publish the Japanese criteria for IgG4-related disease.

TREATMENT OF IgG4-RELATED DISAESE

Not only good glucocorticoid responsiveness, but also cases showing spontaneous regression without any treatment have been reported. Therefore, it is necessary to make some choices with regard to treatment strategy, such as watchful waiting or surgical resection only. However, without a randomized control study among groups treated using glucocorticoid *vs.* watchful waiting, definitive conclusions cannot be made. In addition, it is necessary to determine which types of IgG4-related disease case must be treated.

Fibrosis or sclerosis is usually the result of relatively long-term inflammatory processes, and these features are correlated with refractoriness and irreversibility of common diseases other than IgG4-related disease. Surprisingly, glucocorticoid treatment can improve some fibrotic or sclerotic lesions in patients with IgG4-related disease. Early initial response of glucocorticoid is usually dramatically in IgG4-related disease, however more longer ignorance may cause irreversibility and function failure of organs. Therefore, it is necessary to determine which organs are mainly affected and the extent of the disease spread. ^{18}FDG-PET scan is very useful to determine the distribution of IgG4-related disease, and therefore this technique is highly recommended to determine treatment indications and strategy ; unfortunately, however, ^{18}FDG-PET scan is not covered by health insurance in Japan at present. ^{67}Garium-scan may serve as an alternative if ^{18}FDG-PET is not available. Irreversible functional failure of the pancreas, kidney, lung, or liver will adversely affect the patient's quality of life and result in poor prognosis. Therefore, glucocorticoid treatment should be applied. Although glucocorticoid treatment is effective in IgG4-related disease, there is no consensus regarding starting dose, period of use, how to taper, and maintenance dose, and these parameters are dependent on the institution and physician's policy.

We planned and began a clinical prospective study to establish optimal treatment strategy (Phase II prospective treatment study for IgG4$^+$ MOLPS : UMIN R000002311). We enrolled patients diagnosed according to our tentative diagnostic criteria into this study, and glucocorticoid treatment was implemented using oral prednisolone at an initial dose of 0.6 mg/kg per day divided into three doses per day, with tapering by 10% every 2 weeks. A maintenance dose of 10 mg per day was continued for at least 3 months, and a further daily dose of prednisolone was left up to the attending physician. Final maintenance dose will be decided with refer-

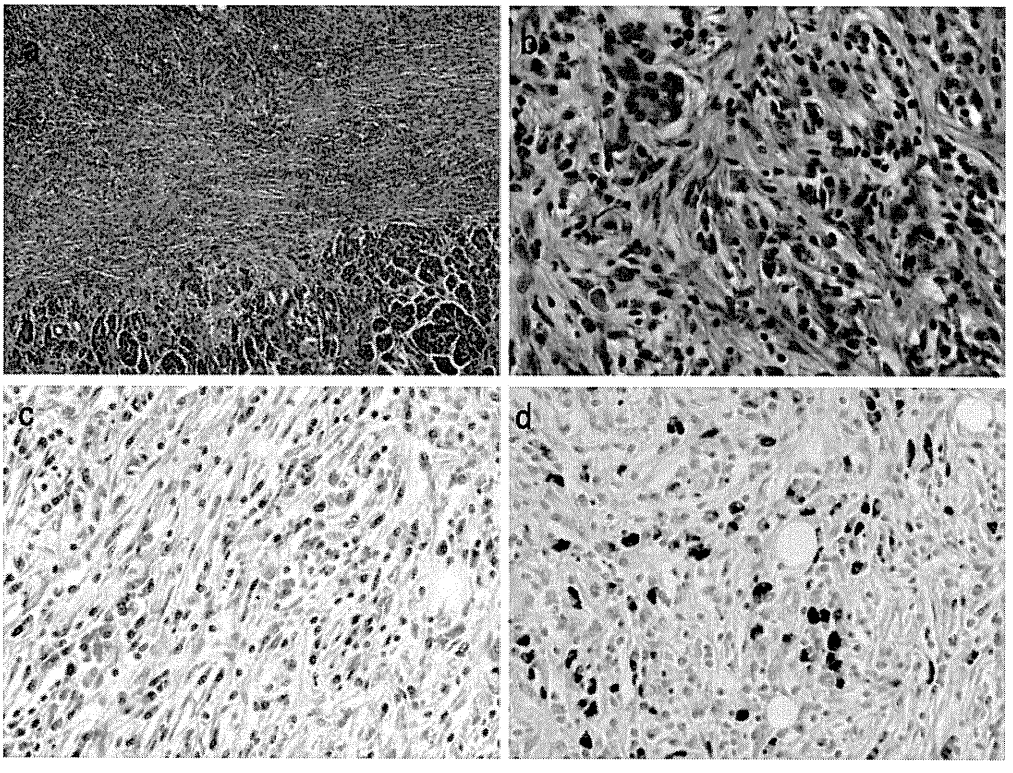

Fig. 2. Histopathological findings of Type 1 autoimmune pancreatitis (AIP). (***2a***, ***2b***) Hematoxylin & eosin staining ; (***2c***) IgG and (***2d***) IgG4 immunostaining. Lymphoplasmacytic infiltration and fibrosis giving rise to storiform fibrosis. Numerous IgG4-positive plasma cells were identified, and the ratio of IgG4$^+$ plasma cells (*2d*)/IgG$^+$ plasma cells (*2c*) was$>$40%.

ence to symptoms and clinical data in each case. In this study, we verified that the majority of patients require 5-10 mg per day of prednisolone as a maintenance dose, because 30%-40% relapse rates have been reported after discontinuation of glucocorticoid.

In typical cases of IgG4-related disease, glucocorticoid response can be confirmed after several days. Although the palpable organs, such as the lacrimal, parotid, and submandibular glands, and lymph nodes, can be confirmed by physical examination, the deep organs, such as the pancreas, should be confirmed by imaging examination (computed tomography) 2 weeks after commencement of glucocorticoid treatment. If the response is not sufficient at 2 weeks, differential diagnosis from other diseases, such as cancer, lymphoma, Castleman's disease, sarcoidosis, *etc.*, should be performed again.

Not only AIP patients, but also those with other types of IgG4-related disease without particular pancreatic lesions, may have glucose intolerance. Thus, glucocorticoid therapy would worsen glucose intolerance, and some patients would require insulin therapy. Informed consent is therefore also important in such cases.

Little evidence of treatment for relapsed and refractory cases have been established. Another course of glucocorticoid is usually effective, but other immunosuppressants, such as azathiopurin,[20] cyclophosphamide, methotrexate, and mizoribine,[21] have also been tried. Furthermore, rituximab[22,23] or bortezomib[24] were reported to show good response rates in studies performed in western countries. However, as mentioned above, it is possible that glucocorticoid refractory cases may be incorrectly diagnosed. It is therefore necessary to establish treatment strategy in a step by step manner, and new agents should be examined in clinical trials.

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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].

