

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 conducting 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

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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)

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- 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.
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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 ⁶⁷Ga-scan or ¹⁸FDG-PET-scan

of allergic factors in this disease.

The majority of MD patients suffer IgG4-related dacryadenitis 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 patients¹² 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 ($\geq 40\%$ 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 cholangiopancreatography (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-(¹⁸F) fluoro-D-glucose-positron emission tomography (¹⁸FDG-PET) scan,⁶⁷ Gallium-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

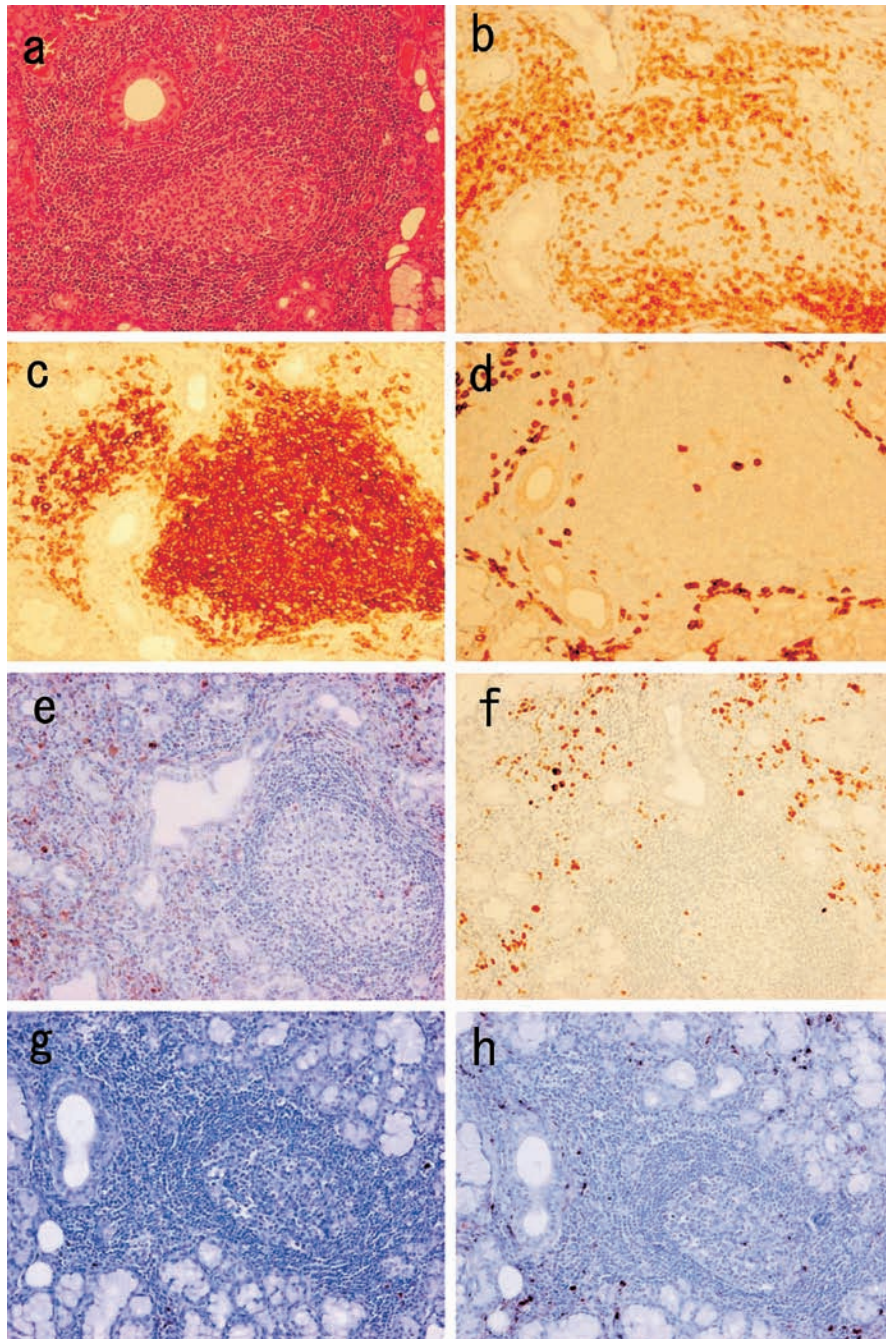


