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J Gastroenterol
DOI 10.1007/s00535-011-0510-y

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Risk factors for pancreatic stone formation in autoimmune pancreatitis over a long-term course

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Received: 21 September 2011 / Accepted: 20 November 2011

Abstract
Background Autoimmune pancreatitis (AIP) has the potential to progress to a chronic state that forms pancreatic stones. The aim of this study was to clarify the risk factors underlying pancreatic stone formation in AIP.
Methods Sixty-nine patients with AIP who had been followed for at least 3 years were enrolled for evaluation of clinical and laboratory factors as well as computed tomography and endoscopic retrograde cholangiopancreatography findings.
Results During the course of this study, increased or de novo stone formation was seen in 28 patients, who were defined as the stone-forming group. No stones were observed in 32 patients, who were defined as the non-stone-forming group. Nine patients who had stones at diagnosis but showed no change during the course of this study were excluded from our cohort. Univariate analysis revealed no significant differences in clinical or laboratory factors associated with AIP-specific inflammation between the two groups. However, pancreatic head swelling ($P = 0.006$) and narrowing of both Wirsung's and Santorini's ducts in the pancreatic head region ($P = 0.010$) were significantly more frequent in the stone-forming group. Furthermore, multivariate analysis identified Wirsung and Santorini duct narrowing at diagnosis as a significant independent risk factor for pancreatic stone formation (OR 4.4, $P = 0.019$).
Conclusions A primary risk factor for pancreatic stone formation in AIP was narrowing of both Wirsung's and Santorini's ducts, which most presumably led to pancreatic juice stasis and stone development.

Keywords Autoimmune pancreatitis · Pancreatic stone · Wirsung duct · Santorini duct

Abbreviations

AIP	Autoimmune pancreatitis
CT	Computed tomography
ERCP	Endoscopic retrograde cholangiopancreatography

Introduction

Autoimmune pancreatitis (AIP) is a specific type of chronic pancreatitis possibly caused by autoimmune mechanisms that is characterized by pancreatic swelling and irregular narrowing of the main pancreatic duct, both of which mimic pancreatic cancer [1]. Other characteristic features of AIP are high serum IgG4 concentration and IgG4-positive plasma cell infiltration in affected pancreatic tissue that also aid in serological and pathological AIP diagnosis [2, 3]. As patients with AIP respond favorably to corticosteroid therapy, the disease was previously believed to be a non-progressive condition which did not progress to an advanced stage of chronic pancreatitis or pancreatic stone formation [4]. However, the short-lived pancreatic swelling and severe lymphoplasmacytic infiltration in acute AIP are now believed to manifest as different clinical features in a chronic state; earlier studies have

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Published online: 21 December 2011

shown that AIP progresses to a chronic stage showing pancreatic stone formation and atrophy resembling ordinary chronic pancreatitis that is closely associated with relapse [5–12]. Moreover, we found that patients with seemingly typical chronic pancreatitis also included several cases with elevated serum IgG4 concentration, which may have been due to chronic stage AIP [6].

Two major mechanisms attempt to explain the formation of pancreatic stones in AIP: severe inflammation specific to AIP and stasis of pancreatic juice due to narrowing of the pancreatic duct [13, 14]. In general, AIP rarely results in severe inflammation or tissue necrosis. Corticosteroid therapy ameliorates irregular narrowing of the pancreatic duct in the majority of patients, although residual stenosis may persist [15]. Additionally, some patients not undergoing corticosteroid therapy show progression of duct changes [16]. On the basis of these findings, we hypothesized that the formation of pancreatic stones in AIP is associated with stasis of pancreatic juice due to stenosis of the pancreatic duct. The aim of the present study was to clarify the risk factors underlying pancreatic stone formation in AIP by comparing the clinical features and frequency of pancreatic stone formation in a long-term follow-up cohort of AIP patients.

Patients and methods

Study subjects

Ninety-three patients with AIP were examined and treated at Shinshu University Hospital between August 1992 and July 2011. Among them, we enrolled 69 patients who had been followed for at least 3 years (median follow-up 91 months, range 36–230 months), which included 54 men and 15 women (median age 64 years, range 38–84 years). Diagnosis of AIP was based on the Asian diagnostic criteria for AIP [17].

Clinical features and laboratory tests

We reviewed the medical charts of our cohort for observation period, age at diagnosis, gender, alcohol consumption, corticosteroid treatment, and relapse. We also compared serum values representative of AIP activity from blood tests at diagnosis, including those for IgG, IgG4, C3, C4, soluble interleukin 2 receptor (sIL2-R), circulating immune complex (CIC), and amylase.

Evaluation of pancreatic stone formation

The presence of pancreatic stones was assessed by using CT images. We evaluated the location of stones with respect to pancreatic region (head, body, or tail), as well as with respect to the pancreatic duct (in the main pancreatic duct or in parenchyma). We also assessed the size and number of stones during the study period. CT scanning was performed using different protocols during the course of this study. At our institute, CT testing was changed to multidetector computed tomography (MDCT) in 2003, which resulted in clearer CT images.

Evaluation of pancreatic swelling

Swelling of the pancreas in CT images was assessed by three pancreatology experts. Pancreatic swelling was determined using the Haaga criteria [18] or a marked decrease in size after corticosteroid therapy and was classified by its location in the pancreas (head, body, or tail). Swelling restricted to either one area or spanning two or three areas was considered to be focal or segmental-diffuse swelling, respectively.

Evaluation of pancreatic duct narrowing

Narrowing of the pancreatic duct seen in endoscopic retrograde pancreatocholangiography (ERCP) was assessed by three expert endoscopists. Pancreatic duct narrowing was classified by its location in the pancreas (head, body, or tail), and narrowing in the head region was further divided into narrowing of Wirsung's duct and narrowing of Santorini's duct. Narrowing restricted to either one area or spanning two or three areas was considered to be focal or segmental-diffuse narrowing, respectively.

Statistical analysis

The Fisher's exact and Pearson's chi-square tests were adopted to test for differences between subgroups of patients. The Mann–Whitney U test was employed to compare continuous data. Multivariate analyses were performed using a logistic regression model. Variables associated with a P value of less than 0.2 in univariate analyses were included in a stepwise logistic regression analysis to identify independent risk factors associated with the formation of pancreatic stones. All tests were performed using the IBM SPSS Statistics Desktop for Japan ver. 19.0 (IBM Japan Inc, Tokyo, Japan). P values of less than 0.05 were considered to be statistically significant.

Ethics

This study was approved by the ethics committee of Shinshu University (approval number 1805).

Results

Pancreatic stone formation

At diagnosis, pancreatic stones were found in 17 of 69 patients and increased in size and number in 8 patients. De novo stone formation was observed in 20 of the remaining 52 patients. In total, increased or de novo stones were seen in 28 patients during the study period, who were collectively defined as the stone-forming group. The 32 patients in whom no stones were found during the course of the study were defined as the non-stone-forming group (Fig. 1). Nine patients who had stones at diagnosis but showed no change during the course of this study were excluded from our cohort.

There were no significant differences in the frequency of pancreatic stone formation among pancreatic areas between the stone increase and de novo stone cases. However, stone formation in the main pancreatic duct was more frequently seen in de novo cases, but not significantly ($P = 0.151$) (Table 1). Thus, there were no fundamental differences in the manner of new stone formation. For de novo stone patients, the median and range of the study period between diagnosis of AIP and stone formation were 57 and 8–138 months, respectively.

Correlation between pancreatic stone formation and clinical and laboratory features associated with AIP-specific inflammation

We next searched for risk factors of pancreatic stone formation by comparing several parameters between the stone-forming and non-stone-forming groups. Univariate analysis revealed no significant differences in observation period, age, gender, alcohol consumption, or corticosteroid treatment between the stone-forming group and the non-stone-forming group. Relapse was more frequently seen in the stone-forming group, but not significantly ($P = 0.093$). We also found no significant differences in serum values of disease activity markers, such as IgG, IgG4, C3, C4, sIL2-R, and CIC, between the two groups (Table 2).

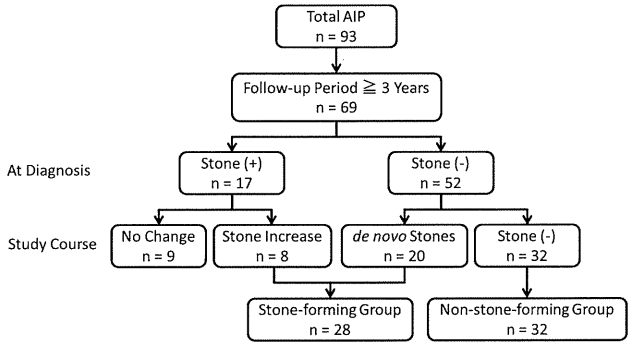

Fig. 1 Study participation flowchart and outcome of 69 patients with AIP who were followed for at least 3 years (mean 91 months, range 36–230 months)

Table 1 Location of pancreatic stone formation

	Stone increase cases ($n = 8$)	De novo stone cases ($n = 20$)	P value
Head/body/tail	6/8/5	17/20/15	NS
In MPD/in parenchyma	3/16	18/34	0.151

MPD main pancreatic duct, *NS* not significant

Correlation between pancreatic stone formation and pancreatic swelling

We examined whether pancreatic stone formation was associated with the extent or location of pancreatic swelling. Univariate analysis showed no significant differences in the extent of pancreatic swelling in the focal area versus in the segmental-diffuse area between the stone-forming group and the non-stone-forming group. However, pancreatic head swelling was significantly more frequent in the stone-forming group ($P = 0.006$). No significant differences were seen for pancreatic body or tail swelling (Table 3, Fig. 2).