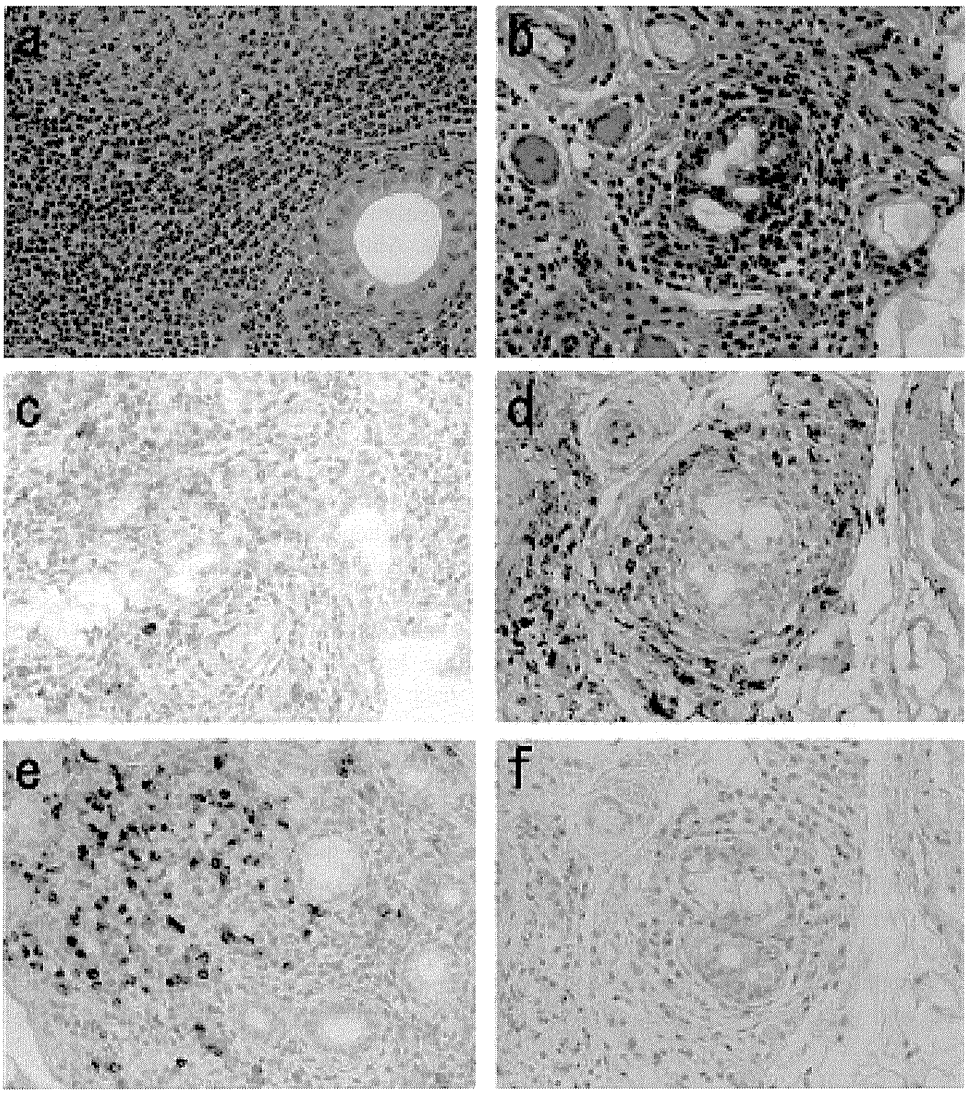

Figure 1. Histopathological findings of labial minor salivary gland biopsy in patients with IgG4+ MOLPS/Mikulicz's disease (a, c, e) and Sjögren's syndrome (b, d, f). (a, b) Hematoxylin and eosin staining; (c, d) IgG immunostaining; (e, f) IgG4 immunostaining. (a) Massive lymphocyte and plasmacyte infiltration 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

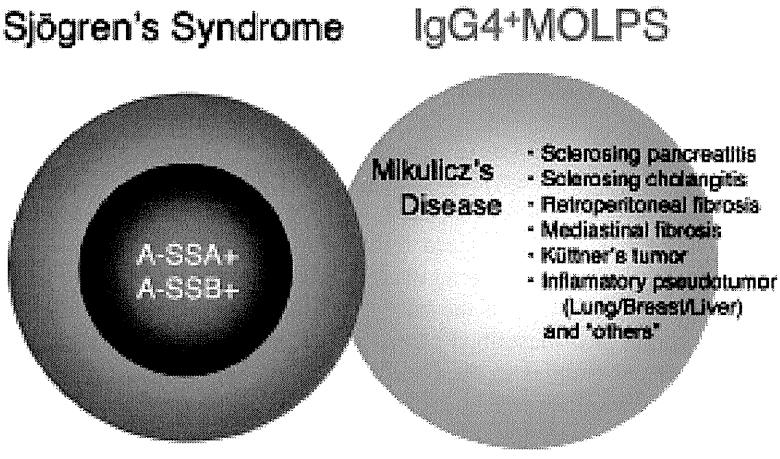

Figure 2. IgG4+ MOLPS should be defined as a distinct clinicopathological entity that includes Mikulicz's disease (MD), autoimmune pancreatitis (AIP), sclerosing cholangitis, and other clinical conditions with good response to glucocorticoids. Although the diagnostic criteria of SS may include some patients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

□ CASE REPORT □

IgG4-related Tubulointerstitial Nephritis and Hepatic Inflammatory Pseudotumor without Hypocomplementemia

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Abstract

Immunoglobulin G4 (IgG4)-related tubulointerstitial nephritis (TIN) is often accompanied by autoimmune pancreatitis (AIP) or chronic sclerosing dacryoadenitis and sialoadenitis. However, IgG4-related TIN without AIP or lacrimal and/or salivary gland lesions has not been well recognized. Here, we report a case of IgG4-related TIN associated with hepatic inflammatory pseudotumor without AIP or lacrimal and/or salivary gland lesions. A 58-year-old Japanese man with epigastralgia underwent contrast-enhanced computed tomography (CT), which revealed multiple low-density lesions in both kidneys and a low density hepatic mass. Laboratory tests showed an extremely high level of serum IgG4. Percutaneous renal and hepatic biopsies showed diffuse infiltration of lymphocytes and IgG4-positive plasma cells with fibrosis in both tissues. Two months after administration of oral prednisolone, both lesions decreased in size on follow-up CT, and the serum creatinine level also improved. No recurrence has been detected for two years with a maintenance dose of prednisolone.

Key words: IgG4-related tubulointerstitial nephritis, hepatic inflammatory pseudotumor

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Introduction

Immunoglobulin G4 (IgG4)-related disease is a recently proposed clinical entity characterized by marked infiltration of lymphocytes and IgG4-positive plasma cells with fibrosis in affected organs and increased serum levels of IgG4 (1). Although autoimmune pancreatitis (AIP) is a well-recognized IgG4-related disease, detailed analysis of patients with AIP has revealed that marked IgG4 positive plasma cell infiltration is not restricted to the pancreas but is also often found in other organs such as salivary glands, lacrimal glands, lungs, liver, kidneys, and prostate (1-4).