Fig. 1. Histopathological findings of labial minor salivary gland biopsy in IgG4-multiproliferative syndrome (IgG4⁺ MOLPS)/Mikulicz's disease (*1a-1h*). (*1a*) Hematoxylin & eosin staining; (*1b*) CD3; (*1c*) CD20; (*1d*) CD38; (*1e*) IgG; (*1f*) IgG4 immunostaining. (*1g*) κ and (*1h*) λ -*in situ* 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

publish the Japanese criteria for IgG4-related disease.

TREATMENT OF IgG4-RELATED DISEASE

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. ¹⁸F-DG-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, ¹⁸F-DG-PET scan is not covered by health insurance in Japan at present. ⁶⁷Gallium-scan may serve as an alternative if ¹⁸F-DG-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 R00002311). 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-

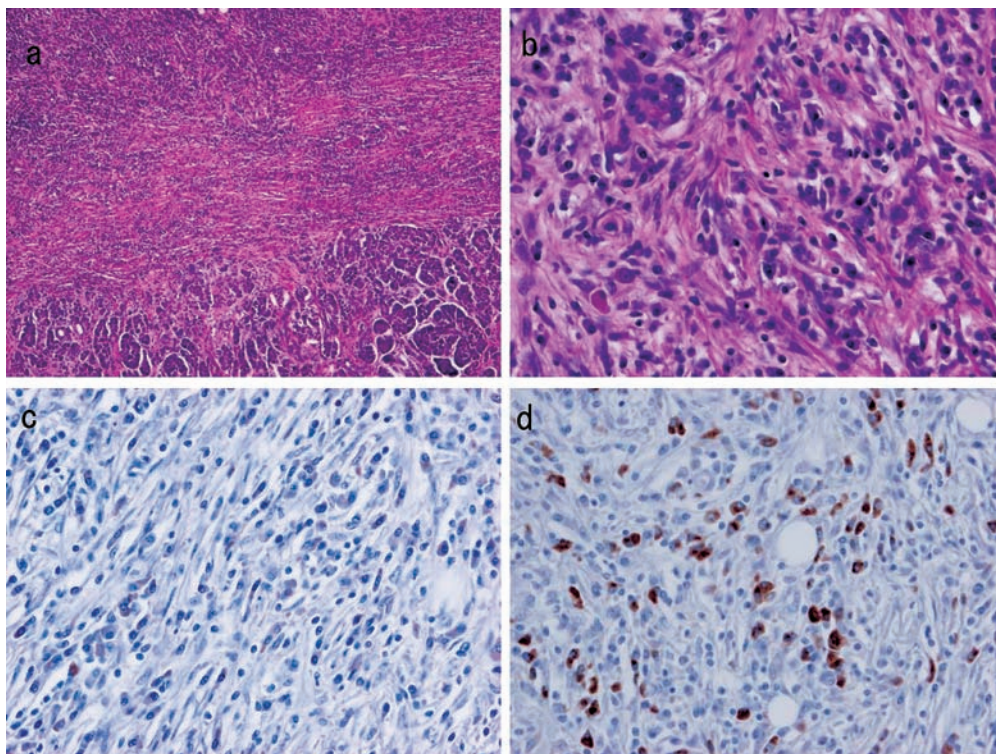


Fig. 2. Histopathological findings of Type 1 autoimmune pancreatitis (AIP). (2a, 2b) Hematoxylin & eosin staining; (2c) IgG and (2d) IgG4 immunostaining. Lymphoplasmacytic infiltration and fibrosis giving rise to storiform fibrosis. Numerous IgG4-positive plasma cells were identified, and the ratio of 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 bortezomib²⁴ 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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