Table 2 Clinical features and laboratory tests at diagnosis

	Stone-forming group ($n = 28$)[a]	Non-stone-forming group ($n = 32$)[a]	P value
Clinical features			
Observation period[b]	100 (36–165)	90 (36–230)	0.524
Age	67 (47–84)	64.5 (38–81)	0.543
Sex (M/F)	24/4	22/10	0.140
Alcohol (+/−)	20/8	19/12	0.582
Prednisolone (+/−)	25/3	28/4	1.000
Relapse (+/−)	11/17	6/26	0.093
Laboratory tests			
Amylase	94 (17–431)	86 (22–478)	0.678
IgG	2,187 (892–7,236)	2,183 (1,194–5,545)	0.686
IgG4	640 (154–2,855)	424 (4–2,970)	0.916
C3	91 (33–157)	87 (29–199)	0.538
C4	20.1 (7.7–39.7)	21.3 (1.1–38.7)	0.627
sIL2-R	738 (132–2,260)	940 (257–4,695)	0.130
CIC	5.1 (1.9–40)	5.5 (1.9–27.5)	0.392

sIL2-R soluble interleukin 2 receptor, *CIC* circulating immune complex

[a] Values are expressed as median (range)

[b] Period from diagnosis of AIP to the most recent observation (months)

Correlation between pancreatic stone formation and pancreatic duct narrowing

We next examined whether pancreatic stone formation was associated with the extent or location of pancreatic duct narrowing. Univariate analysis revealed no significant differences in the extent of pancreatic duct narrowing in the focal area versus in the segmental-diffuse area between the stone-forming group and the non-stone-forming group, nor were there significant differences in the location of pancreatic duct narrowing between the two groups. However, among cases with narrowing of the head region, patients with narrowing of both Wirsung's and Santorini's ducts were significantly more frequent in the stone-forming group ($P = 0.010$) (Table 3, Fig. 3).

In the stone-forming group, 4 patients showed duct narrowing in the body and tail regions, but 2 of them showed parenchymal pancreatic stones in the downstream pancreatic region.

Table 3 Pancreatic morphology at diagnosis

	Stone-forming group ($n = 28$)	Non-stone-forming group ($n = 32$)	P value
Swelling (by CT)			
Head (+/−)	26/2	20/12	0.006*
Body (+/−)	20/8	19/13	0.419
Tail (+/−)	17/11	19/13	1.000
Focal/segmental-diffuse	7/21	12/20	0.406
Ductal narrowing (by ERCP)			
Head (+/−)	24/4	22/10	0.140
Wirsung + Santorini (+/−)	21/7	13/19	0.010*
Body (+/−)	15/13	19/13	0.795
Tail (+/−)	22/6	24/8	0.770
Focal/segmental-diffuse	6/22	11/21	0.390

* $P < 0.05$

Multivariate analysis of pancreatic stone formation in AIP at diagnosis

Multivariate analysis was performed for gender, relapse, sIL2-R, pancreatic head swelling, and Wirsung and Santorini duct narrowing, all of which had P values of less than 0.2 in univariate studies. We identified that narrowing of both Wirsung's and Santorini's ducts at diagnosis was a significant determinant of pancreatic stone formation in AIP (odds ratio 4.4, 95% confidence interval 1.3–15.5, $P = 0.019$).

Correlation between pancreatic stone formation and residual pancreatic swelling or residual pancreatic duct narrowing after prednisolone (PSL) therapy

We further assessed whether pancreatic stone formation was associated with the extent or location of residual pancreatic swelling or residual pancreatic duct narrowing 4 weeks after PSL therapy between stone-forming patients and non-stone-forming patients. Univariate analysis showed that residual pancreatic head swelling was more

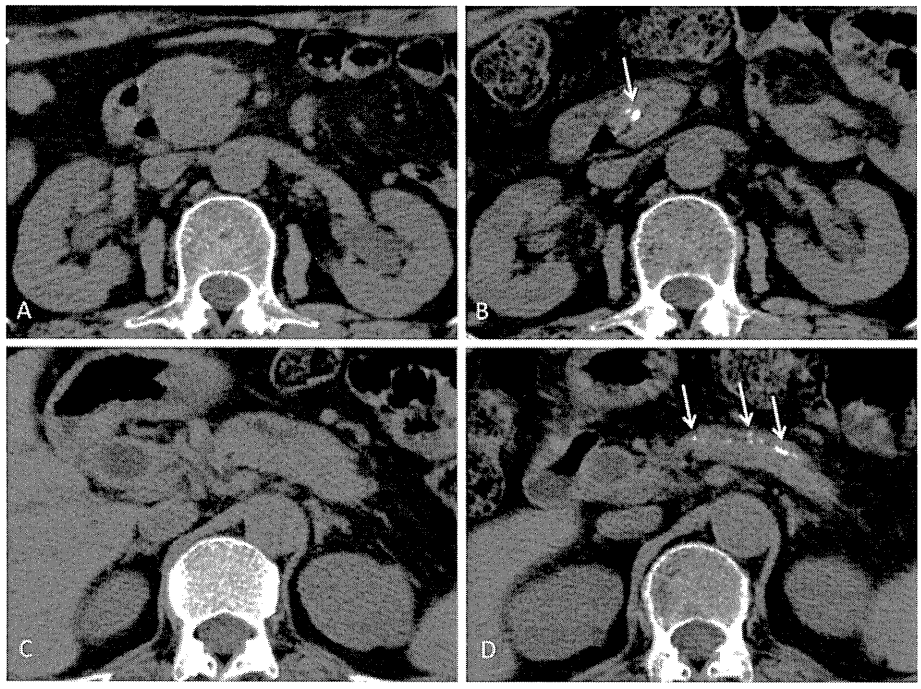

Fig. 2 CT findings in a 67-year-old female with pancreatic head swelling. **a**, **c** CT at diagnosis in May 2005 showing pancreatic head swelling. **b**, **d** CT 27 months later in August 2007 showing pancreatic stone formation (*arrows*) and pancreatic atrophy

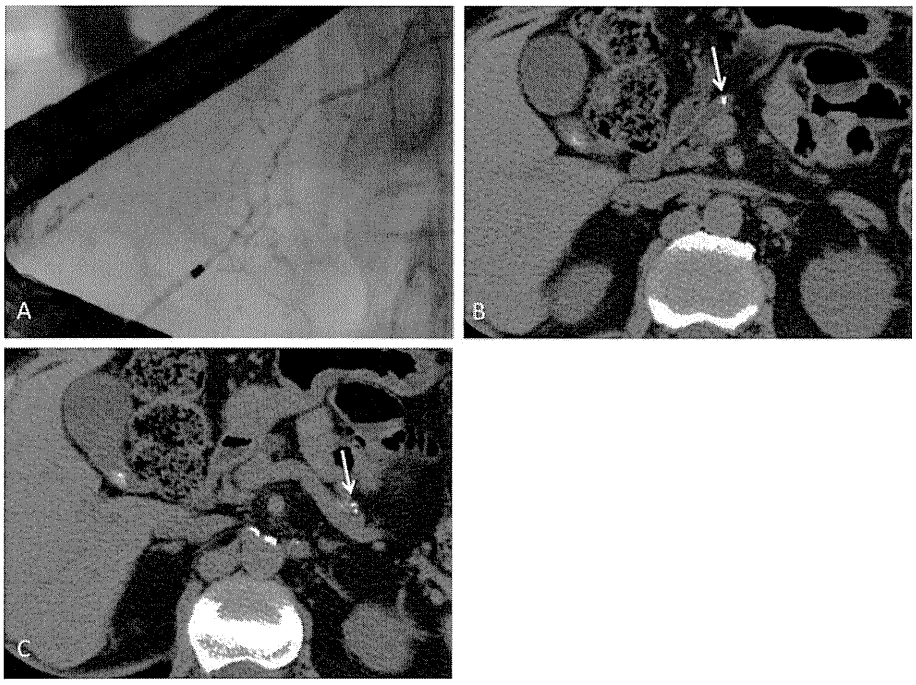

Fig. 3 ERCP and CT findings in a 69-year-old male with narrowing of both Wirsung's and Santorini's ducts. **a** ERCP at diagnosis in April 2001 showing Wirsung's and Santorini's duct narrowing. **b**, **c** CT 105 months later in December 2009 showing pancreatic stone formation (*arrows*) and pancreatic atrophy

Table 4 Pancreatic morphology after corticosteroid therapy

	Stone-forming patients ($n = 24$)	Non-stone-forming patients ($n = 26$)	*P* value
Swelling (by CT)			
Head (+/−)	7/17	2/24	0.069
Body (+/−)	3/21	3/23	1.000
Tail (+/−)	7/17	6/20	0.866
Focal/segmental-diffuse	7/4	2/4	0.334
	Stone-forming patients ($n = 22$)	Non-stone-forming patients ($n = 20$)	
Ductal narrowing (by ERCP)			
Head (+/−)	17/5	11/9	0.229
Wirsung + Santorini (+/−)	11/11	4/16	0.088
Body (+/−)	4/18	2/18	0.665
Tail (+/−)	7/15	10/10	0.376
Focal/segmental-diffuse	10/8	3/10	0.139

frequently seen in stone-forming patients, but not significantly ($P = 0.069$). In addition, cases with residual narrowing of both Wirsung's and Santorini's ducts in the pancreatic head region tended to be more frequently seen among stone-forming patients ($P = 0.088$) (Table 4).

Correlation between pancreatic stone formation and pancreatic function during the course of the study

We compared serum levels of amylase and HbA1c at diagnosis, at 5 years, and at 8 years among non-stone-forming patients, stone-forming patients, and intraductal stone-forming patients, who seemed to be at a more advanced stage of stone formation. Although we found no significant differences among the groups, both enzyme and HbA1c values tended to be at abnormal levels in intraductal stone-forming patients compared with non-stone-forming patients (Table 5).

