquisition correction was implemented. Technical parameters were as follows: repetition time/echo time = respiratory rate/78 ms, field of view = 380 mm, acquisition matrix = 81×175, slice thickness of 7 mm, intersection gap of 2.3 mm, and water excitation with b values of 0, 50, and 800 mm^2/s. The motion-probing gradient pulses were placed in the X-, Y-, and Z-axes. The total acquisition time for the DWI examination in each patient was ~3.5 min.

As the signal intensity on DWI can be affected by the signal intensity on T2WI, high-intensity tissues on T2WI may exhibit increased signal intensity on DWI with a low b value. In reality, on $b=0$ mm^2/s images, the fat tissue signal is suppressed, and water appears bright, whereas $b=50$ mm^2/s images are often called black-blood images because the loss of signal intensity caused by blood flow renders vessels dark. DWI with a higher b value (800 mm^2/s) may be required to avoid the influence of intensity on T2WI, the so-called T2 shine-through effect. Therefore, all DWI images were acquired with a diffusion factor, b, of 0, 50, or 800 s/mm^2, and ADC maps were reconstructed in all cases.

High-signal intensity areas on DWI were assessed in AIP and pancreatic cancer cases on the basis of the following points: extent of the area; diffuse or segmental (solitary or multiple); and shape of segmental lesions (nodular or longitudinal). The maximum diameter of the largest segmental lesion was measured. The investigator was blinded to the clinical diagnosis.

Calculation of ADC values

All ADC values were calculated on a workstation with standard software (ShadeQuest; Yokogawa Electric, Tokyo, Japan). The ADC values of primary tumors were determined by measuring the region of interest (ROI) created on each ADC map. ADC maps were constructed from images with three different b factors (0, 50, and 800 mm^2/s). Three different circular ROIs were drawn on the images of the ADC map at the slice with the greatest area of lesions by two separate technologists (19). The most representative image was used. Care was taken to avoid pancreatic ducts, cystic lesions, and artifacts within the ROIs. The mean value of a total of six different ADCs was defined as the ADC value. In patients with multifocal-type AIP, ADC values were measured in the largest lesion.

Statistical analysis

All data are expressed as means ± s.d. The Mann–Whitney *U*-test was used to compare the differences in ADC values. To determine the ADC values that could be used to distinguish AIP from pancreatic cancer, receiver operator characteristic (ROC) curves were used. All *P* values were two-sided, and the significance level was 0.05. All statistical analyses were performed using Dr SPSSII for Windows (Statistical Package for Social Science, release 11.0.1J, SPSS Japan, Tokyo, Japan). All patients provided their written informed consent for these tests.

RESULTS

On DWI with a high *b* value, nine AIP cases and all pancreatic cancer cases were clearly detected as high-signal intensity areas relative to the surrounding pancreatic tissue; however, the intensity was lower in the other four AIP cases compared with pancreatic cancer. The high-intensity areas were diffuse ($n=4$, **Figure 1a** and **b**), solitary ($n=6$), and multiple ($n=3$) in AIP patients, but all pancreatic cancer patients showed a solitary area ($P<0.001$). With regard to the shape of the high-intensity area, a longitudinal shape was significantly more frequent in AIP (**Figure 2a** and **b**), and a nodular shape was more frequently found in pancreatic cancer (**Figure 3a** and **b**, $P=0.005$). There was no significant difference in the maximum diameter of segmental high-intensity areas between the two diseases (**Table 1**).

The ADC values were $1.012\pm0.112\times10^{-3}$ mm²/s in AIP, $1.249\pm0.113\times10^{-3}$ mm²/s in pancreatic cancer, and $1.491\pm0.162\times10^{-3}$ mm²/s in normal pancreatic tissue. The ADC values were significantly lower in AIP and pancreatic cancer than in normal pancreatic tissue ($P<0.001$). Furthermore, the ADC values were significantly lower in AIP than in pancreatic cancer (**Figure 4**, $P<0.001$).

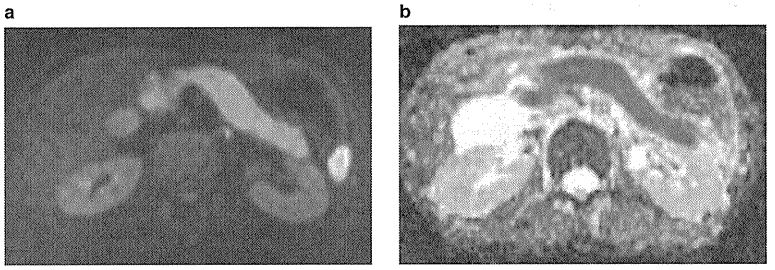

Figure 1. Diffuse-type autoimmune pancreatitis. (**a**) Diffusion-weighted magnetic resonance image showing a diffusely swollen high-intensity area ($b=800$ mm²/s). (**b**) ADC map in the same patient. ADC, apparent diffusion coefficient.