While reports of IgG4-related tubulointerstitial nephritis (TIN) with AIP or chronic sclerosing dacryoadenitis and sialoadenitis have been accumulated recently, IgG4-related TIN without AIP or chronic sclerosing dacryoadenitis and sialoadenitis has not been well recognized, and only a few reports are available in the English language literature (5-9). Here, we describe a case of IgG4-related TIN associated with hepatic inflammatory pseudotumor without AIP or chronic sclerosing dacryoadenitis and sialoadenitis.

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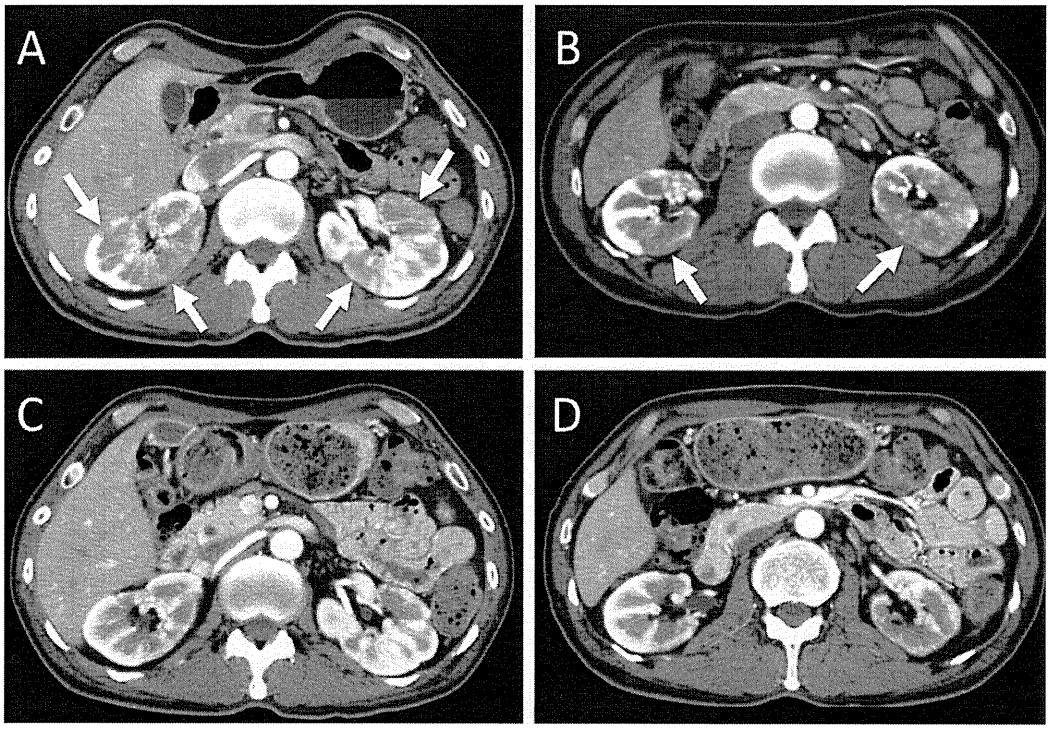

Figure 1. Contrast-enhanced computed tomography of the abdomen before (A, B) and after (C, D) treatment. Multiple low-density lesions in both kidneys were observed (A, B), which were ameliorated after steroid administration (C, D). Arrows indicate the abnormal regions in the kidneys.

Case Report

A 58-year-old Japanese man was admitted to our hospital for investigation of a solitary hepatic mass and multiple low-density lesions in the bilateral kidneys on enhanced computed tomography (CT). Two weeks before entry, he had undergone gastroscopy because of a 4-month history of epigastralgia, and a diagnosis of gastric ulcer with *Helicobacter pylori* infection was made. Abdominal ultrasonography showed a heterogeneous mass in the umbilical part of the liver. A contrast-enhanced CT scan of the abdomen revealed multiple low-density lesions in both kidneys (Fig. 1A, B). All lesions were well circumscribed and variously shaped. The hepatic lesion was also detected as a mass of decreased enhancement along with the left portal vein. Based on these CT findings, IgG4-related disease was suspected, and malignant lymphoma was also considered.

Physical findings were normal. He had neither parotid gland nor submandibular gland swelling. Urinalysis revealed no hematuria or proteinuria. The level of urinary N-acetyl-β-D-glucosaminidase (NAG) was 1.6 IU/L (normal, 1.0 to 4.2 μg/L) and that of urinary β2-microglobulin was 335 μg/L (normal, 16 to 518 μg/L). Other laboratory findings were as follows: leukocyte count 7,389/μL, eosinophil count 487/μL, hemoglobin 13.8 g/dL, CRP 0.1 mg/dL, IgG 2,850 mg/dL (normal, 739 to 1,649 mg/dL), IgG4 1,470 mg/dL (normal, 30 to 135 mg/dL), IgE 456 U/mL (normal, less than 250 U/mL), C3 81 mg/dL (normal, 44 to 102 mg/dL), C4 16 mg/dL (normal, 14 to 49 mg/dL), total hemolytic complement (CH50) 34 U/mL (normal, 31 to 49 U/mL), soluble interleukin-2 receptor (sIL-2R) 1,300 U/mL (normal, 220 to 530 U/mL). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum electrolytes were normal. Serum creatinine (Cr) level was 1.15 mg/dL. Positron emission tomography (PET) showed accumulation of fluorodeoxyglucose (FDG) in liver and kidney lesions suggestive of metastatic tumors (Fig. 2A, B). In addition, accumulation of FDG was detected along the left C6 nerve (Fig. 3).

The renal and hepatic lesions were subjected to percutaneous biopsy, with two samples secured from a renal lesion. Light microscopic examination of the renal lesion showed severe renal interstitial infiltration of lymphocytes and plasma cells with fibrosis and tubular atrophy in one sample (Fig. 4A-C). A lymphatic follicle was also observed (data not shown). However, the other sample showed normal glomeruli with little interstitial fibrosis. In all sections, the glomeruli and blood vessels showed only minor abnormalities. On immunostaining of specimens, more than half of the plasma cells infiltrating the interstitium were IgG4-positive (Fig. 4D). On the biopsied specimens of the hepatic lesion, light microscopic examination showed diffuse infiltration of lymphocytes and plasma cells in fibrous connective tissue without a normal liver architecture, and many plasma cells were IgG4-positive by immunostaining (Fig. 4E, F).