Discussion

Autoimmune pancreatitis and pancreatic stone formation

An early study reported that AIP was characterized by the absence of pancreatic stones [5, 6]. Later, hallmark histological findings of marked lymphoplasmacytic infiltration representing acute AIP inflammation were found to give way to other features in the chronic stage; we reported that several patients with AIP formed pancreatic stones during the disease course [5, 6], which has been confirmed by other studies [7]. Since pancreatic stones are a major characteristic of ordinary chronic pancreatitis, such as alcoholic pancreatitis, it appears that chronic stage AIP

Table 5 Pancreatic function during the course of the study

	Non-stone-forming patients[a]	Stone-forming patients[a]	*P* value[b]	Intraductal stone-forming patients ($n = 9$)[a]	*P* value[c]
Amylase					
At diagnosis	86 (22–478)	94 (17–431)	0.678	102 (62–323)	0.490
5 years later	85 (45–160)	80 (42–136)	0.497	92 (46–134)	0.569
8 years later	83 (59–130)	75 (37–128)	0.230	75 (48–98)	0.313
HbA1c					
At diagnosis	5.7 (4.1–11.2)	5.7 (4.5–9.5)	0.536	6.0 (4.5–9.5)	0.549
5 years later	5.8 (5.1–10.4)	6.0 (4.6–10.2)	0.366	6.0 (5.4–10.2)	0.289
8 years later	5.8 (5.1–9.8)	6.0 (5.1–10.3)	0.504	6.8 (5.1–10.3)	0.293

[a] Values are expressed as median (range)

[b] Non-stone-forming patients versus stone-forming patients

[c] Non-stone-forming patients versus intraductal stone-forming patients

may present symptoms resembling those of ordinary chronic pancreatitis. Indeed, elevation of serum IgG4 was found in 7% of ordinary chronic pancreatitis in one study, which may have in fact represented chronic stage AIP [6]. Similarly to alcoholic pancreatitis in which recurrent attacks facilitate pancreatic stone formation, stone formation in AIP is preferentially seen in relapsed cases [5].

For de novo stone cases, the median and range of the study period between diagnosis of AIP and stone formation were 57 and 8–138 months, respectively. However, since we had no prospective protocol for CT testing, the duration of pancreatic stone formation may have been affected by the timing of CT tests.

Risk factors for pancreatic stone formation

Pancreatic stone formation implies the progression of pancreatic tissue damage. Accordingly, identification of the direct risk factors of stone formation is expected to disclose the mechanism of tissue injury in order to develop treatments that suppress this progressive damage. We postulated two mechanisms for pancreatic stone formation in AIP in this study, namely severe tissue injury attributed to the specific inflammatory process of AIP and pancreatic juice stasis due to pancreatic duct narrowing, and sought to clarify the risk factors responsible for stone development.

Correlation between pancreatic stone formation and clinical and laboratory features associated with AIP-specific inflammation

There were no significant differences in observation period, age, gender, alcohol consumption, or corticosteroid treatment between the stone-forming group and the non-stone-forming group, nor were there any notable changes in serum amylase concentration at diagnosis. Therefore, acute attacks seemed not to contribute to stone formation.

In a highly active stage of AIP, serum concentrations of various markers vary in parallel with disease activity; serum IgG, IgG4, sIL2-R, and CIC increase at relapse and decrease after corticosteroid therapy, while serum C3 and C4 show reciprocal changes [19]. To determine whether the specific inflammatory process of AIP was associated with pancreatic stone formation, we investigated the correlation between stone formation and published activity markers, but found no significant differences between the two groups. However, although we could not confirm a correlation between the intensity of the inflammatory process in AIP and pancreatic stone formation, we could not completely exclude a relationship since we did not check the values of these markers throughout the patients' clinical course. In addition, serum IgG4 concentration remained slightly elevated in 60% of patients in a clinically inactive state after corticosteroid therapy, which suggested that active inflammatory processes may have persisted even when the patients were in apparent remission [20]. On the other hand, it was reported that the histology of characteristic inflammatory changes in AIP normalized after corticosteroid therapy [21, 22], and so it appears unlikely that the inflammatory process in AIP progresses to an advanced stage of severe necrosis and fibrosis like the one found in ordinary chronic pancreatitis, which also induces pancreatic stone formation.

Correlations between pancreatic stone formation and pancreatic swelling and pancreatic duct narrowing

Univariate analysis disclosed that the factors of pancreatic head swelling and narrowing of both Wirsung's and Santorini's ducts were significantly associated with pancreatic stone formation, and multivariate analysis confirmed the latter as a significant independent risk factor for pancreatic stone formation in AIP. Severe inflammation in the pancreatic head region results in swelling and Wirsung and Santorini duct narrowing, and therefore these two findings may be considered to represent the same pathophysiological feature. Diffuse irregular narrowing is a typical duct finding in AIP [4], but some cases showed duct stenosis in an area other than the head region [16]. With progression of the disease, restricted duct stenosis may

progress to diffuse lesions [15, 16]. Residual pancreatic head swelling and residual narrowing of both Wirsung's and Santorini's ducts after corticosteroid therapy were also more frequently found in stone-forming patients compared to non-stone-forming patients in our cohort, strengthening the notion that Wirsung and Santorini duct narrowing in the pancreatic head region caused pancreatic juice stasis in the pancreas and eventual stone formation. In the stone-forming group, 4 patients showed duct narrowing in the body and tail region, but 2 of them showed parenchymal pancreatic stones in the downstream pancreatic region. Accordingly, some stone formation may be due to factors other than pancreatic juice stasis.

There is a lack of consensus as to what causative factors lead to chronic pancreatitis. Hypotheses include the oxidative stress theory, toxic-metabolic theory, stone and duct obstruction theory, necrosis-fibrosis theory, primary duct hypothesis, and sentinel acute pancreatitis event hypothesis [23, 24]. With respect to pancreatic stone formation, the stone and duct obstruction theory postulates that alcohol modulates exocrine function to increase the lithogenicity of pancreatic juice, leading to the formation of protein plugs and stones in the duct. This concept presupposes that alcohol must primarily modulate the properties of pancreatic fluid to promote stone formation [25]. On the other hand, partial outflow obstruction of the pancreatic duct was also proved to induce stone formation. This condition was found in cases with Vater ampulla carcinoma and pancreatic mucin-producing adenocarcinoma [now recognized as intraductal papillary-mucinous carcinoma (IPMC)] [26, 27], and was used in experimental dog models to demonstrate that incomplete ligation of the main pancreatic duct resulted in the formation of calculi [13, 14]. The present study showed that many AIP patients with stone formation had Wirsung and Santorini duct narrowing, which supported the condition of incomplete ligation of the main pancreatic duct seen in the dog model.

Correlation between pancreatic stone formation and pancreatic function during the course of the study

In comparisons among non-stone-forming patients, stone-forming patients, and intraductal stone-forming patients at diagnosis and 5 and 8 years afterwards, both serum amylase and HbA1c values tended to be at abnormal levels in intraductal stone-forming patients compared with non-stone-forming patients, but not significantly. We believe that further observation may disclose a significant deterioration of pancreatic function in stone-forming patients despite the notion that stone-forming AIP might have a different pathophysiology from that of ordinary chronic pancreatitis.

Prevention and management of pancreatic stone formation

Our findings imply that prophylactic measures for reduction of pancreatic head swelling and duct narrowing would prevent increased or de novo stone formation. For patients presenting with narrowing of both Wirsung's and Santorini's ducts, intensive therapy that includes corticosteroids may be needed from an early stage, even when clinical symptoms, such as obstructive jaundice or abdominal pain, have not yet manifested. Furthermore, it is advisable to check for residual changes in pancreatic head swelling and Wirsung and Santorini duct narrowing after corticosteroid therapy.

Limitation of the present study

At our institute, CT has been done by MDCT since 2003, which results in improved images. Accordingly, pancreatic stone detection was likely biased by CT imaging as scans were obtained using different CT protocols during the course of this study.

In conclusion, the main risk factor for pancreatic stone formation in AIP was narrowing of both Wirsung's and Santorini's ducts at diagnosis, which most presumably led to pancreatic juice stasis in the pancreas and stone development.

Acknowledgments This work was supported partially by the Research Program of Intractable Disease provided by the Ministry of Health, Labor, and Welfare of Japan, and in part by Grants-in-aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan (23591012). We thank Trevor Ralph for his English editorial assistance.

Conflict of interest None of the authors have any conflicts of interest associated with this study.

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IgG4-Related Disease (IgG4+MOLPS) – Diagnostic Criteria and Diagnostic Problems

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Abstract: Since the first report on patients with elevated serum IgG4 in sclerosing pancreatitis in 2001, various systemic disorders, described by many names, have been reported. Despite similarities in the organs involved in IgG4-related Mikulicz's disease and Sjögren's syndrome, there are marked clinical and pathological differences between the two conditions. On the other hand, differential diagnosis of IgG4-related Mikulicz's disease and Küttner's tumor is very difficult, since their pathological features are closely related except severe fibrosis. Most patients diagnosed with autoimmune pancreatitis in Japan have IgG4-related sclerosing pancreatitis, a disease distinct from the western type. It is likely that patients formerly diagnosed with Castleman's disease with good response to glucocorticoid treatment may have had IgG4-related lymphadenopathy, and should be re-assessed in light of recent findings. Diagnosis of IgG4-related disease is characterized by both 1) elevated serum IgG4 (>135 mg/dl) and 2) histopathological features including lymphocyte and $IgG4^+$ plasma cell infiltration ($IgG4^+$ plasma cells/IgG^+plasma cells >40% on a highly-magnified slide checked at five points). Differential diagnosis from other distinct disorders, such as sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, cancer, and other existing conditions that show the high serum IgG4 level or abundant IgG4-bearing plasma cells in tissues is necessary.

Keywords: Mikulicz's disease, Küttner's tumor, autoimmune pancreatitis, Castleman's disease, Sjögren's syndrome, IgG4-related diseases.