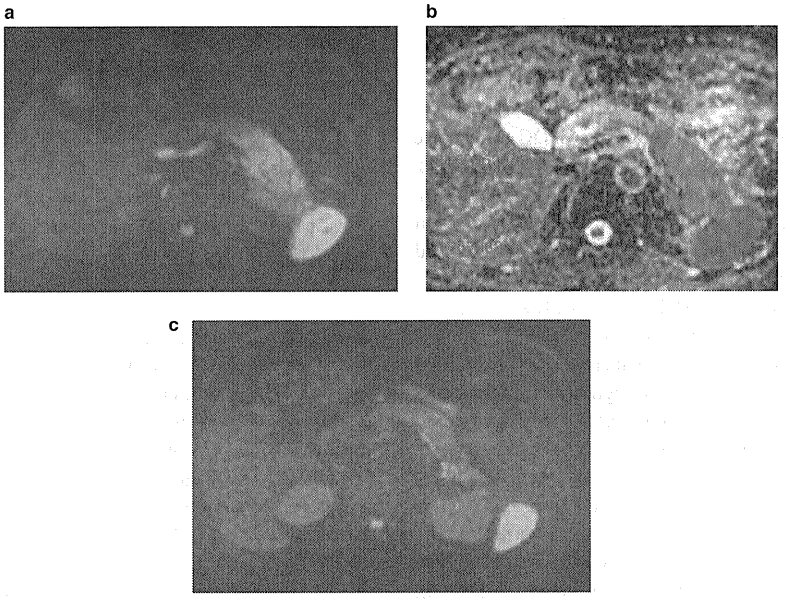

Figure 2. Segmental-type autoimmune pancreatitis. (**a**) Diffusion-weighted magnetic resonance imaging showing a longitudinal high-intensity area ($b=800$ mm²/s). (**b**) ADC map in the same patient. (**c**) Diffusion-weighted magnetic resonance imaging showing a markedly decreased high-intensity area 2 months after starting steroid therapy ($b=800$ mm²/s). ADC, apparent diffusion coefficient.

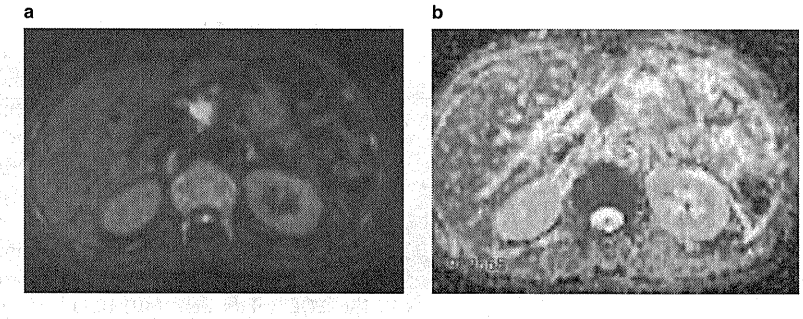

Figure 3. Pancreatic head cancer. (**a**) Diffusion-weighted magnetic resonance imaging showing a nodular high-intensity area (b=800 mm²/s). (**b**) ADC map in the same patient. ADC, apparent diffusion coefficient.

Table 1. High-intensity areas on DWI in AIP and pancreatic cancer

High-intensity area	AIP (n=13)	Pancreatic cancer (n=40)	P value
Extent			
Diffuse	4	0	0.002
Segmental			
Solitary	6	40	<0.001
Multiple	3	0	0.012
Shape			
Nodular	2	30	0.005
Longitudinal	7	10	
Maximum diameter of segmental area (mm)	65.9±31.6[a]	45.4±16.1	0.068

AIP, autoimmune pancreatitis; DWI, diffusion-weighted magnetic resonance imaging.
[a]Data are expressed as mean±s.d.

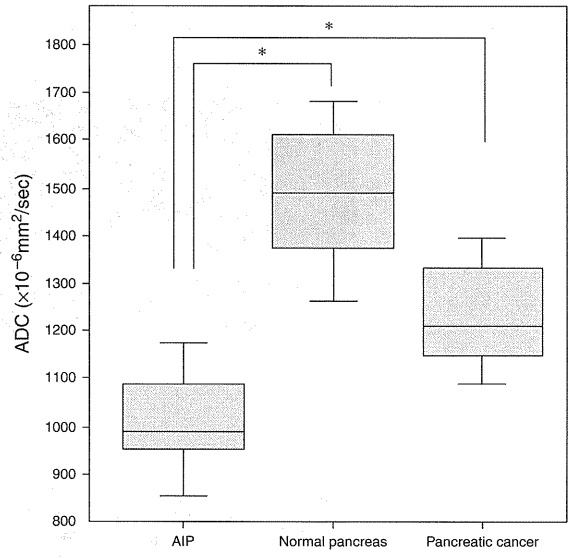

Figure 4. Box plots of ADC values of AIP, normal pancreas, and pancreatic cancer. The ADC values for AIP (1.015±0.122×10⁻³ mm²/s) were significantly lower than those for pancreatic cancer (1.225±0.113×10⁻³ mm²/s) and normal pancreas (1.488±0.185×10⁻³ mm²/s) (*P<0.001). ADC, apparent diffusion coefficient; AIP, autoimmune pancreatitis.