A diagnosis of IgG4-related TIN and IgG4-related hepatic pseudotumor was made based on the imaging studies, pathological findings of kidney and liver, and serum elevated IgG4 levels. His serum Cr level gradually increased to 1.30 mg/dL (eGFR 45.4 mL/min/1.73 m^2), and 30 mg per day of

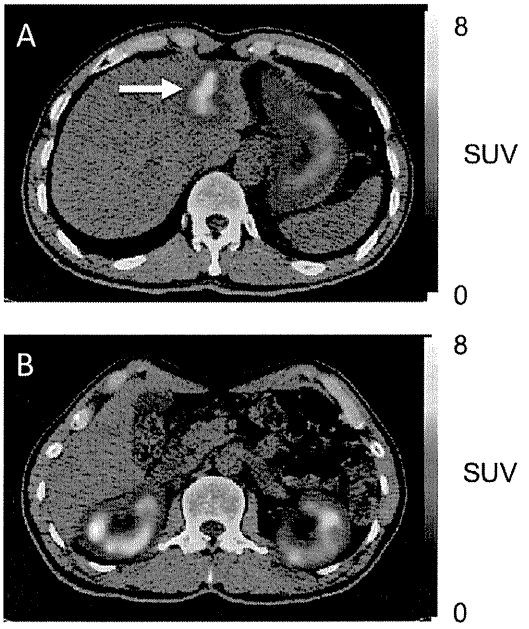

Figure 2. Combined positron emission tomography (PET)/computed tomography (CT) scans showed accumulation of ^{18}F-fluorodeoxyglucose (FDG) in a liver lesion (A) and the kidney lesions (B). More marked FDG uptake was shown in the affected areas of the kidney lesions consistent with the multiple low-density lesions detected by CT. An arrow indicates the abnormal region in the liver.

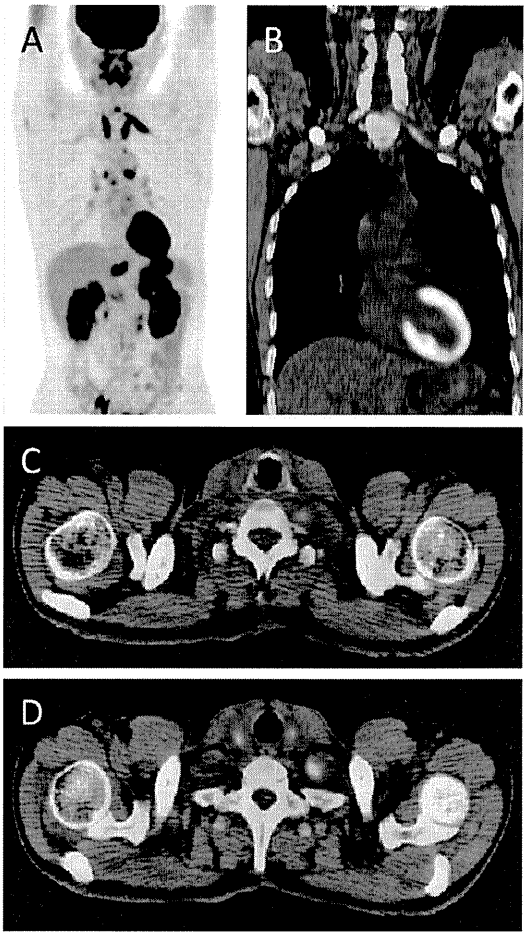

Figure 3. FDG-PET coronal maximum intensity projection image showed left C6 nerve involvement in addition to hepatic and renal accumulation (A). This nerve lesion was confirmed anatomically using PET/CT scans (B-D).

oral prednisolone was started.

Two months later, his serum IgG4 level was decreased to 470 mg/dL, and Cr level recovered to 1.02 mg/dL (eGFR 58.6 mL/min/1.73 m^2). Enhanced computed tomography showed that the hepatic pseudotumor and renal low-density lesions had become smaller (Fig. 1C, D). Prednisolone was tapered one month after the start of administration. Two years later, he showed no recurrence with improved renal function (Cr 0.89 mg/dL, eGFR 68.0 mL/min/1.73 m^2), with a maintenance dose of 7 mg per day of prednisolone (Fig. 5). During the clinical course, serum C3 levels and serum C4 levels fluctuated between 78 mg/dL and 103 mg/dL, and 15 mg/dL and 28 mg/dL, respectively without influence of steroid therapy.

Discussion

IgG4-related systemic disease sometimes affects the kidneys (4). In early reports, most reported cases of IgG4-related TIN were associated with AIP or Mikulicz's disease (10-12). However, reports of IgG4-related TIN without AIP or chronic sclerosing dacryoadenitis and sialoadenitis have also accumulated recently, because the common clinical features of IgG4-related disease have become more widely recognized (5-9). These include elderly onset, male predominance, positive history of allergies, and hypergammaglobulinemia (4). Therefore, in patients with TIN who have these clinical features, IgG4-related disease should be considered in the differential diagnosis.

IgG4-related disease is a systemic disease characterized by multi-organ involvement of IgG4 positive plasma cell infiltration and fibrosis. Although the mechanism by which the disease affects multiple organs has not been clarified, the histopathological findings of affected organs are very similar. In this regard, we previously showed the presence of two pairs of genetically related cells between lacrimal glands and circulating peripheral blood in a patient with Mikulicz's disease (13). This finding may support the hypothesis that memory B cells or long-lived plasma cells migrate from lacrimal or salivary glands to bone marrow or directly to other target organs.

To detect extra-pancreatic lesions of this disease, several radiologic approaches are recommended. These include gallium-67 (Ga-67) scintigraphy (14), contrast-enhanced computed tomographic (CT) imaging (15), and FDG-PET/CT imaging (16, 17). In the present case, contrast-enhanced CT and FDG-PET/CT were very useful in detecting the renal lesions. However, interstitial nephritis associated with IgG4-related disease is sometimes suspected in patients with AIP with deteriorated renal function without urinary abnor-