1. INTRODUCTION

Since Hamano *et al.* first reported hyper-IgG4 gammaglobulinemia in sclerosing pancreatitis in 2001 [1], various systemic conditions correlating with IgG4 have been described. Since these conditions usually coexist with each other, various term have been proposed as systemic conditions. The most classical one is "multifocal idiopathic fibrosclerosis (MIF)" that was reported by Comings *et al.* [2], although association with IgG4, of course, have not been known. In the IgG4-era, Kamisawa *et al.* reported IgG4-related autoimmune disease [3] or IgG4-related sclerosing disease [4], Yamamoto *et al.* reported IgG4-related plasmacytic disease [5] or systemic IgG4 plasmacytic syndrome (SIPS) [6], and we proposed IgG4-related multiorgan lymphoproliferative syndrome ($IgG4^+$MOLPS) [7]. All of these terms refer to the same conditions, confusing the understanding of IgG4-related diseases.

Multicenter clinical research is ongoing in Japan, and multicenter prospective clinical trials (UMIN: R000002820, R000002823) have been designed to formulate better diagnostic criteria, to identify novel diagnostic and prognostic factors, and to design better treatment strategies for IgG4-related disease.

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2. SJÖGREN'S SYNDROME AND MIKULICZ'S DISEASE OR KÜTTNER'S TUMOR

In 1892, Mikulicz described a male patient with symmetrical lacrimal, parotid and submandibular glands [8], a condition since called Mikulicz's disease. However, Morgan *et al.* have 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) in 1953 [9]. Due to the wide acceptance of these conclusions, there have been few reports regarding MD in western countries. However, many cases of MD have been reported in Japan, and there has been debate regarding the differences and similarities between MD and SS. More recently, MD was reported to be a type of IgG4-related disease [10].

To assess the clinicopathological characteristics of IgG4-related diseases, we established, in September 2004, the $IgG4^+$MOLPS/Mikulicz's disease research group as a part of the Japanese Sjögren's syndrome research group, and we started a retrospective clinical study. Furthermore, as so-called MD may include various conditions and consist of IgG4-related and unrelated subtypes, we established tentative criteria for $IgG4^+$MD (See Yamamoto M, *et al.* Mikulicz's disease and its extraglandular lesion, in this issue).

Of the 140 patients with possible IgG4-related diseases, 114 were diagnosed with $IgG4^+$MOLPS using our tentative diagnostic criteria (Table **1**). We retrospectively analyzed the

1573-3955/11 $58.00+.00

differences between patients with IgG4-related diseases and those with definite SS. This analysis showed many differences between the two groups; 1) The gender distribution was quite different. Male patients with SS are very rare (2 of 31), whereas about half (60 of 114) of patients with IgG4-related diseases were male; 2) Significantly fewer patients with IgG4-related diseases than with SS had symptoms of xerostomia, xerophthalmia, and arthralgia (Fig. **1a**); 3) The incidences of rheumatoid factor (RF), anti-nuclear antibody (ANA), anti-SS-A/Ro antibody, and anti-SS-B/La antibody were significantly lower in patients with IgG4-related diseases than in those with SS (Fig. **1b**); 4) Not only IgG4 but total IgG, IgG2, and IgE levels were significantly higher in patients with IgG4-related diseases than in SS (Fig. **1c**, **d**); 5) Histological specimens from patients with IgG4-related diseases showed marked $IgG4^+$ plasma cell infiltration, with occasional lymphocytic follicle formation, but without lymphoepithelial lesions; this may explain the marked swelling of the glands without symptoms of severe dryness in patients with IgG4-related diseases; 6) Glucocorticoid treatment of patients with IgG4-related diseases resulted in marked clinical improvements in almost all (Fig. **2a**), whereas the effects of glucocorticoids on SS are not so dramatic. We concluded that IgG4-related diseases and SS are different conditions, with distant clinical and pathological characteristics, despite similarities in involved organs [7].

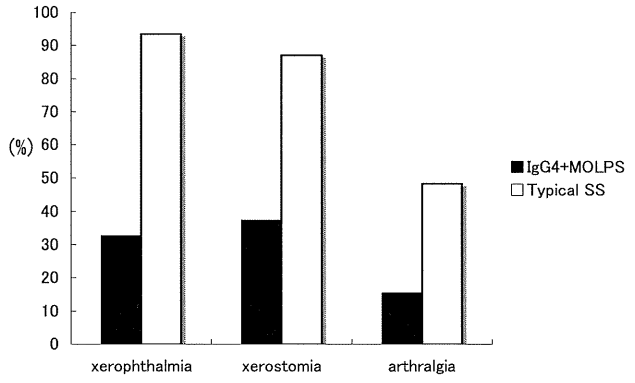

Fig. (1a). Symptoms of $IgG4^+$MOLPS and Typical SS. Significant fewer patients with $IgG4^+$MOLPS than with SS showed symptoms of xerostomia, xerophthalmia, and arthralgia.

Küttner's tumor, a unilateral sclerosing inflammation of the submandibular gland, has also been reported to be an IgG4-related disease [11]. Mikulicz's disease and Küttner's tumor are similar because both are IgG4-related sialadenitis. Histologic examination of Küttner's tumor showed $IgG4^+$ plasma cells surrounded by severe fibrotic lesions. In contrast, fibrosis is not so severe in the tissue of MD patients. However, we could not clearly distinguish between these two conditions and suspected that they occur sequentially. The severity of fibrosis of the major and minor salivary glands in patients with MD has been found to differ. Moreover, since MD patients are usually diagnosed by biopsy of the labial minor salivary glands, fibrosis may have been underestimated.

What are the most particular differences between IgG4-related diseases and SS? In addition to those mentioned above, patients with SS must have dacryoadenitis and sialadenitis even if they show subclinical symptoms, whereas only some parts of patients of IgG4-related disease associate with dacryoadenitis and/or sialadenitis, and are diagnosed as MD or Küttner's tumor.

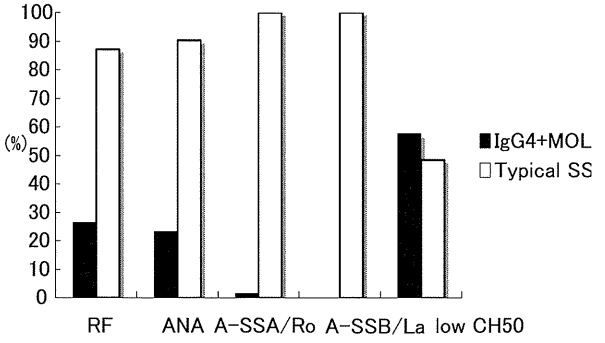

Fig. (1b). Autoantibodies and low CH50 in $IgG4^+$MOLPS and Typical SS. The incidences of rheumatoid factor (RF), anti-nuclear antibody (ANA), anti-SS-A/Ro antibody, and anti-SS-B/La antibody were significantly lower in $IgG4^+$MOLPS than in SS patients. Low CH50 was observed in almost half of $IgG4^+$MOLPS patients.

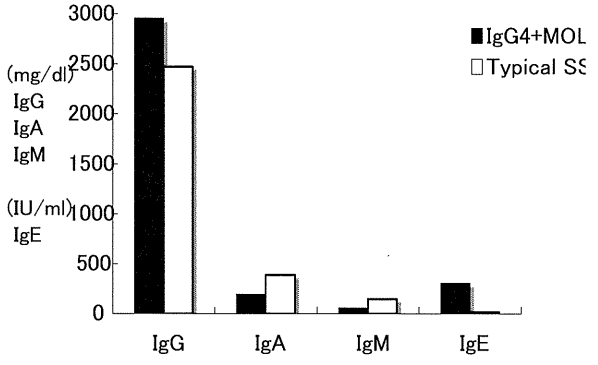

Fig. (1c). Immunoglobulin classes in $IgG4^+$MOLPS and Typical SS. Total IgG, and IgE concentrations were significantly higher in $IgG4^+$MOLPS than in typical SS patients. In contrast, IgA and IgM concentrations were significantly lower in $IgG4^+$MOLPS than in typical SS patients.

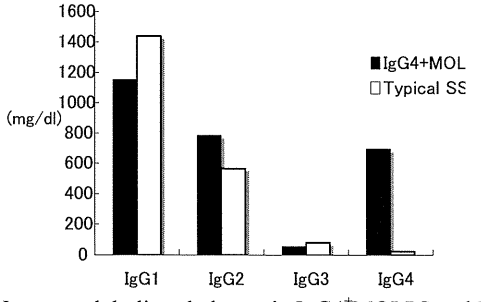

Fig. (1d). Immunoglobulin subclasses in $IgG4^+$MOLPS and Typical SS. Both IgG4 and IgG2 concentrations were significantly higher in $IgG4^+$MOLPS than in typical SS patients. In contrast, IgG and IgG3 levels were significantly lower in $IgG4^+$MOLPS than in typical SS patients.

3. IgG4-RELATED PANCREATITIS (SO-CALLED AUTOIMMUNE PANCREATITIS)

Autoimmune pancreatitis (AIP), first described in 1961, is a unique form of chronic pancreatitis characterized by

infrequent attacks of abdominal pain, jaundice, irregular narrowing of the pancreatic duct, and swelling of the pancreatic parenchyma [1, 12-17]. The first definitive description of a patient with AIP disclosed that the patient had swelling of the lacrimal glands, salivary glands and pancreas, and was diagnosed with a mass-forming pancreatitis associated with SS [13]. Patients who also had similar pathological features in the common bile duct, gallbladder, and minor salivary glands, were later described, suggesting a systemic disorder [14]. Typical features of AIP include hyper-gammaglobulinemia, the presence of autoantibodies (rheumatoid factor; RF and anti-nuclear antibody; ANA), lymphocytic infiltration of the pancreatic tissue, coexistence of other manifestations, such as sicca complex, and good responsiveness to glucocorticoids [15]. Histopathological examination of the pancreas of AIP patients demonstrate marked fibrosis and prominent infiltration of lymphocytes and plasma cells, which is called lymphoplasmacytic sclerosing pancreatitis (LPSP). Since high serum IgG4 concentrations in patients with sclerosing pancreatitis were first reported in 2001 [1], AIP in Japan subsequently considered an IgG4-related disease.