On the basis of the ROC curve data, the optimal ADC cutoff value to distinguish AIP from pancreatic cancer was 1.075×10⁻³ mm²/s. Using this cutoff value, sensitivity was 92.5%, specificity was 76.9%, and the area under the curve was 0.87 (**Figure 5**). ADC values in 37 of 40 pancreatic cancer patients were >1.075×10⁻³ mm²/s, and in 10 of 13 AIP patients they were <1.075×10⁻³ mm²/s (P<0.001). The three AIP patients, whose ADC values (1.218×10⁻³ mm²/s, 1.163×10⁻³ mm²/s, and 1.153×10⁻³ mm²/s) were >1.075×10⁻³ mm²/s, could be differentiated from those with pancreatic cancer by their elevated serum IgG4 levels. There were no significant differences in ADC values between diffuse AIP (1.005±0.112×10⁻³ mm²/s) and solitary AIP (1.037±0.123×10⁻³ mm²/s).

After steroid therapy, the enlarged pancreas decreased to its normal size, and the high-intensity area on DWI disappeared or was markedly decreased in all six AIP patients (**Figure 2c**). The ADC values of the reduced pancreatic lesions increased almost to the values of normal pancreas after steroid therapy (**Figure 6**). Posttreatment ADC values of lesions (1.469±0.194×10⁻³ mm²/s) were significantly higher than pretreatment ADC values (0.967±0.117×10⁻³ mm²/s) (P=0.003).

DISCUSSION

As AIP can mimic pancreatic cancer clinically and radiologically, it is of utmost importance to differentiate between these two diseases. Imaging studies have an important function, as there is no definite serological marker for AIP. Typical AIP cases showing diffuse enlargement of the pancreas with a capsule-like rim on CT or MRI are diagnosed relatively easily. However, segmental AIP cases are sometimes difficult to distinguish from pancreatic cancer cases, even with CT, MRI, and FDG-PET (1–7).

DWI is a method of probing the random motion of water molecules, which depends on their microenvironment. DWI of the brain has been used clinically for more than a decade, and the usefulness of DWI for imaging of various cancers in abdominal organs has been reported (9,11,12,14–16). On DWI, AIP and pancreatic

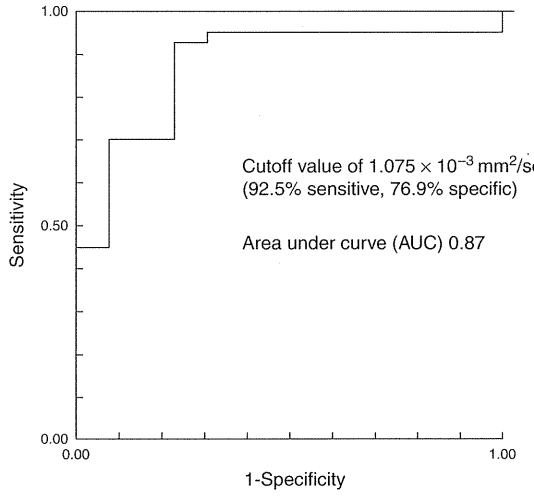

Figure 5. The receiver operating characteristic curve evaluating the optimal ADC cutoff value to distinguish AIP from pancreatic cancer. ADC, apparent diffusion coefficient; AIP, autoimmune pancreatitis.

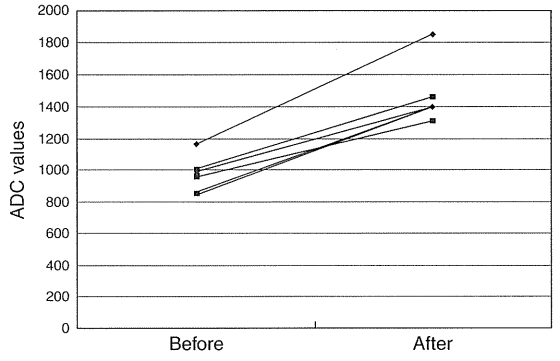

Figure 6. ADC values ($\times 10^{-6}$ mm²/s) of the pancreas with autoimmune pancreatitis before and after steroid therapy. ADC, apparent diffusion coefficient.

cancer were detected as high-signal intensity areas. However, as all pancreatic cancers showed a solitary area, diffuse or multiple high-intensity areas suggested AIP. A longitudinal high-intensity area also suggested AIP more than pancreatic cancer.