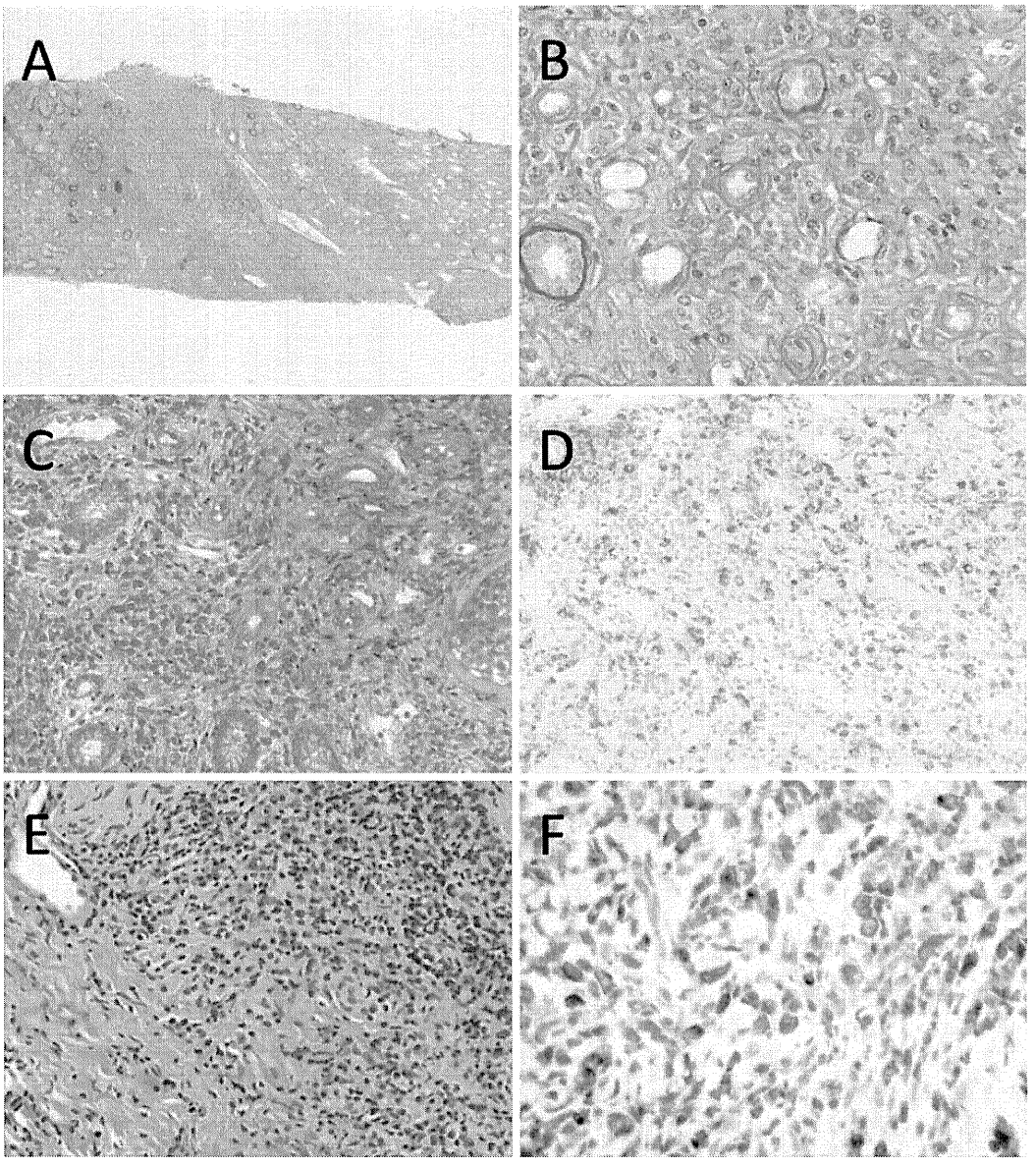

Figure 4. Light microscopy findings of the kidney (A-C), immunostaining of IgG4 in renal interstitium (D), light microscopy findings of the liver biopsy specimens (E), and immunostaining of IgG4 in liver parenchyma (F). Severe renal interstitial infiltration of lymphocytes and plasma cells with fibrosis and tubular atrophy were observed (A-C). More than half of the plasma cells infiltrating the interstitium were IgG4-positive (D). Liver biopsy showed diffuse infiltration of lymphocytes and plasma cells in fibrous connective tissue without normal liver architecture (E), and many plasma cells were IgG4-positive by immunostaining (F). [(A) kidney, Periodic acid-Schiff stain, ×40, (B) kidney, Periodic acid-Schiff stain, ×400, (C) kidney, Azan, ×200, (D) kidney, IgG4, ×200, (E) liver, Hematoxylin and Eosin staining, ×200, (F) liver, IgG4, ×400]

malities, and the use of contrast medium in CT should be avoided in such cases. Therefore FDG-PET/CT imaging is a promising tool to detect renal lesions in IgG4-related disease with renal dysfunction.

Hypocomplementemia is a frequently observed characteristic finding in IgG4 related renal disease (4). About 80% of previously reported TIN cases associated with IgG4 related disease had hypocomplementemia. In contrast, Muraki et al reported that 36% of AIP cases have hypocomplementemia (18). This suggests that hypocomplementemia is closely associated with IgG4-related TIN. In IgG4-related disease, the kidney is the most frequently reported organ in which electron-dense deposits are detected. Cornell et al found electron-dense deposits in the tubular basement membrane (TBM) in four of five IgG4-related TIN cases (19). Only one patient without TBM deposits did not have chronic interstitial fibrotic change. They speculated that immune deposits, which occur after tubular atrophy and interstitial fibrosis, are a late phenomenon of this disease. However, as the relationship between TBM immune deposits and

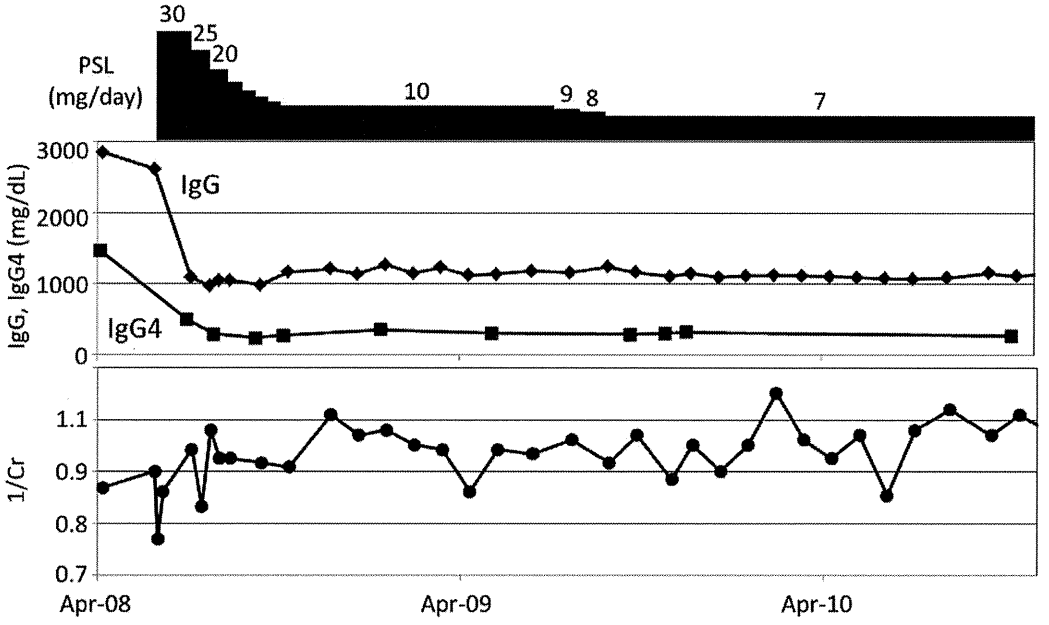

Figure 5. Clinical course of the patient. After steroid administration, serum IgG and IgG4 concentrations decreased, and normal renal function was maintained without recurrence. *Diamonds*, serum IgG (mg/dL); *squares*, serum IgG4 (mg/dL); *circles*, serum creatinine 1/Cr (dL/mg).

hypocomplementemia was not mentioned in their report, whether normal complement levels were limited to the early stage of this disease or not is unclear. The present case had normal complement levels without TBM immune deposits by electron microscopy (EM) and by immunofluorescence (IF), but the light microscopic finding of moderate fibrosis suggested a relatively advanced stage rather than an early stage. Interestingly, two reported cases with normal complement levels also had fibrosis suggestive of chronic change. These findings suggest that marked infiltration of IgG4 positive plasma cells in the interstitium and TBM immune deposits are independent phenomena in the pathogenesis of IgG4-related TIN.

