

IgG4-Related Disease: Diagnostic Methods and Therapeutic Strategies in Japan

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This review describes methods utilized in Japan to diagnose and treat patients with IgG4-related disease. A diagnosis of IgG4-related disease is based on elevated serum IgG4 concentration and an increased number of IgG4⁺ plasma cells. Differentiating IgG4-related disease from other disorders, especially malignancy, is quite important. Consensus treatment in Japan consists of an initial dose of prednisolone at 0.5-0.6 mg/kg/day, followed by careful and gradual dose reduction. Most patients require maintenance treatment at 5 to 10 mg/day. Patients refractory to glucocorticoids are either truly refractory or have been misdiagnosed, therefore requiring reassessment. [*J Clin Exp Hematop* 54(2) : 95-101, 2014]

Keywords: glucocorticoid, rituximab, ¹⁸FDG-PET, lymphoma, multicentric Castleman's disease

INTRODUCTION

IgG4-related disease (IgG4-RD) is a newly recognized disorder, characterized by massive IgG4⁺ lymphocyte and plasma cell infiltration and fibrosis, causing enlargement, nodules, or thickening of various organs, either simultaneously or metachronously.¹⁻⁵ Its etiology is currently unknown. Most patients show the involvement of multiple organs, with a minority having single-organ disease.

IgG4-RD was first described in 2001 in patients with sclerosing pancreatitis, called autoimmune pancreatitis (AIP) type 1,⁶ and later observed in other organs. This disease is characterized by 1) elevated serum IgG4 concentration, 2) increased numbers of IgG4-positive cells in tissue, and 3) various degrees of sclerotic and/or fibrotic changes in affected organs. In addition, most patients show multiple-organ involvement, and IgG4-RD is frequently accompanied by allergic conditions, such as allergic rhinitis and bronchial asthma. Furthermore, most patients with IgG4-RD are responsive to

glucocorticoid treatment, at least during early stages of the disease. Other patients may show spontaneous improvement, indicative of a relatively benign disease.¹⁻⁹

This review describes the Japanese consensus for the diagnosis and treatment of IgG4-RD.

DIAGNOSIS

Diagnosis of systemic IgG4-RD by comprehensive diagnostic criteria for IgG4-RD

Since elevated plasma IgG4 was first reported in patients with sclerosing pancreatitis, IgG4 enhancement has been reported in other systemic disorders. Since most patients have multiple, rather than single organ involvement, various terms indicative of a systemic disorder have been proposed, including IgG4-related autoimmune disease,¹⁰ IgG4-related sclerosing disease,⁵ IgG4-related plasmacytic disease,¹¹ systemic IgG4 plasmacytic syndrome (SIPS),¹² and IgG4⁺ multiorgan lymphoproliferative syndrome (IgG4 + MOLPS).³ Owing to confusion due to the use of various terms to describe the same condition, Japanese specialists reached a consensus to call this condition IgG4-RD,² a term confirmed internationally.¹³ The comprehensive diagnostic criteria (CDC) for IgG4-RD¹⁴ consist of three items: 1) diffuse or partial enlargement, swelling, nodules, or thickening lesions on single or multiple organs, 2) a serum IgG4 concentration > 135 mg/dL, and 3) histopathological findings including a) massive lymphocytic and plasmacytic infiltration and sclerosis, b) increased numbers of

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IgG4⁺ plasma cells; and IgG4⁺/IgG⁺ plasma cell ratio > 40% and > 10 cells per high-powered field. Patients fulfilling all three criteria are defined as having a definite diagnosis of IgG4-RD, those who fulfill criteria 1 and 3 as having a probable diagnosis, and those who fulfill criteria 1 and 2 as having a possible diagnosis. Patients with probable and possible IgG4-RD may be definitively diagnosed with this condition by using the criteria established for AIP type 1,¹⁵ IgG4-related Mikulicz's disease,⁷ IgG4-related kidney disease,¹⁶ or IgG4-related sclerosing cholangitis.¹⁷ Most patients with AIP could not be definitively diagnosed by CDC because of the difficulty of obtaining an appropriate biopsy sample, thus requiring diagnosis using the criteria for AIP.

It is important to differentiate IgG4-RD from malignan-

cies in various organs, including solid tumors and lymphomas, and from other inflammatory disorders, such as sarcoidosis, collagen disease, vasculitis, and multicentric Castleman's disease. Although some of these disorders may demonstrate high serum IgG4 concentration or an increased number of IgG4⁺ plasma cells, they differ in clinical course and/or response to glucocorticoid treatment. A definitive diagnosis of another disorder would therefore rule out IgG4-RD.