It is reported that pancreatic cancer showed lower ADC values ($1.27\pm0.52\times10^{-3}$ mm²/s (15) or $1.44\pm0.20\times10^{-3}$ mm²/s (14)) compared with normal pancreas because of increased cellularity and fibrosis (desmoplasia) of the tumor, which cause restricted diffusion. In this study, the ADC value of pancreatic cancer was $1.249\pm0.113\times10^{-3}$ mm²/s, which was also significantly lower than that of normal pancreatic tissue. On the other hand, the ADC value of AIP was $1.012\pm0.112\times10^{-3}$ mm²/s, which was significantly lower than that of pancreatic cancer. There are only two reports of ADC values in AIP. Feuerlein *et al.* (20) reported an ADC value of 0.799×10^{-3} mm²/s in one patient with diffuse AIP. Taniguchi *et al.* (19) reported that the ADC values of four AIP patients ($0.97\pm0.18\times10^{-3}$ mm²/s) were significantly lower than those of normal controls. ADC values, which are quantitative expressions of tissue diffusion characteristics, are related to the proportion of extracellular components. Guo *et al.* (21) reported a clear inverse relationship between ADC values and the cellular component of brain tumors, such as lymphoma and high-grade astrocytoma. The ADC value was significantly lower in lymphomas than in high-grade gliomas, whereas the cellular component was significantly greater in lymphomas than in high-grade gliomas. These findings suggest that increased cellularity is associated with more restricted diffusion. Thus, ADC values tend to decrease with increased tissue cellularity or cell density.

The histopathology of the pancreas in AIP is very characteristic: dense infiltration of lymphocytes and plasma cells with dense fibrosis or edema in the involved pancreatic lesion (1–4). Although cancer cell infiltration with desmoplastic stroma is the typical histopathological feature of pancreatic cancer, the cellularity of dense lymphoplasmacytic infiltration in AIP is obviously greater than that of pancreatic cancer. Increased cellularity and edematous change in AIP may induce lower ADC values in AIP than in pancreatic cancer. Using an ADC cutoff value (1.075×10^{-3} mm²/s) seems to be useful for distinguishing AIP from pancreatic cancer.

After steroid therapy, high-intensity areas on DWI disappeared or were markedly decreased with improvement in pancreatic enlargement. The ADC values of reduced pancreatic lesions increased to nearly that of normal pancreas after steroid therapy. DWI may also be useful for evaluating the effect of steroid therapy and for monitoring relapse during follow-up.

This study had some limitations. The first limitation was the lack of histopathology of the pancreas in 10 AIP patients, so that the degree of lymphoplasmacytic infiltration could not be assessed. The second limitation was the small number of AIP patients examined. Moreover, as AIP is a relatively rare disease, there were only 13 AIP patients. A further study of more cases is necessary. However, this is the first report about the utility of DWI to distinguish AIP from pancreatic cancer; therefore, a prospective, differential diagnostic study on using this cutoff value will further elucidate the utility of DWI.

In conclusion, DWI is useful for detecting AIP and for evaluating the effect of steroid therapy. ADC values were significantly lower in AIP than in pancreatic cancer. An ADC cutoff value may be useful for distinguishing AIP from pancreatic cancer.

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CONFLICT OF INTEREST

Guarantor of the article: Terumi Kamisawa, MD.
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Financial support: None.
Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ It is sometimes difficult to differentiate autoimmune pancreatitis (AIP) from pancreatic cancer.

WHAT IS NEW HERE

✓ On diffusion-weighted magnetic resonance imaging (DWI), diffuse or multiple high-signal intensity areas suggest autoimmune pancreatitis (AIP) rather than pancreatic cancer.

✓ The apparent diffusion coefficient (ADC) values for AIP were significantly lower than those for pancreatic cancer.

✓ An ADC cutoff value of 1.075×10^{-3} mm^2/s may be useful for distinguishing AIP from pancreatic cancer.

✓ After steroid therapy, the ADC values of the reduced pancreatic lesion increased almost to the values of normal pancreas.

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Possible involvement of T helper type 2 responses to Toll-like receptor ligands in IgG4-related sclerosing disease

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ABSTRACT

We report a case of immunoglobulin G4 (IgG4)-related sclerosing disease involving the pancreas, liver and salivary glands. Massive infiltration of IgG4-expressing plasma cells was seen in the liver and submandibular lymph nodes. Interestingly, accumulation of IgG4-expressing plasma cells was also seen in the colon and terminal ileum. Peripheral blood mononuclear cells (PBMCs) isolated from this patient exhibited enhanced production of IgG4 and interleukin-10 upon stimulation with Toll-like receptor (TLR) ligands as compared with those from a healthy control. In contrast, production of tumour necrosis factor α and interferon γ by PBMCs from this patient was markedly reduced. Since colonic mucosa is always exposed to TLR ligands derived from commensal organisms, the results of immunological studies suggest that enhanced T helper type 2 responses to intestinal microflora may underlie the immunopathogenesis in this patient with IgG4-related sclerosing disease.

INTRODUCTION

Autoimmune pancreatitis (AIP) is an inflammatory disorder which is characterised by increased serum levels of immunoglobulin G4 (IgG4) or by an IgG4-positive plasmacytic infiltrate into the inflamed tissue.[1] Another important feature of AIP is a wide variety of extrapancreatic manifestations such as sialadenitis, cholangitis, retroperitoneal fibrosis and inflammatory pseudotumour of the liver and lung.[2] Since these extrapancreatic and pancreatic lesions share common histopathological findings (ie, abundant infiltration by $IgG4^+$ plasmacytes), Kamisawa *et al* proposed a new clinicopathological entity: 'IgG4-related sclerosing disease'.[2] However, little is understood regarding the role played by this IgG subtype in the inflammatory process. In this regard, IgG4 itself does not seem to be responsible for the development of tissue damage since this IgG subtype does not cause cell-mediated lysis due to poor binding activity to complement.[3] In addition, anti-inflammatory activity of IgG4 has been shown.[4] Consistent with these biological functions of IgG4, clinical manifestations of immune complex disease such as arthritis and glomerulonephritis are rarely seen in patients with IgG4-related sclerosing disease.[5] These facts suggest that abnormal immunological environments leading to enhanced IgG4 responses, rather than IgG4 antibody itself, underlie the pathogenesis of this disease.