Recently, IgG4-related inflammatory pseudotumor involving a unilateral trigeminal nerve was reported (20). The presenting symptom in this case was left-sided facial numbness. In the present case, although the patient did not have neurological symptoms, and this lesion was not biopsied, the FDG-PET/CT finding suggested that he also had a perineural lesion of IgG4-related disease along the left C6 nerve.

In conclusion, we describe a case of IgG4-related TIN associated with hepatic inflammatory pseudotumor without AIP. The present case suggests that severe TIN can occur without hypocomplementemia, and immune complexes are not always necessary for the pathogenesis of IgG4-related TIN. Further investigations are needed to clarify the etiopathological significance of hypocomplementemia in IgG4-related disease.

The authors state that they have no Conflict of Interest (COI).

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INTERNAL MEDICINE

□ CASE REPORT □

IgG4-related Skin Lesions in a Patient with IgG4-related Chronic Sclerosing Dacryoadenitis and Sialoadenitis

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Abstract

We describe a 60-year-old man with IgG4-related chronic sclerosing dacryoadenitis and sialoadenitis associated with lymphoplasmacytic and eosinophilic infiltration in erythematous nodules. Physical examination revealed left eye extrusion and small itchy nodules on the scalp and neck. The serum IgG level was 1,570 mg/dL, IgG4 463 mg/dL (29.5%), and IgE 4,554 IU/mL. Lacrimal gland biopsy disclosed prominent infiltrates of IgG4-positive plasma cells and scattered eosinophilic infiltrates with fibrosis, consistent with IgG4-related disease. A skin biopsy of a cutaneous nodule demonstrated that the infiltrated plasma cells around arterioles or venules in the deep dermis and subcutaneous fat tissue were strongly positive for IgG4. Although the swollen lacrimal and parotid gland and itchy subcutaneous erythematous nodules improved rapidly with oral prednisolone at a dose of 20 mg per day, the skin, lacrimal, and parotid lesions deteriorated simultaneously during steroid tapering and improved after increasing the dosage. As skin lesions are easy to biopsy, further study of the skin manifestations of IgG4-related disease will be important in further clarifying the clinical spectrum, pathophysiology and response to therapy of this disorder.

Key words: IgG4-related disease, cutaneous lymphoid infiltrate, IgG4-related chronic sclerosing dacryoadenitis and sialoadenitis

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Introduction

After the establishment of the entity of autoimmune pancreatitis (AIP) (1, 2), a variety of associated extra-pancreatic lesions have been reported including those of the lacrimal glands, salivary glands, lungs, kidneys, liver, bile duct, retroperitoneum, breast, aorta, pituitary gland, and prostate (3-6). In 2003, Kamisawa et al (3) proposed the new clinicopathological entity of "IgG4-related autoimmune disease" based on common pathological features of many IgG 4-positive plasma cell infiltrates with fibrosis and increased serum IgG4 levels, which are representative findings of autoimmune pancreatitis. Since then, many case reports or case series have accumulated, and IgG4-related disease has been accepted as a new clinical entity. IgG4-related chronic sclerosing dacryoadenitis and sialoadenitis are major components of this disease.

However, only a few reports have focused on the skin lesions associated with autoimmune pancreatitis, chronic sclerosing dacryoadenitis and sialoadenitis or systemic IgG4-related lymphoadenopathy (7, 8). Here, we describe a case of IgG4-related chronic sclerosing dacryoadenitis and sialoadenitis with nodular skin lesions with marked IgG4-positive plasma cell infiltration and scattered eosinophil infiltration, which appeared in parallel with exacerbation of

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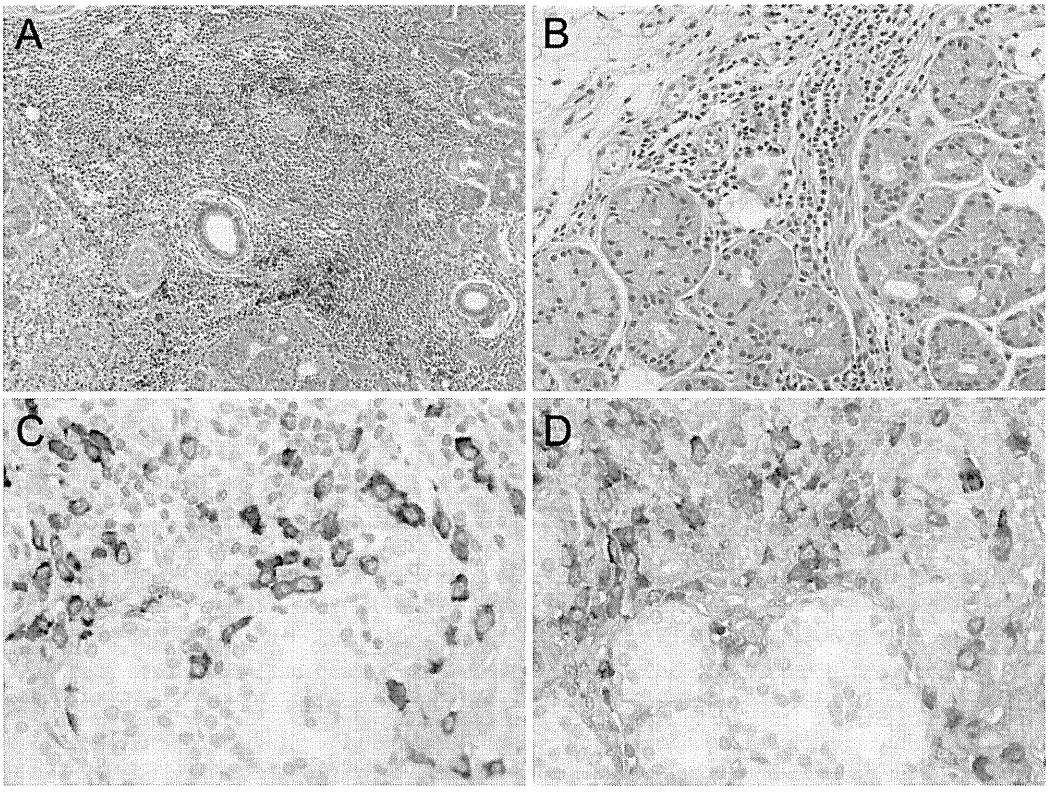

Figure 1. Lacrimal gland biopsy shows marked infiltration of lymphocytes and plasma cells (A) with mild fibrosis (B). Many infiltrating plasma cells are IgG4 positive (C), with an IgG4/IgG ratio of 84.8% (C and D). [(A) lacrimal gland, Hematoxylin and Eosin (HE) staining, ×100, (B) HE staining, ×200, (C) IgG4, ×400, (D) IgG, ×400]

the dacryoadenitis and improved after the corticosteroid dosage was increased.