Table 1. Proposed Diagnostic Criteria of IgG4$^+$MOLPS Diagnosis of IgG4$^+$MOLPS is Defined with Both 1) and 2)

1) Elevated serum IgG4 (>135 mg/dl)
AND
2) Histopathological features including lymphocyte and IgG4$^+$ plasma cell infiltration (IgG4$^+$ plasma cells/IgG$^+$plasma cells >40%) with typical tissue fibrosis or sclerosis.

Note:

- It is necessary to distinguish IgG4$^+$MOLPS from other distinct disorders, including sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer.
- Patients fulfilling only one of the above criteria are classified as "suspected IgG4$^+$MOLPS".
- Patient fulfilling both (1) and (2) and having other distinct disorders (designated as "XX"), are classified as having "XX disease with suspected association with IgG4$^+$MOLPS".
- Patients diagnosed with IgG4$^+$MOLPS, but refractory to glucocorticoid treatment, should be re-diagnosed.

AIP has also been reported in western countries [16, 17], and differences in clinicopathological features between western (especially European) and Japanese AIP patients have been described. Some AIP in western countries is associated with the involvement of neutrophilic granulocytes and is called idiopathic duct-centric chronic pancreatitis (IDCP) [16] or autoimmune pancreatitis with granulocytic epithelial lesion (GEL) [17], a condition that differs from IgG4-related AIP. Although the diagnostic criteria for AIP worldwide are under discussion, IgG4-related disease (LPSP) and neutrophilic granulocyte disease (GEL) differ and should be considered as separate entities (Table **2**).

Using MacKay's criteria for autoimmune diseases, IgG4-related sclerosing pancreatitis may be compatible with common autoimmune diseases, since it is characterized by hypergammaglobulinemia; lymphocytic infiltration into tissues; and good responsiveness to glucocorticoids. However, IgG4-related sclerosing pancreatitis is not compatible with common autoimmune disease since the presence of autoantibodies, such as RF and ANA, is significantly lower than in SS, and no disease-specific autoantibodies have been reported. Moreover, IgG4-related sclerosing pancreatitis is associated with MD not SS. Thus, it remains to be elucidated that IgG4-related sclerosing pancreatitis is an "autoimmune" disorder or not.

Table 2. Differences Between LPSP and IDCP (GEL) Histopathological Presentations of the Autoimmune Pancreatitis

	LPSP	IDCP (GEL)
Age	Elderly	Young adult
Sex	Male dominant	No gender bias
Distribution	Whole world	Western countries
Serum IgG4	Elevated	Not elevated
Infiltrating cells	IgG4+plasma cells	Granulocytes
Complication	Various general disorders	Inflammatory bowel disease

LPSP, lymphoplasmacytic sclerosing pancreatitis; IDCP, idiopathic duct-centric chronic pancreatitis; GEL, autoimmune pancreatitis with granulocytic epithelial lesion.

4. IgG4-RELATED DISEASE AND CASTLEMAN'S DISEASE, CROW - FUKASE SYNDROME, WEGENER'S GRANULOMATOSIS, SARCOIDOSIS, ETC.

Some patients with IgG4-related disease are characterized primarily by lymphadenopathy (Fig. **2a**) [18], which may differ from that observed in patients with multicentric Castleman's disease (MCD). MCD in western countries is usually associated with acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV) infection. Furthermore, most patients with HIV-positive MCD, and 40% of patients with HIV-negative MCD, are also positive for human herpesvirus-8 (HHV-8) [19]. In contrast, patients diagnosed with MCD in Japan are usually negative for both HIV and HHV-8, suggesting differences in MCD in western and Japanese patients. Japanese patients diagnosed with MCD and who show good response to glucocorticoid treatment, should be reassessed to determine whether they actually had IgG4-related diseases. Although the clinical and pathological features of IgG4-related diseases and MCD are similar, differential diagnosis is important, because patients with MCD show a suboptimal response to glucocorticoid, and also require treatment with anti-IL-6 receptor antibody (tocilizumab) [20]. Both conditions are characterized by polyclonal hypergammopathy and mass formation in various organs. Patients with IgG4-related disease are characterized primarily by hyper-IgG4-gammaglobulinemia and IgG4+ plasma cell infiltration (Fig. **2b**), with occasional mild elevation of serum IL-6, with relatively mild inflammation (CRP elevation) and anemia [6]. In contrast, MCD patients showed markedly elevated serum IL-6 and marked inflammation (elevated CRP and fibrinogen), anemia, thrombocytosis and hypoalbuminemia [20]. Since, some MCD patients also show hyper-IgG4-gammaglobulinemia [21] and/or IgG4+ plasma cell infiltration, differential diagnosis may be difficult in some patients. Patients who demonstrate severe inflammatory responses with hyper-IL-6 should be diagnosed with MCD rather than with IgG4-related diseases.

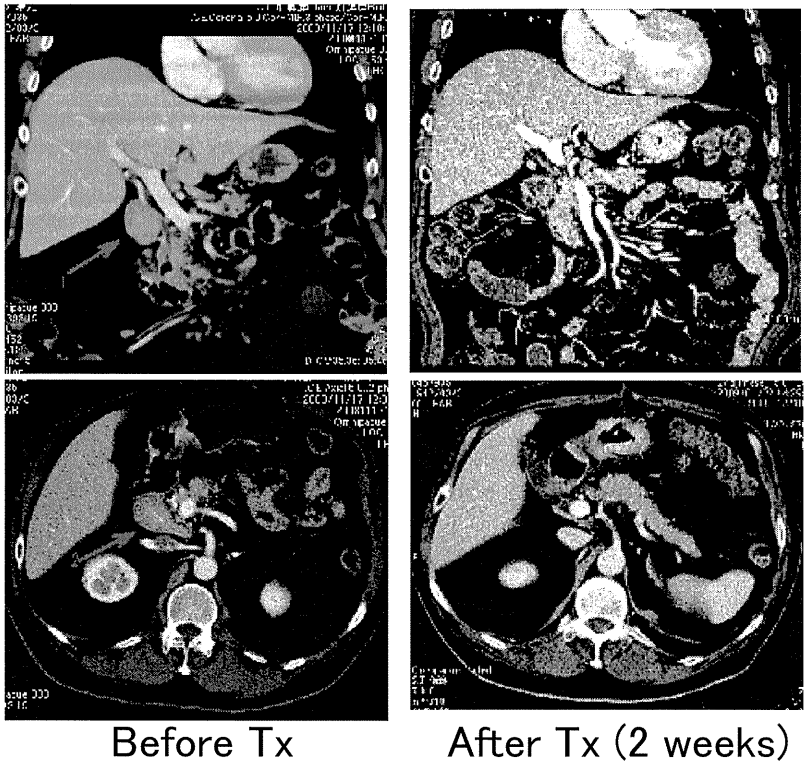

Fig. (2a). Abdominal enhanced CT in patient with IgG4-related lymphadenopathy. Abdominal lymph node swelling completely disappeared after treatment with glucocorticoids for two weeks.

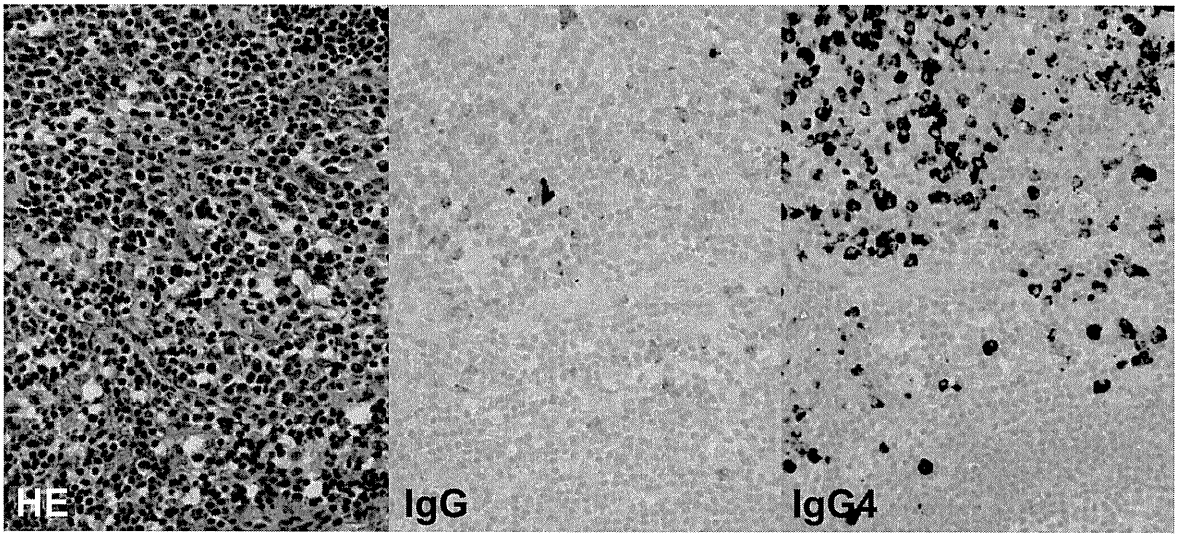

Fig. (2b). Histopathological fingings of abdominal lymphnode. Many plasma cells were scattered around the lymphoid follicle, and the majority of plasma cells were IgG and IgG4 positive.

Although it may be difficult to distinguish MCD from IgG4-related diseases, other polyclonal hypergammopathies, such as Crow-Fukase syndrome, Wegener's granulomatosis [22] and sarcoidosis, may also demonstrate hyper-IgG4-gammaglobulinemia and/or IgG4+ plasma cell infiltration, making these differential diagnoses more difficult.