Distribution of IgG4-expressing plasmacytes in the gastrointestinal tract of patients with AIP has been observed.[6 7] However, it is unknown whether this distribution of $IgG4^+$ cells is directly induced by immune reactions occurring in the gastrointestinal tract or is indirectly induced by systemic IgG4 responses. Given the fact that mucosa of the gastrointestinal tract is always exposed to antigens derived from intestinal microflora, it is tempting to speculate that immune responses against microbial antigens create abnormal environments leading to enhanced IgG4 responses in the gut. Indeed, we experienced a case of IgG4-related sclerosing disease in which accumulation of IgG4-expressing plasmacytes was visualised as colonic inflammatory pseudopolyps.[8] Here we report a case with IgG4-related sclerosing disease whose ileal and colonic mucosa bore a marked infiltration of IgG4-expressing plasma cells. Interestingly, peripheral blood mononuclear cells (PBMCs) isolated from this case show enhanced T helper type 2 (Th2) and IgG4 responses upon stimulation with Toll-like receptor (TLR) ligands. These results indicate possible involvement of excessive Th2 responses against intestinal microflora in some cases with IgG4-related sclerosing disease.

CASE REPORT

A 70-year-old asymptomatic man was admitted for further investigation of swelling of the pancreas and submandibular lymph nodes. He had a history of systemic lymphadenopathy of unknown aetiology at the age of 45. Laboratory tests revealed elevation of serum levels of amylase (229 IU/l; normal range <129 IU/l) and IgG (2144 mg/dl; normal range <1840 mg/dl). Abdominal CT using contrast reagent showed focal swelling of the pancreatic head without an enhancement effect. Endoscopic retrograde cholangiopancreatography revealed irregular narrowing of the main pancreatic duct and the stricture of the lower bile duct. These radiographic findings were consistent with those of AIP.[1] A hypoechoic tumour was detected in the lateral segment of the liver on abdominal ultrasonography. Since a marked elevation of serum IgG4 level was detected (918 mg/dl; normal range <135 mg/dl), this patient was strongly suspected to have IgG4-related scrclosing disease involving the pancreas, bile duct and liver. Biopsy of the liver tumour revealed massive infiltration of plasmacytes expressing IgG and IgG4 around the bile duct (figure 1). More than 50% of IgG-expressing cells

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were positive for IgG4 staining, which suggests that this liver tumour was a pseudotumour due to IgG4-associated cholangitis. Similar histological findings were obtained in the immunohistochemical analyses using biopsy specimens from submandibular lymph nodes (figure 1). Based on these results, this patient was finally diagnosed as having IgG4-related sclerosing disease.

Colonoscopy was performed to exclude the involvement of the gastrointestinal tract before starting prednisolone treatment. Although no inflammatory mucosa was seen from the terminal ileum to the rectum on colonoscopic examination, biopsy specimens taken from the intact mucosa of the terminal ileum and colon revealed a marked infiltration of plasmacytes expressing IgG into the submucosa without destruction of crypt architecture or fibrosis (figure 1). Interestingly, >50% of IgG-expressing cells were positive for IgG4 staining. Accumulation of IgG4-expressing plasma cells in the colonic mucosa led us to hypothesise that abnormal immunological responses to gut microbial antigens might underlie the development of enhanced IgG4 responses. PBMCs from this case and healthy controls were stimulated with TLR ligands to see immune responses against antigens derived from intestinal microflora.[9] Ethical permission for this study was granted by the review board of Kyoto University. As shown in figure 2, production of IgG4 as well as interleukin-10 (IL-10) was enhanced upon stimulation with TLR4 (lipopolysaccharide (LPS)) and TLR5 (flagellin) ligands. Production of IgG4 was also enhanced by stimulation of a TLR2 ligand (peptidoglycan (PGN)). In contrast, production of Th1 cytokines (interferon γ (IFNγ) and tumour necrosis factor α (TNFα)) in response to TLR ligands by the patient's PBMCs was impaired as compared with that by control PBMCs. No difference was seen in the production of IL-8 or IL-17 upon stimulation with TLR ligands or TNFα. These data suggest that activation of TLRs generates both IgG4 and Th2 responses in PBMCs from this case since IFNγ and IL-10 are prototypical Th1 and Th2 cytokines, respectively.[9] We determined the type of immune cells producing these cytokines by cell depletion study