Furthermore, the involved site and disease distribution in each case should be assessed generally before treatment.¹⁸ Fluorine-labeled fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) is a very sensitive method to identify involved lesions¹⁸⁻²⁰ (Fig. 1), and thus it is strongly recom-

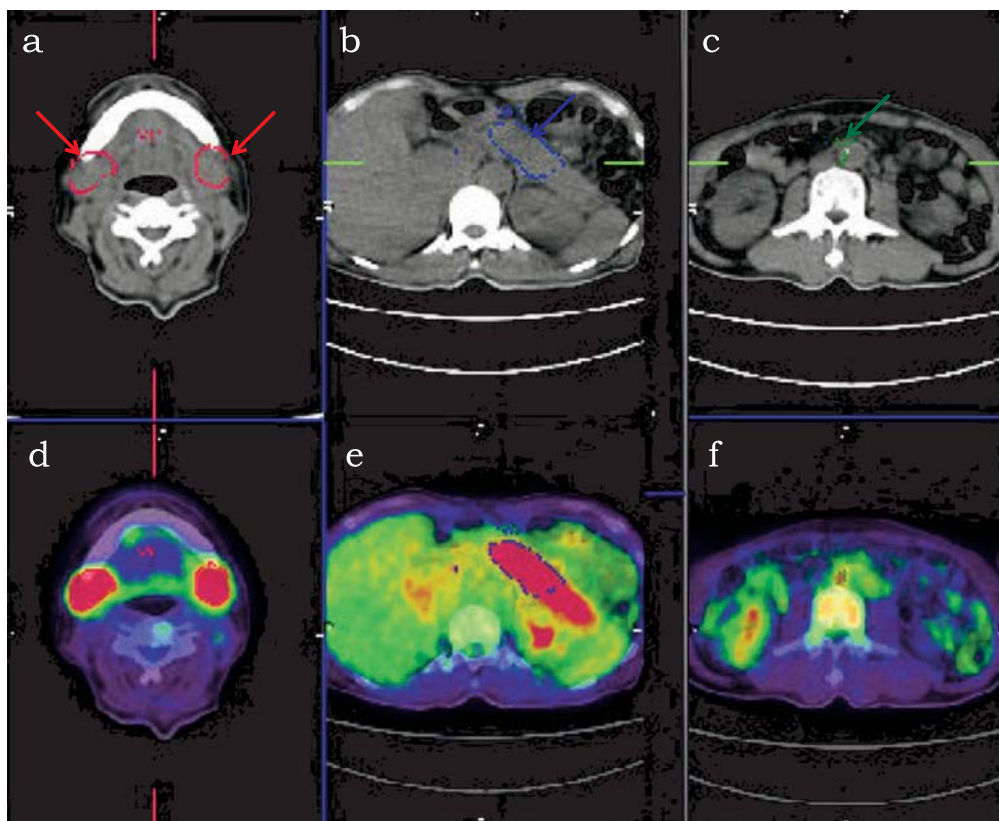


Fig. 1. ¹⁸Fluorine-labeled fluorodeoxyglucose positron emission tomography-computed tomography (¹⁸FDG-PET-CT) finding in a patient with IgG4-related disease who had Mikulicz's disease, autoimmune pancreatitis, and subclinical aortitis.

(1a-1c) Standard CT scan image and (1d-1f) fusion image of ¹⁸FDG-PET and CT scan. Submandibular gland level (1a, 1d), pancreas level (1b, 1e), and kidney level, which includes abdominal aorta (1c, 1f). (1a) Red dotted line indicated by red arrows corresponds to strong accumulation to both sides of submandibular glands in (1d). (1b) Blue dotted line indicated by a blue arrow corresponds to strong accumulation to pancreas in (1e). (1c) Green dotted line indicated by a green arrow corresponds to weak accumulation to subclinical abdominal aorta (1f) (SUVmax 4.14). We cannot identify such small subclinical lesions without ¹⁸FDG-PET-CT.

mended, although the Japanese public health insurance system does not cover the use of ^{18}F FDG-PET-CT for diagnosis of IgG4-RD patients at present.