5. IgG4-RELATED DISEASE AND LYMPHOMA OR CANCER

Patients with SS are at a high risk of lymphoma, 6.5 to 18.8-fold higher than in the general population according to a recent meta-analysis, and long-term lymphocyte activation may cause lymphoma [23, 24]. In contrast, the risk of lymphoma development in patients with IgG4-related diseases has not yet been determined. Since some lymphomas have been associated with IgG4-related diseases, we should examine the association between lymphoma and IgG4-related disease, especially in patients with ocular adnexa [25, 26]. Although B-cells in the majority of patients with IgG4-related diseases are polyclonal [27], prolonged activated inflammation in these patients may cause lymphocytic monoclonality, as it dose in patients with SS. Furthermore, MALT lymphomas associated with SS have

been reported to develop from lymphoepithelial lesions formed primarily by lymphocytic infiltration toward ductal cells in the salivary gland. In IgG4-related diseases, however, formation of lymphoepithelial lesions is rare, even in patients with severe lymphocytic infiltration. Thus, the source of lymphomas in patients with IgG4-related disease is unclear and the pathophysiology of lymphoma development may differ between SS and IgG4-related disease.

Differential diagnosis for IgG4-related disease is important in some lymphomas, especially if tumor-related hypercytokinemia causes polyclonal hypergammaglobulinemia, as observed in angioimmunoblastic T-cell lymphomas, which may demonstrate hyper-IgG4 gammopathy and IgG4+ plasma cell infiltration into tissues. To distinguish between these two conditions in difficult cases, it is necessary to confirm the rearrangement of the T-cell receptor gene.

The risk of cancer development in patients with IgG4-related diseases is not known. However, every patient with sclerosing pancreatitis must be carefully diagnosed, to distinguish this condition from pancreatic cancer. Some patients with solid tumors have been reported to have hyper-IgG4 gammopathy and IgG4+plasma cell infiltration into tissues [28, 29]. Early diagnosis and treatment of cancer is important, even in patients suspected of having IgG4-related disease.

6. IgG4-RELATED DISEASE AND OTHER SYSTEMIC COMPLICATIONS – IMPORTANCE OF COMPREHENSIVE DIAGNOSTIC CRITERIA

In addition to sclerosing dacryoadenitis, sialadenitis (MD [5, 7, 10] and Küttner's tumor [11]), sclerosing pancreatitis (Japanese type of AIP) [1, 3, 4], and lymphadenopathy [18] IgG4 has been associated with sclerosing cholangitis [3, 30], inflammatory pseudotumor of the lungs [31], liver [30], and breasts [30, 32], retroperitoneal or mediastinal fibrosis [33], interstitial nephritis [34-36], hypophysitis [5], inflammatory aortic aneurysm [37, 38], tumorous lesions of the coronary artery [38], hypertrophic pachymeningitis [39], skin lesions [40], arthritis, thyroiditis [41], and prostatitis [42], and other inflammatory conditions. Although the proposed diagnostic criteria of IgG4+MD [43] and AIP [44, 45] are distinct, attempts are underway to formulate diagnostic criteria for each organ associated with IgG4. The involvement of a particular organ may cause particular symptoms, and the ease and safety of obtaining biopsy material are different in each organ. Principles for the diagnostic criteria of IgG4-related diseases in general must be defined. One such candidate is our diagnostic criteria for IgG4$^+$MOLPS [7] (Table **1**). IgG4-related disease is a distinct clinicopathological entity characterized by hyper-IgG4-gammopathy and IgG4+plasma cell infiltration into tissues, is distinguished from other distinct disorders, and shows good response to treatment with glucocorticoids. Organs difficult to biopsy can be assessed by imaging methodologies, such as ultrasonography (US), computed tomography (CT), magnetic resonance computed tomography (MRCT) or 2-fluoro-2-D-glucose positron emission tomopgaphy (^{18}FDG-PET), for diagnosis, but efforts should be made to obtain biopsy samples. It is important to distinguish IgG4-related disease from MCD, lymphoma, and solid tumors. In addition, patients diagnosed with IgG4-related disease, but refractory to glucocorticoid treatment, should be re-diagnosed.

Although no other key molecules have been identified in sera or tissues, most researchers suspect that IgG4 itself is not the main cause of pathogenesis in IgG4-related diseases, and that upstream molecules may regulate this condition. Antibodies against *Helicobacter pylori* peptides (anti–PBP antibodies) have been detected recently in patients with AIP [46], although caution is necessary in interpreting these results because many of these patients had inflammatory bowel disease, suggesting the European type of AIP [16, 17]; that is, neutrophil granulocytic, not IgG4-related lesions. The identification of additional key molecules may enable these markers to be used as diagnostic criteria, and invasive biopsy may not be unnecessary. Until then, it is important not to over-diagnose IgG4-related disease and to keep in mind the present concept of IgG4-related disease, including high-IgG4 concentrations in sera and tissues, differential diagnosis and good response to glucocorticoid treatment.

ACKNOWLEDGEMENTS

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

THE SOURCES OF SUPPORT IN THE FORM OF GRANTS

This work was supported by grants from Intractable Diseases, the Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare and the Japanese Ministry of Education, Culture, Sports, Science and Technology (13557160, 15024236, 15390313, and 13877075 to Umehara and 17591060 to Masaki), the Uehara Memorial Foundation (to Umehara), the Vehicle Racing Commemorative Foundation, and the Kanazawa Medical University Research Foundation (C2009-4 to Umehara and S2004-16 and S2007-5 to Masaki).

ABBREVIATIONS

MOLPS	=	Multiorgan lymphoproliferative syndrome
MD	=	Mikulicz's disease
SS	=	Sjögren's syndrome
RF	=	Rheumatoid factor
ANA	=	Anti-nuclear antibody
AIP	=	Autoimmune pancreatitis
LPSP	=	Lymphoplasmacytic sclerosing pancreatitis
IDCP	=	Idiopathic duct-centric chronic pancreatitis
GEL	=	Autoimmune pancreatitis with granulocytic epithelial lesion
MCD	=	Multicentric Castleman's disease

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Received: December 12, 2009 Revised: April 8, 2010 Accepted: August 27, 2010

J Clin Exp Hematopathol
Vol. 51, No. 1, May 2011

Review Article

IgG4-Related Disease : A Novel Lymphoproliferative Disorder Discovered and Established in Japan in the 21st Century

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IgG4-related disease is a novel lymphoproliferative disorder that shows hyper-IgG4-γ-globulinemia and IgG4-producing plasma cell expansion in affected organs with fibrotic or sclerotic changes. Patients show systemic inflammatory conditions and various symptoms depending on the affected organ. Since the first report of patients with elevated serum IgG4 in sclerosing pancreatitis in 2001, various systemic disorders described by many names have been reported. Despite similarities in the organs involved in IgG4-related Mikulicz's disease and Sjögren's syndrome, there are marked clinical and pathological differences between these conditions. Most patients diagnosed with autoimmune pancreatitis in Japan have IgG4-related pancreatitis [Type 1 autoimmune pancreatitis (AIP), lymphoplasmacytic sclerosing pancreatitis (LPSP)], a disease distinct from some of the western type [Type 2 AIP, idiopathic duct-centric chronic pancreatitis (IDCP), autoimmune pancreatitis with granulocytic epithelial lesions (GEL)]. Diagnosis of IgG4-related disease is characterized by both elevated serum IgG4 (>135 mg/dL) and histopathological features including lymphocyte and $IgG4^+$ plasma cell infiltration ($IgG4^+$ plasma cells/IgG^+ plasma cells> 40%). Differential diagnosis from other distinct disorders, such as sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, cancer, and other existing conditions associated with high serum IgG4 level or abundant IgG4-bearing plasma cells in tissues is necessary. We have begun a clinical prospective study to establish a treatment strategy (Phase II prospective treatment study for IgG4-multiorgan lymphoproliferative syndrome : UMIN R000002311). 〔*J Clin Exp Hematopathol 51(1) : 13-20, 2011*〕

Keywords: Mikulicz's disease, Sjögren's syndrome, autoimmune pancreatitis, Castleman's disease, glucocorticoid

WHAT IS IgG4-RELATED DISEASE ?

IgG4-related disease is a lymphoproliferative disorder that shows hyper-IgG4-γ-globulinemia and IgG4-producing plasma cell expansion in affected organs with fibrotic or sclerotic changes. Patients show systemic inflammatory conditions and various symptoms depending on the affected organ. Although the lacrimal glands, salivary glands, and pancreas are the major affected organs, the involvement of various other organs has been reported, and it is questionable whether all of these represent the same conditions. Another feature of IgG4-related disease is particular glucocorticoid responsiveness. Furthermore, spontaneous regression without any treatment may occur. Thus, the most important purpose of diagnosis of IgG4-related disease is the definition of therapeutic strategy. There are a number of disorders with similar characteristics, and differential diagnosis must be made for diseases with poor responsiveness to glucocorticoid or different clinical courses.

We are now conducing multicentric cooperative research and continuing critical discussion regarding this condition, with financial support from Intractable Diseases, Health, and Labor Sciences Research Grants from the Ministry of Health, Labor, and Welfare to two groups led by Prof. Kazuichi Okazaki and by Prof. Hisanori Umehara.

There are many synonyms because IgG4-related disease is a systemic disease, such as IgG4-multiorgan lymphoproliferative syndrome ($IgG4^+$ MOLPS),[1] IgG4-related sclerosing disease,[2] systemic IgG4-related plasmacytic syndrome (SIPS),[3] *etc.* As the use of many different names for the same disease entity causes confusion and misunderstanding, the standardized official term "IgG4-related disease" was decided upon at the second meeting of the Umehara group on 11 Feb 2010.[4]

Received : October 15, 2010
Accepted : October 20, 2010
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DIAGNOSIS OF IgG4-RELATED DISEASE

Although IgG4-related disease is a newly defined clinical entity and is not yet well known, it is not an extremely rare condition. The incidence rate of new cases of IgG4-related disease calculated using the data for Ishikawa prefecture is 2.63-10.2 per 1 million people ; therefore, 336 to 1,300 new cases may develop every year in Japan (reported by Suzuki R, *et al.*).[4] Even if there are some differences in local distribution of incidence, several new cases may be encountered at main hospitals, such as university hospitals.