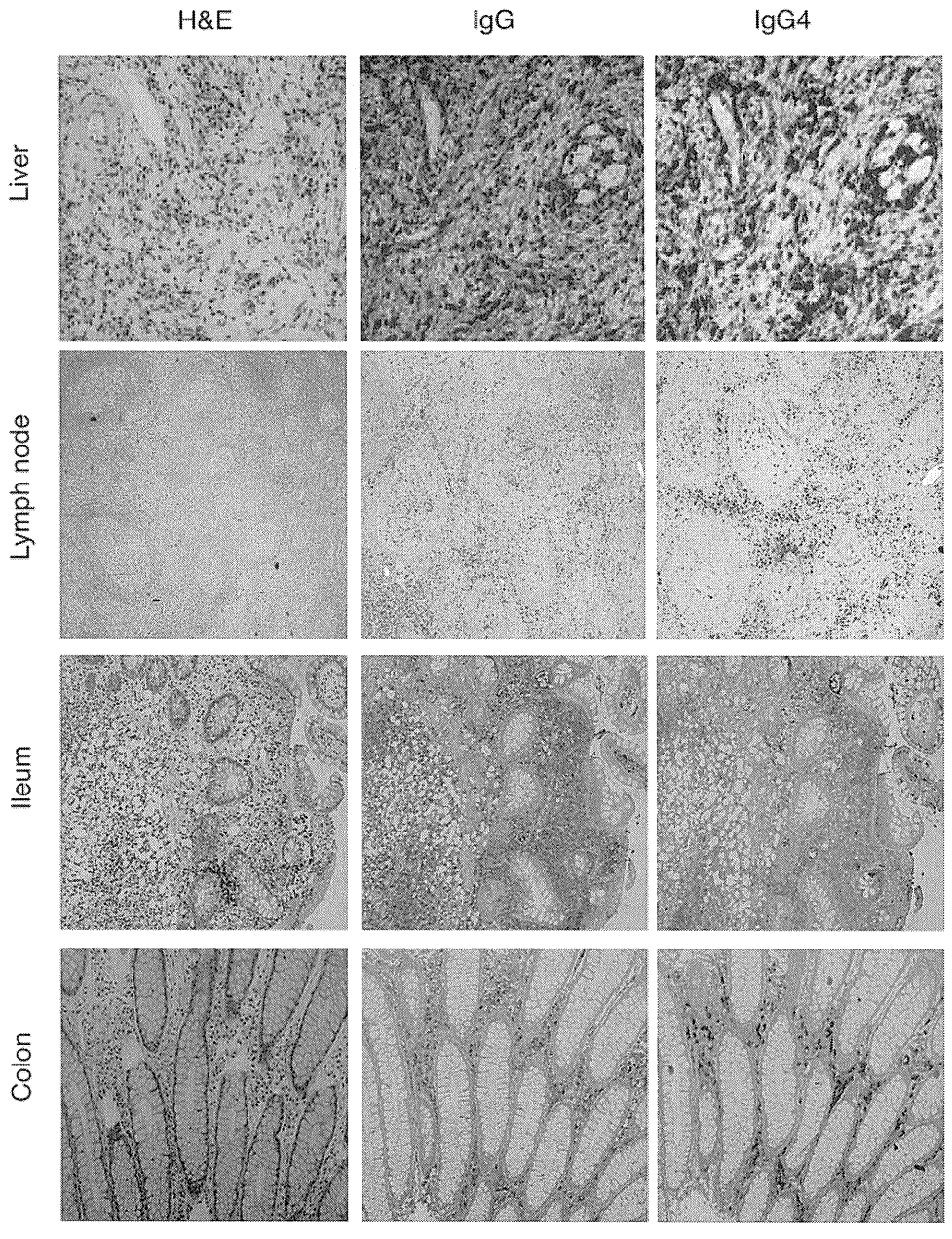

Figure 1 Immunohistochemical staining of immunoglobulin G4 (IgG4) and IgG. Biopsy specimens obtained from the liver, submandibular lymph nodes, terminal ileum and colon were stained with anti-IgG4 or anti-IgG antibody for visualisation of plasma cells expressing IgG4 or IgG.