Case Report

A 60-year-old man was admitted to our hospital for close examination of impaired glucose tolerance and systemic evaluation of IgG4-related disease. One year before entry, a high fasting plasma glucose level had been pointed out for the first time on an annual health checkup and he began treatment for diabetes mellitus. Six months before admission, he noticed protrusion of his left eye, and two months later itchy nodules on his scalp and neck. Magnetic resonance imaging revealed left external eye muscle hypertrophy and multiple mass lesions in the left orbital cavity. As malignant lymphoma was strongly suspected, a left lacrimal gland biopsy was performed. The biopsy specimen was composed of inflammatory tissue with marked infiltrates of IgG4-positive plasma cells and scattered eosinophilic infiltrates with fibrosis suggesting IgG4-related disease (Fig. 1A, 1B). The average ratio of IgG4/IgG positive plasma cells in five different high power fields (hpf) with intense infiltration was 84.8% (Fig. 1C, 1D). On admission to our hospital, physical examination revealed left eye extrusion with obvious lacrimal gland swelling (Fig. 2A). Small itchy nodules were found on the parietal scalp, and 7 little finger tip-sized itchy subcutaneous erythematous nodules on the neck without any palpable lymph nodes (Fig. 2B). The bilateral parotid glands were swollen, while the submandibular glands were of normal size. He had no history of allergies. Blood eosinophil count was 993/mL accounting for 12.9% of the total white blood cell count. Fasting plasma glucose was 100 mg/dL, and HbA1c 6.4%. Liver function tests, electrolytes, and renal function tests were all within the respective normal ranges. Serum IgG level was 1,570 mg/dL, IgG4 463 mg/dL (29.5%), and IgE 4,554 IU/mL, rheumatoid factor 12 IU/mL, and soluble interleukin 2 receptor 692 U/mL (normal 220-530 U/mL). Antinuclear antibodies were negative. Computed tomography (CT) scans revealed bilateral lacrimal gland and parotid gland swelling without lymphadenopathy. Abdominal CT showed a normal-sized pancreas without pancreatic duct abnormalities or mass formation. A skin biopsy of a cutaneous nodule was performed. On light microscopy, there was moderate lymphocyte and plasma cell infiltration around arterioles and adnexal structures in the dermis (Fig. 3A). In particular, severe lymphocytic infiltration with plasma cells and eosinophils around arterioles or venules was evident in the deep dermis (Fig. 3B, 3C) and subcutaneous fat tissue, and the majority of infiltrating plasma cells were IgG4 positive (average IgG4 positive cell count in five different hpf with intense infiltration was 47/hpf) (Fig. 3D). A diagnosis of IgG 4-related systemic disease was made because of an elevated serum level of IgG4, marked infiltration of IgG4-positive

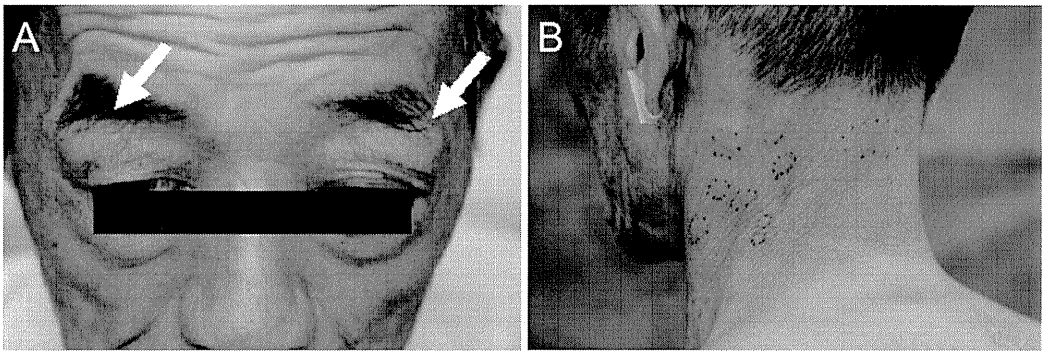

Figure 2. Bilateral swelling of the lacrimal glands is noted (A, arrows). Little finger tip-sized subcutaneous erythematous nodules are present on the neck (B).

plasma cells in the lacrimal glands, and typical features of Mikulicz's disease with symmetrical lacrimal and parotid gland swelling. After the administration of 20 mg of prednisolone, a rapid response was obtained and the multiple nodules in the scalp and neck disappeared. The bilateral parotid swelling was also improved. The prednisolone dose was reduced at the rate of 5 mg every two weeks to 10 mg, which was adopted as the maintenance dose. Six months thereafter, the left eye protrusion, bilateral parotid swelling, and multiple subcutaneous nodules recurred, and the dose of prednisolone was increased to 20 mg after a second skin biopsy. The histopathological findings were similar to those of the previous biopsy with marked IgG4-positive plasma cell infiltration with scattered eosinophils, supporting the recurrence of IgG4-related disease. Twenty days after readministration of 20 mg of prednisolone, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) was performed. However, no FDG-PET positive lesion was detected, this being consistent with the rapidly improved clinical findings. After that, prednisolone was carefully decreased without recurrence of the eye protrusion, parotid swelling, or appearance of new skin lesions.

Discussion

We report a patient with clinical and histological features of chronic sclerosing dacryoadenitis and sialoadenitis and multiple nodular itchy skin lesions on the scalp and neck. The histological findings of the skin lesions were very similar to those previously reported in IgG4-related disease (3-5, 8), suggesting that the skin lesions of this case should be included as one of the extra-pancreatic manifestations of autoimmune pancreatitis and other IgG4-related disease.

To identify new organ involvement of IgG4-related disease, two approaches to identification exist. One is to find marked IgG4-positive plasma cell infiltration in a suspicious lesion, and to confirm an elevated serum IgG4 level. The other is to find an associated lesion in patients with typical IgG4-related disease, such as autoimmune pancreatitis or IgG4-related chronic sclerosing dacryoadenitis and sialoadenitis, and to prove similar IgG4-positive plasma cell infiltration in the newly recognized lesion. However, the former approach has not yet been fully accepted because some patients with well established diseases such as Churg-Strauss syndrome (9) and Castleman's disease (6, 10, 11) also have similar IgG4-positive plasma cell infiltration with high serum IgG4 levels.