Similar to other diseases, it is not possible for physicians to make a correct diagnosis if they do not suspect a particular clinical entity and if there is no established diagnostic approach for IgG4-related disease. Although it is not so difficult for physicians to suspect IgG4-related disease if they have some experience with typical cases, it is difficult to make a diagnosis on first encountering this disease. Therefore, we proposed diagnostic criteria for IgG4$^+$ MOLPS and prepared diagnostic guidelines (Table 1).[5]

Diagnosis of IgG4-related Mikulicz's disease

Mikulicz's disease (MD) is a clinical condition that shows bilateral symmetrical dacryoadenitis (swelling of the lacrimal glands) and sialadenitis (swelling of the parotid glands and submandibular glands). Since Morgan *et al.* reported that MD is not a distinct clinical and pathological disease but is merely one manifestation of a more generalized symptom complex known as Sjögren's syndrome (SS),[6] MD has attracted very little interest in western countries. However, MD has attracted attention and been reported in Japan. Yamamoto *et al.* reported that MD is also a subtype of IgG4-related disease,[7] and an IgG4$^+$ MOLPS/MD research group was organized in September 2004 to perform a retrospective national study. The results of this study revealed many differences between MD and SS[1,8] : 1) male SS patients are very rare, but almost half of MD patients are male ; 2) swelling of glands (lacrimal, parotid, and submandibular) is remarkable, but symptoms of dryness (xerostomia, xerophthalmia) are unobtrusive in patients with IgG4$^+$ MD ; 3) the incidence of autoantibodies is lower in patients with IgG4$^+$ MD than in SS (the incidence of rheumatoid factor and anti-nuclear antibodies in IgG4$^+$ MD is almost one quarter that in SS, and most cases of IgG4$^+$ MD are negative for anti-SSA antibodies and anti-SSB antibodies) ; 4) serum IgG4 level is high and IgG4$^+$ plasma cell concentration is high in IgG4$^+$ MD ; and 5) rates of allergic rhinitis and bronchial asthma, serum IgE concentrations, and eosinophil count among white blood cells are higher in IgG4$^+$ MD than in SS, suggesting the involvement

Table 1. Proposed diagnostic criteria for systemic IgG4-related diseases : IgG4$^+$ MOLPS (the grant from Intractable Diseases, Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare. Entitled the research for establishing a novel disorder, IgG4-related multiorgan lymphoproliferative syndrome ; IgG4$^+$ MOLPS ; Umehara's group). Diagnosis of IgG4$^+$ MOLPS is defined with both 1) and 2)

1) Elevated serum IgG4 (>135 mg/dL)
AND
2) Histopathological features including lymphocyte and IgG4$^+$ plasma cell infiltration (IgG4$^+$ plasma cells/IgG$^+$ plasma cells>40%) with typical tissue fibrosis or sclerosis.

Note :
- It is necessary to distinguish IgG4$^+$ MOLPS from other distinct disorders, including sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer.
- Patients fulfilling only one of the above criteria are classified as "suspected IgG4$^+$ MOLPS."
- Patient fulfilling both (1) and (2) and having other distinct disorders (designated as "XX"), are classified as having "XX disease with suspected association with IgG4$^+$ MOLPS."
- Patients diagnosed with IgG4$^+$ MOLPS, but refractory to glucocorticoid treatment, should be re-diagnosed.

Diagnostic guideline ; Suspicious of IgG4$^+$ MOLPS

1. Presence of only one can be enough the suspicious IgG4$^+$ MOLPS lesion.
   1) Symmetrical swelling of one of the lacrimal, parotid or submandibular glands
   2) Autoimmune pancreatitis
   3) Inflammatory pseudotumor
   4) Retroperitoneal fibrosis
   5) Histopathological findings are similar to lymphoplasmacytosis or suspected Castleman's disease.
2. Presence of at least two would be sufficient for suspected IgG4$^+$ MOLPS.
   1) unilateral swelling of one of the lacrimal, parotid, or submandibular glands ; 2) orbital tumorous lesion, 3) autoimmune hepatitis, 4) sclerosing cholangitis, 5) prostatitis, 6) patchy meningitis, 7) interstitial pneumonitis, 8) interstitial nephritis, 9) mediastinal fibrosis, 10) thyroiditis or hypothyroidism, 11) hypophysitis, 12) inflammatory aneurysm.
3. Common findings in patients with IgG4$^+$ MOLPS.
   1) polyclonal hyper-IgG-gammopathy, 2) elevation of serum IgE or eosinophilia, 3) hypocomplementemia or presence of immune complex in serum, 4) tumorous lesion or lymphadenopathy with strong accumulation in ^{67}Ga-scan or ^{18}FDG-PET-scan

of allergic factors in this disease.

The majority of MD patients suffer IgG4-related dacryoadenitis and sialadenitis, but other conditions, such as SS, sarcoidosis, and lymphoma (especially, mucosa-associated lymphoid tissue, MALT lymphoma) may present symmetrical swelling of lacrimal and salivary glands. Thus, the clinical definition of IgG4-negative MD is still a contentious issue.

We have proposed diagnostic criteria for $IgG4^+$ MD as part of the $IgG4^+$ MOLPS/MD research group, which were approved by the Japanese Sjögren's Syndrome Society at the meeting in September 2008 (Table 2).[5] The therapeutic effect of glucocorticoid treatment in SS is insufficient, and use of glucocorticoid is not generally recommended due to its adverse effects. In contrast, glucocorticoid therapy can reduce $IgG4^+$ MD patients' symptoms dramatically, so we strongly recommend its use. This is therefore an important criterion because it is related to therapeutic strategy.

For diagnosis, high serum concentration of IgG4 (>135 mg/dL) or histopathological findings of $IgG4^+$ plasma cell infiltration in swollen lacrimal, parotid, or submandibular glands ($IgG4^+$ plasma cells/IgG^+ plasma cells > 40%, in 5 high-power fields) is required. As biopsy may be invasive and may cause some complications, informed consent is required following extensive discussion with an ophthalmologist and/or otorhinolaryngologist. Minor salivary gland biopsy may sometimes be substituted when biopsy of major salivary glands is difficult. The sensitivity of detection of $IgG4^+$ plasma cells is relatively low (although this is sometimes sufficient for diagnosis), and sclerosis/fibrosis is unremarkable in minor salivary gland specimens.

Diagnosis of type 1 autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is a pancreatitis that is suspected autoimmune mechanism with symptoms similar to those of pancreatic cancer ; therefore, differential diagnosis between these conditions is critical.

This pathology was named lymphoplasmacytic sclerosing pancreatitis (LPSP) by Kawaguchi in 1991,[9] and is characterized by massive lymphocyte and plasma cell infiltration, fibrosis that focally gives rise to a swirling pattern (storiform fibrosis), focal destruction of pancreatic acini, and replacement with fibrosis. The same inflammatory process is observed around the main and interlobular ducts, leaving the duct epithelium and lumen intact. Veins are obliterated by the same inflammatory process (obliterative phlebitis).

In 1995, Yoshida *et al.* proposed the concept of AIP because these patients had hyper-γ-globulinemia, various autoantibodies, lymphocytic infiltration into pancreatic tissue, complication with other autoimmune diseases, and good glucocorticoid responsiveness, which fulfilled MacKay's criteria for autoimmune disease.[10] Diagnostic criteria for AIP were later proposed twice (in 2002 and 2006) by the Japan Pancreas Society (Table 3).[11]

As Hamano *et al.* reported high serum IgG4 concentration in AIP patients[12] and patients were shown to have IgG4-producing plasma cell infiltration in pancreatic tissue,[13] serum and tissue IgG4 became key markers for diagnosis of AIP.

Although AIP has also been reported in western countries, some cases of AIP, especially in Europe, appeared in younger patients and were sometimes complicated with inflammatory bowel diseases ; therefore, at least some of these cases appear to represent a different disorder from AIP in Japan. Histopathologically, some cases of AIP reported in western countries are "idiopathic duct-centric chronic pancreatitis (IDCP)"[14] or "autoimmune pancreatitis with granulocytic epithelial lesions (GEL),"[15] which are caused by neutrophilic granulocyte infiltration and are not related to IgG4. Chari *et*

Table 2. Diagnostic criteria of systemic IgG4-related Mikulicz's disease (Japanese Society of Sjögren's Syndrome, Sep 2008)

1) Persistent (>3 months), symmetrical swelling of the lacrimal, parotid, and submandibular glands, involving at least two pairs.
2) Serologically high levels of immunoglobulin (Ig) G4 (≥135 mg/L).
3) Marked IgG4-positive plasmacyte infiltration (≥40% IgG4-positive/IgG-positive cells in five high-power fields) into lacrimal and salivary gland tissues.

In terms of diagnosis, IgG4-related Mikulicz's disease is defined as satisfying Item 1 and either Item 2 and/or 3. This form of systemic IgG4-related disease is often accompanied by lesions in multiple organs. Sarcoidosis, Castleman's disease, Wegener's granulomatosis, and malignant lymphoma need to be considered as differential diagnoses.

Table 3. Clinical diagnostic criteria for autoimmune pancreatitis 2006 (The research group of refractory pancreatic disease, grant from the Ministry of Health, Labor and Welfare. Japan Pancreas Society)[11]

1) Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas by imaging studies, such as abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI).
2) High serum γ-globulin, IgG or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor.
3) Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas.