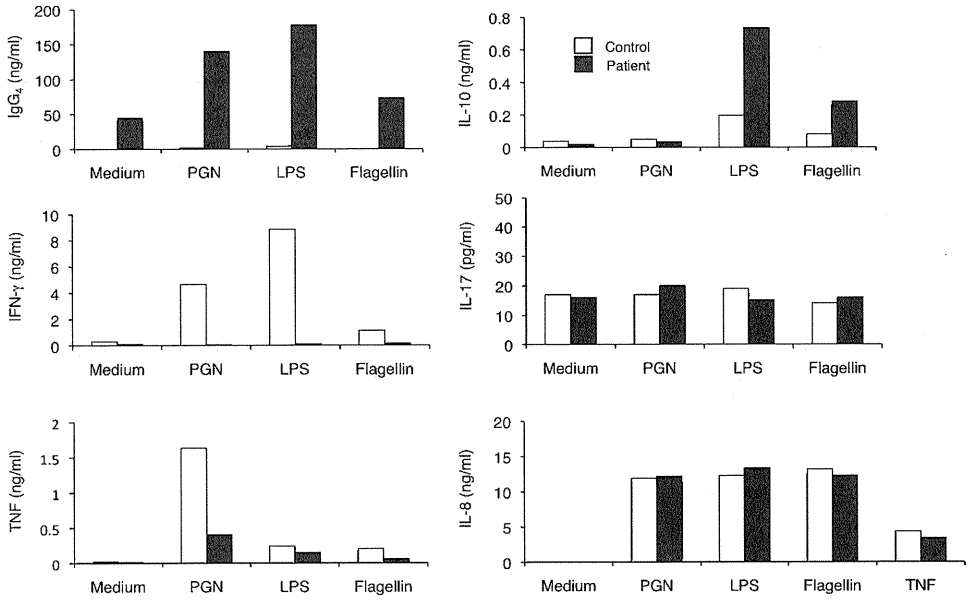

Figure 2 Enhanced T helper type 2 (Th2) responses to Toll-like receptor (TLR) ligands by peripheral blood mononuclear cells (PBMCs) isolated from the patient. PBMCs (2×10^6/ml) isolated from the patient and healthy controls were stimulated with peptidoglycan (PGN, 10 μg/ml), lipopolysaccharide (LPS, 1 μg/ml), flagellin (1 μg/ml) or tumour necrosis factor (TNF, 20 ng/ml). PBMCs were cultured for 48 h for interleukin-8 (IL-8) and TNF assay, and for 14 days for IgG4, interferon γ (IFNγ), IL-10 and IL-17 assay. Results shown are means of triplicate wells.

using control samples. We found that $CD3^+$ T cells produced IFNγ and IL-10 whereas $CD14^+$ monocytes produced IL-10 and TNFα (data not shown).

DISCUSSION

An interesting observation in this case with IgG4-related sclerosing disease was a marked infiltration of IgG4-expressing plasmacytes into the colonic mucosa which appeared to be normal on endoscopic examination. It remains unclear whether we can regard this case as IgG4-related sclerosing disease involving the colonic mucosa since no pathological findings were present in colonic biopsy specimens other than marked infiltration of $IgG4^+$ cells. Thus, unlike our previous case in which infiltration of IgG4-expressing plasmacytes was visualised as colonic polypoidal lesions,[8] we have to be cautious in the interpretation of infiltration of IgG4-expressing plasma cells into endoscopically normal colonic mucosa in the setting of IgG4-related sclerosing disease.

Immune responses leading to accumulation of IgG4-expressing plasmacytes in the gastrointestinal tract are poorly understood. PBMCs isolated from this case exhibited enhanced production of IgG4 and Th2 cytokines upon stimulation with TLR ligands, suggesting that enhanced immune reactions against microbial antigens cause infiltration of lymphocytes as in the case of inflammatory bowel disease (IBD).[10] In fact, this idea is supported by clinical evidence that a significant population of patients with AIP have a diagnosis of IBD.[11] Importantly, IgG4 responses induced by TLR activation are associated with enhanced IL-10 production. In this regard, two different groups report involvement of regulatory T cells (Tregs) producing IL-10 in IgG4-related sclerosing disease.[12 13] Thus, enhanced IL-10 production seen in this case may be partially mediated by circulating Tregs. Given the fact that IL-10 is an important cytokine for IgG4 class switching,[14] we assume that excessive Th2 responses triggered by TLR ligands together with activation of Tregs create abnormal immunological environments leading to enhanced IgG4 responses. This idea partially explains immunological mechanisms of enhanced Th2 responses in patients with IgG4-related sclerosing disease.[12]

Although storiform fibrosis is a characteristic pathological finding of IgG4-related sclerosing disease,[2] molecular mechanisms of fibrosis in this disorder are poorly understood. Th2 cytokines mediated by activation of TLRs on macrophages have been identified as positive regulators of tissue fibrosis in the liver and lung.[15] Thus, enhanced Th2 responses to TLR ligands might be involved in the development of storiform fibrosis in IgG4-related sclerosing disease. However, analysis of expression of both Th2 cytokines and TLRs using fibrotic tissue samples is necessary to address this issue.

What is the mechanism by which enhanced Th2 responses against intestinal microflora cause IgG4-related sclerosing disease without the development of colitis? In this regard, immune reactions causing tissue injury and those causing IgG4 responses should be considered separately as shown by the fact that IgG4 antibody itself has anti-inflammatory properties.[4] Indeed, tissue destruction was not seen in the lower gastrointestinal tract of this case despite a marked infiltration of IgG4-expressing plasmacytes into the submucosa. Several mechanisms for preventing hyper-responsiveness to microbial antigens operate in the gut. For example, the intestine is the preferential site where naïve T cells differentiate into Tregs.[10] Thus, one possible explanation is that pathogenic immune reactions causing tissue injury are suppressed in the gut by regulatory mechanisms, whereas such reactions cause tissue injury in other sterile organs such as the pancreas and bile duct due to the lack of regulatory mechanisms. Based on this, it is tempting to speculate that the gastrointestinal tract is an induction site for systemic IgG4 responses and functions as a reservoir for IgG4-expressing plasmacytes even if disease-associated pathogenic changes are absent. Alternatively, distribution of IgG4-expressing plasmacytes into the colonic mucosa may be an epiphenomenon associated with systemic IgG4 responses.