Kuo et al (12) contended that cutaneous Rosai-Dorfman (RD) disease is an IgG4-related sclerosing disease according to identification by the former approach. They analyzed the skin lesions of 12 patients with RD disease, and noted that all but one of them had more than 30 IgG4 positive cells/hpf. They also found an elevated serum IgG4 level in one patient. Shrestha et al (13) analyzed lung lesions of 8 patients with nodal and extranodal RD disease, and found that 6 of 8 RD cases showed an increased number of IgG4-positive plasma cells in the lung. Although these findings suggest that some relationship may exist between RD disease and IgG4-related disease, the finding of S-100-protein-positive large histiocytes, a histopathological feature of RD disease, is very unusual in IgG4-related disease, making it difficult to regard cutaneous RD disease as a cutaneous manifestation of IgG4-related disease. However, Shrestha et al (13) showed that 2 of 6 patients with lung lesions associated with IgG4-related autoimmune pancreatitis had prominent lymphatic dilatation with emperipolesis and S-100 protein-positive histiocytes in the lung. Therefore, further studies are needed to classify RD disease as an IgG4-related disease.

Miyagawa-Hayashino et al (14) claimed that cutaneous plasmacytosis is a cutaneous manifestation of IgG4-related disease as identified by the former approach. Although hypergammaglobulinemia is common to both cutaneous plasmacytosis and IgG4-related disease, an elevated serum interleukin 6 (IL-6) level, which is a common feature of cutaneous plasmacytosis (15), is very uncommon in IgG4-related disease (7). In addition, an association of pancreatic, lacrimal or salivary gland lesions with cutaneous plasmacytosis has not been reported previously. Therefore, careful judgment is needed to classify cutaneous plasmacytosis as an IgG4-related disease.

In contrast, the present case showed that skin might also be involved in IgG4-related disease as identified by the lat-

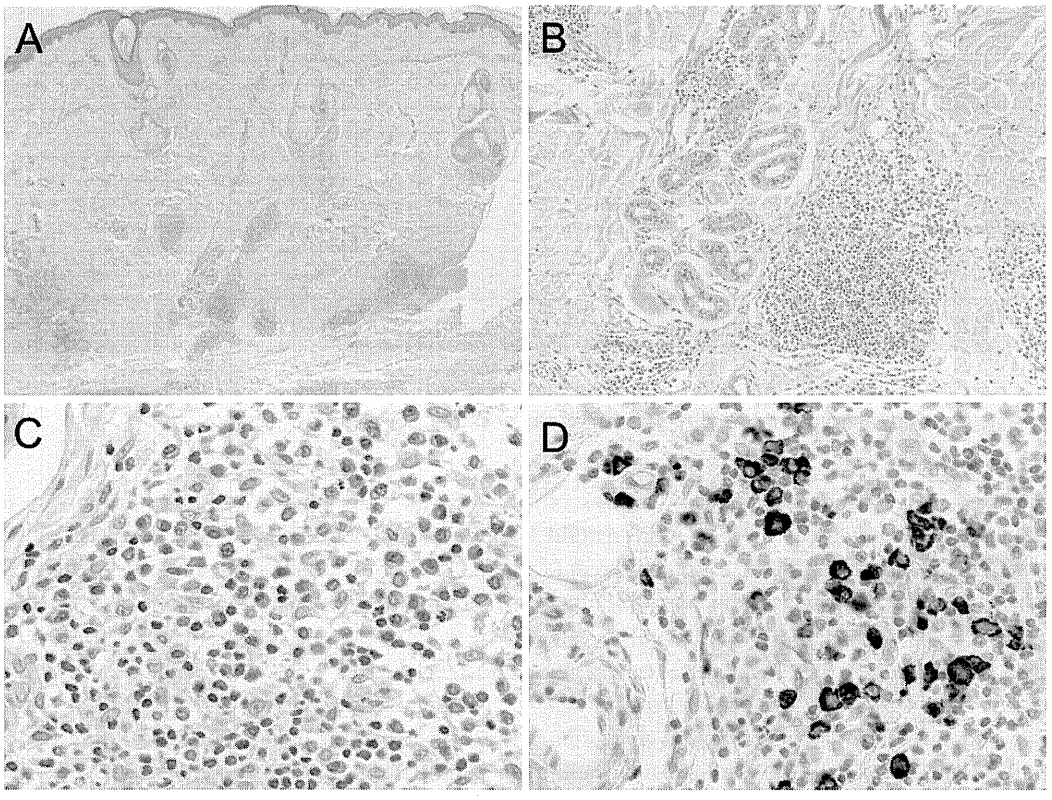

Figure 3. Moderate infiltration of lymphocytes and plasma cells is noted around arterioles or venules in the deep dermis and subcutaneous fat tissue (A). Marked lymphocyte and plasma cell infiltration is noted in the deep dermis without evident fibrosis (B). There are many infiltrating eosinophils (C). Many IgG4-positive plasma cell infiltrates in the skin lesion are seen [average IgG4 positive cell count in five different high power fields (hpf) with intense infiltration: 47/hpf] (D). [(A) skin, Hematoxylin and Eosin (HE) staining, ×40, (B) HE staining, ×100, (C) HE staining, ×400, (D) IgG4, ×400]

ter approach. In our case, the histological findings of the skin lesions with eosinophil infiltration were very similar to those of AIP or IgG4-related chronic sclerosing dacryoadenitis or sialoadenitis (3, 5, 6). Moreover, the skin, lacrimal, and parotid lesions deteriorated simultaneously during steroid tapering and improved after increasing the dosage of corticosteroid, suggesting a similar pathophysiological involvement in these organs.

Only two papers referring to the skin lesions of IgG4-related disease identified by the latter approach are available, but the clinical features of the skin lesions were not fully described and their response to corticosteroid therapy was not mentioned in detail. Sato et al (7) showed that 3 of 9 patients with systemic IgG4-related lymphoadenopathy had skin lesions, and demonstrated that one of them had cutaneous pathological findings typical of IgG4-related disease. However, macroscopic findings and the distribution of the skin lesions were not shown in their paper, making it difficult to compare their lesions with those of the present case. Cheuk et al (8) proposed that cutaneous pseudolymphoma might be a skin manifestation of IgG4-related sclerosing disease. Their two cases had lacrimal or salivary gland lesions with markedly elevated serum IgG4 levels. The cutaneous lesions of the present case were itchy and erythematous, which were consistent with those of their case. The distribution of the skin lesions in the scalp, face and neck was also very similar in their cases and ours. Although the histological findings had many similarities, our patient did not have evident fibrosis with Azan stain (data not shown) and showed less marked lymphocyte and plasma cell infiltration than their cases with pseudolymphoma formation. Therefore, we speculate that the lesion in our case was of an earlier stage than that described by Cheuk et al (8), and that our case if left untreated might also develop a similar pseudolymphoma in the future.

Further study of the skin manifestations of IgG4-related disease is needed so as to enhance our understanding of the clinical spectrum, pathophysiology and response to therapy of this disorder.

The authors state that they have no Conflict of Interest (COI).

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