For diagnosis, criterion 1 must be present, together with criterion 2 and/or criterion 3. Diagnosis of autoimmune pancreatitis is established when criterion 1, together with criterion 2 and/or criterion 3, are fulfilled. However, it is necessary to exclude malignant diseases, such as pancreatic or biliary cancers.

al. referred to IgG4-related AIP (LPSP) as type 1 and neutrophilic granulocyte lesions of AIP (IDCP, GEL) as type 2 (Table 4).[16] Although these two entities are similar in their good glucocorticoid responsiveness, they are completely different disorders so using the same disease category seems to be inappropriate.

Several international meetings have been held to determine diagnostic criteria for AIP,[17] but a final decision has yet to be made. The consensus regarding type 1 AIP is swelling of the pancreas, hyper-IgG4-γ-globulinemia, pathological features of LPSP, including fibrosis, obliterative phlebitis, and $IgG4^+$ plasma cell infiltration, and good glucocorticoid responsiveness. However, the pancreas is an organ from which sufficient biopsy specimens are difficult to obtain using standard procedures, except open laparotomy. Many Japanese physicians and researchers seem to exclude addition of glucocorticoid responsiveness to the diagnostic criteria of type 1 AIP without sufficient imaging examination, including endoscopic retrograde cholangiopancreatoscopy (ERCP). In contrast, because invasive examinations including ERCP are rarely performed in western countries, many researchers and physicians have proposed adding glucocorticoid responsiveness to the criteria. This controversy makes it difficult to reach a consensus.

IgG4-related disease and other organ involvement

Reports of IgG4-related disease in type 1 AIP are followed by cholangitis, cholecystitis, dacryoadenitis,[1,2,8,18] sialadenitis,[1,2,8] retroperitoneal fibrosis, mediastinal fibrosis, tubulointerstitial nephritis,[19] pulmonary lesions such as interstitial pneumonitis, inflammatory pseudotumor of the lung, liver, or breast, lymphadenopathy,[18] hypophysitis, pachymeningitis, arthritis, skin lesions, inflammatory aortic aneurysm, tumorous lesion of coronary artery, some types of autoimmune hepatitis, thyroiditis, prostatitis, gastritis, major duodenal papilla lesions, colitis or colon polyps, pouchitis, *etc.*

IgG4-related disease occurs in various systemic organs, and as the difficulty and invasiveness of biopsy procedures differ among organs, the diagnostic criteria may also differ for each organ. As a systemic disorder, both serum and histopathological findings (Fig. 1) should be present, such as our criteria for $IgG4^+$ MOLPS (Table 1).[5]

With regard to the diagnostic criteria of $IgG4^+$ MD, the involved organs, *i.* e., the lacrimal and/or salivary glands, are located relatively close to the body surface. Therefore, histopathological findings are important for diagnosis. However, both clinical disease distribution and serum data can also be used for diagnosis of $IgG4^+$ MD.

For diagnosis of AIP, however, it is extremely difficult to obtain biopsy tissue samples from the pancreas. Therefore, diagnosis is centered around serum data, pathological findings, imaging examination, and/or glucocorticoid responsiveness, as mentioned above.

For diagnosis in other organs, although it is important to obtain biopsy specimens, it may be difficult to perform biopsy of deep lesions, such as those in the retroperitoneum, aorta, hypophysis, or dura mater in addition to the pancreas. Therefore, serum data and imaging findings must be considered. Occasionally, patients are diagnosed with a solitary lesion, but the majority of cases have multiple organ involvement. Therefore, it may be possible to obtain biopsy specimens from organs that can be reached more easily and in a less invasive manner, and to examine the distribution of lesions by 2-deoxy-2-(^{18}F) fluoro-D-glucose-positron emission tomography (^{18}FDG-PET) scan, ^{67}Garium-scan, *etc.*, and finally to estimate glucocorticoid responsiveness.

Related groups are working to develop diagnostic criteria and guidelines for IgG4-related nephropathy and IgG4-related lung disease, as subsidiaries of the Umehara group of Health and Labor Sciences Research Grants from Ministry of Health, Labor and Welfare. These groups are also collaborating with the Japanese Society of Nephrology and the Japanese Respiratory Society, respectively.

An international conference of IgG4-related disease will be held in Boston, USA, in October 2011. Before this conference, selected members of Japanese researchers will meet and

Table 4. Differences between Type 1 (LPSP) and Type 2 (IDCP, GEL) histopathological presentations of the autoimmune pancreatitis.

	Type 1	Type 2
Age	Elderly	Young adult
Sex	Male dominant	No gender bias
Distribution	Whole world	Western countries
Serum IgG4	Elevated	Not elevated
Histopathology	LPSP	IDCP, GEL
Infiltrating cells	$IgG4^+$ plasma cells	Granulocytes
Complication	Various general disorders	Inflammatory bowel disease

LPSP, lymphoplasmacytic sclerosing pancreatitis ; IDCP, idiopathic duct-centric chronic pancreatitis ; GEL, autoimmune pancreatitis with granulocytic epithelial lesion

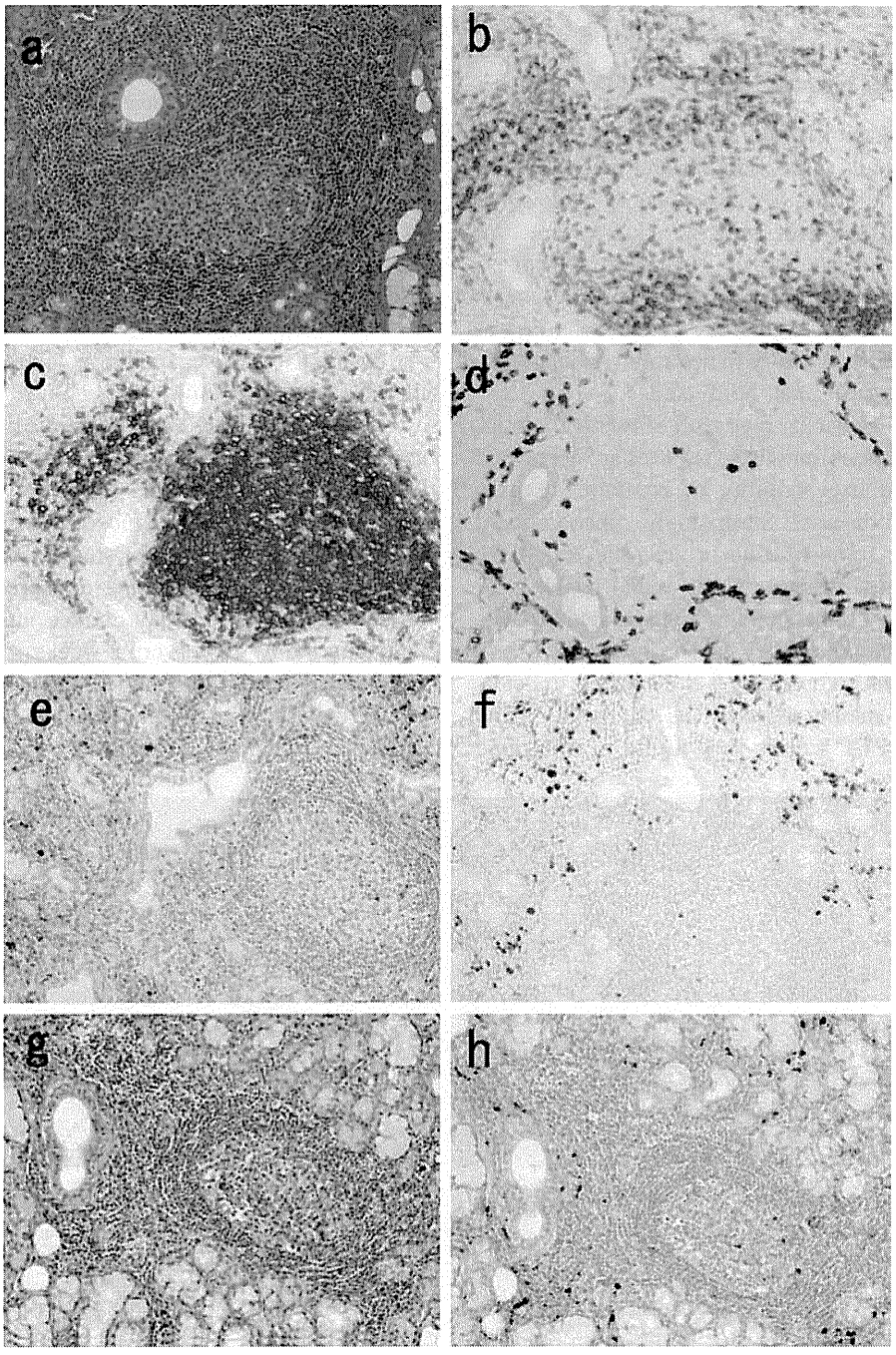

Fig. 1. Histopathological findings of labial minor salivary gland biopsy in IgG4-multiorgan lymphoproliferative syndrome (IgG4$^+$ MOLPS)/Mikulicz's disease (*1a-1h*). (***1a***) Hematoxylin & eosin staining ; (***1b***) CD3 ; (***1c***) CD20 ; (***1d***) CD38 ; (***1e***) IgG ; (***1f***) IgG4 immunostaining. (***1g***) κ and (***1h***) λ-*in situ* hybridization. Massive lymphocyte and plasmacyte infiltration and lymphoid follicle formation were seen in IgG4$^+$ MOLPS. The ducts remained clear without lymphocytic infiltration. CD20$^+$ B cells remained in the follicle, and CD3$^+$ T cells were seen around the follicle. CD38$^+$ plasma cells, IgG$^+$ cells, and IgG4$^+$ plasma cells were scattered in the periphery of the follicle. The ratio of IgG4$^+$ plasma cells/IgG$^+$ plasma cells was$>$40%. There was no remarkable monoclonality between κ and λ-positive B cells (λ showed clearer staining but the differences were small). Revised figure from Masaki *et al.*[1]