In conclusion, the results of immunological studies using PBMCs from this case suggest involvement of excessive Th2 responses to intestinal microflora in the development of IgG4-related sclerosing disease. Confirmation of this idea awaits further studies using a large number of patients with IgG4-related sclerosing disease.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Kyoto University review board.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Pathologic Findings of Autoimmune Pancreatitis and IgG4-Related Disease

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Abstract: Autoimmune pancreatitis (AIP) is pathologically characterized by lymphoplasmacytic infiltration and fibrosis. However, AIP is not a single entity, but rather includes two histological types—lymphoplasmacytic sclerosing pancreatitis (LPSP) and idiopathic duct-centric chronic pancreatitis (IDCP)—of which the former constitutes the pancreatic manifestation of IgG4-related disease. The inflammation seen in peripancreatic adipose tissue and the interlobular area in LPSP, such as dense lymphoplasmacytic infiltration with fibrosis, storiform fibrosis, and obliterative phlebitis, is common among the various lesions that belong to IgG4-related disease. However, some lesions in the family of IgG4-related disease, such as IgG4-related sclerosing sialadenitis and lymphadenopathy, often lack prominent fibrosis, suggesting the histological variation of this entity. Nonetheless, histological features are important in the formation of a pathological diagnosis of IgG4-related disease because the presence of numerous IgG4-positive plasma cells is not necessarily specific to this disease.

Keywords: Autoimmune pancreatitis (AIP), lymphoplasmacytic sclerosing pancreatitis (LPSP), idiopathic duct-centric chronic pancreatitis (IDCP), immunoglobulin G4 (IgG4), IgG4-related disease.

INTRODUCTION

The pathology of autoimmune pancreatitis (AIP) is characterized by dense lymphoplasmacytic infiltration and fibrosis, and these characteristics are thought to support the autoimmune etiology of AIP. These features are in contrast to the scarce inflammatory cell infiltration seen in other pancreatic inflammatory conditions, including alcoholic chronic pancreatitis. Thus, even before the concept of AIP was proposed by Yoshida and colleagues [1], these features have been reported under various designations, such as chronic inflammatory sclerosis of the pancreas [2], lymphoplasmacytic sclerosing pancreatitis (LPSP) [3], non-alcoholic duct destructive chronic pancreatitis [4], and inflammatory pseudotumor [5]. On the other hand, lymphoplasmacytic infiltration and fibrosis are nonspecific histological findings common to various chronic inflammatory conditions, and it has been pointed out that more than one pathological entity is included in what has been called AIP and related pathological entities [6-9].

Elevated serum immunoglobulin G4 (IgG4) levels in AIP patients were reported by Hamano and colleagues [10]. Another noteworthy achievement of theirs was the immunohistochemical demonstration of numerous IgG4-positive plasma cells in the affected tissues of AIP [11]. The following immunohistochemical studies revealed that the increase in IgG4-positive plasma cells is characteristically seen in LPSP but absent in the other AIP group, called idiopathic duct-centric chronic pancreatitis (IDCP), which is also called AIP with granulocytic epithelial lesion (GEL) [12, 13]. This finding facilitated the notion that there are at least two histological types of AIP, of which LPSP represents the IgG4-related disease of the pancreas. Recently, Western authors proposed a new terminology, type 1 and type 2 AIP, which corresponds to LPSP and IDCP, respectively [14].

Extrapancreatic lesions commonly coexist with AIP [15]. They are histologically similar to LPSP, and immunostaining reveals numerous IgG4-positive plasma cells in the affected tissues [16]. AIP/LPSP and its extrapancreatic lesions have therefore been regarded as a group with a common etiology, for which the term IgG4-related disease has been coined [17]. IgG4-related disease probably corresponds to the concept known as multifocal fibrosclerosis [16]. Identification of numerous IgG4-positive plasma cells with archival tissues facilitated the identification of numerous lesions that are potentially included in IgG4-related disease.

This review article describes the histology of AIP, mainly focusing on LPSP, and the extrapancreatic lesions that belong to IgG4-related disease. Pathological issues in diagnosing IgG4-related disease are also discussed.

PATHOLOGY OF AUTOIMMUNE PANCREATITIS

Pathology of Lymphoplasmacytic Sclerosing Pancreatitis (LPSP)

LPSP was proposed by Kawaguchi and colleagues in 1991 [3]. AIP without GEL [7, 8] and lobulocentric AIP [9] may be synonymous. In addition to diffuse lymphoplasmacytic infiltration and fibrosis, LPSP consists of unique histological features that distinguish it from other chronic inflammatory diseases.

Radiologically, the affected pancreas reveals diffuse or focal swelling and irregular narrowing of the main pancreatic duct. Thus, from a clinical standpoint, it is hard to distinguish LPSP from pancreatic carcinoma, and that is why

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