Diagnosis of IgG4-related sclerosing pancreatitis or AIP type 1

AIP can be divided into two subgroups.^{21,22} AIP type 1, also called lymphoplasmacytic sclerosing pancreatitis,²³ is a type of IgG4-RD, whereas AIP type 2, also called idiopathic duct-centric pancreatitis or AIP with granulocytic epithelial lesions,^{24,25} is a granulocytic lesion unrelated to IgG4. Although these two conditions show similar radiological findings and both are responsive to glucocorticoid treatment, their histopathological findings and other characteristics differ. According to international consensus diagnostic criteria (ICDC),²⁶ most Asian patients with AIP have type 1, and some patients in western countries have type 2. Owing to difficulty in the use of ICDC clinically, the Japanese AIP criteria were proposed and revised.^{27,28} Since few patients in Japan have AIP type 2, the Japanese AIP criteria are primarily for AIP type 1. According to an addendum to the Japanese AIP criteria, patients with normal serum IgG4, typical radiographic features, and good response to glucocorticoids may have AIP type 2. Relative to the ICDC criteria, the Japanese AIP criteria: 1) classify enlargement on pancreatic radiologic imaging as diffuse or segmental/focal, 2) simplify the level 1 or 2 classification of the ICDC, 3) utilize serum IgG4 level as the only laboratory test, 4) assess only lymphoplasmacytic sclerosing pancreatitis histopathologically, and 5) include patients with other organ involvement. Glucocorticoid response is separated from the diagnostic criteria, with trials of glucocorticoid treatment permitted only in special hospitals for patients with AIP.

Patients with segmental/focal AIP must be distinguished from patients with pancreatic cancer. Since the latter may have high serum IgG4 concentration and IgG4⁺ plasma cell infiltration, thus fulfilling the diagnostic criteria for IgG4-RD, they are usually refractory to steroids, thus requiring diagnostic reassessment.

Diagnosis of IgG4-related sclerosing cholangitis

IgG4-related sclerosing cholangitis (IgG4-SC) is characterized by broad smooth enlargement of the bile duct wall. It is rarely a single-organ disease, usually occurring together with AIP.^{29,30} The intra-pancreatic bile duct is usually involved, but there may be limited narrowing at the hepatic portal or extra-hepatic bile duct, or multiple narrowings in the liver. Depending on the involved site, IgG4-SC must be differentiated from primary sclerosing cholangitis or bile duct cancer, since each disorder has a different prognosis and requires a different therapeutic approach. Most patients with

IgG4-SC are elderly males presenting with obstructive jaundice. The 2012 clinical criteria for IgG4-SC in Japan, differentiating it from other disorders, include results obtained from 1) imaging of the biliary duct, 2) serum assays, 3) other organ involvements, and 4) histopathological examinations.¹⁷

Diagnosis of IgG4-related dacryoadenitis and sialadenitis, so-called Mikulicz's disease (MD)

In 1892, Mikulicz reported a male case with symmetrical swelling of lacrimal, parotid, and submandibular glands, and consequently the term "Mikulicz's disease" was established.³¹ After a case of unilateral sclerosing lesion in the salivary gland was reported by Küttner,³² the term "Küttner's tumor" was adopted. Furthermore, Sjögren's syndrome, involving dry eyes and dry mouth due to autoimmune etiology, has become well known,³³ and these medical terms have led to confusion. Since Morgan *et al.* reported that MD was not a distinct clinical and pathological disease but merely one manifestation of Sjögren's syndrome³⁴ in 1953, MD has attracted very little interest. However, many cases of MD were recently reported in Japan, and differences between MD and Sjögren's syndrome were investigated. Yamamoto *et al.* reported that most patients with MD showed IgG4-related disease,³⁵ removing the confusion.

The diagnostic criteria of IgG4-related MD proposed by the Japanese Society of Sjögren's Syndrome in 2008 comprise three items: 1) symmetrical swelling of at least 2 pairs of lacrimal, parotid, or submandibular glands persisting longer 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.⁷ However, the diagnosis of IgG4-related MD requires differential diagnosis from lymphoma (especially MALT lymphoma), sarcoidosis, and multicentric Castleman's disease, so histopathological confirmation is quite important. Compared with organs that are difficult to biopsy such as the pancreas, salivary and lacrimal gland biopsies are relatively easy to perform; therefore, diagnosis without histopathology is problematic. For such reasons, validation and revision of the diagnostic criteria of IgG4-MD are ongoing issues.

Diagnosis of IgG4-related kidney disease

IgG4-related disease frequently involves the kidney. Patients with kidney involvement usually demonstrate subclinical features, but may have edema when they show marked proteinuria. For the diagnosis of IgG4-related kidney disease, if the patient demonstrates 1) renal dysfunction by urine or serum examination or imaging findings, and 2) elevation of serum IgG level, hypocomplementemia, or elevation of serum IgE, diagnosis of IgG4-related kidney disease would

be confirmed by serum IgG4 level and histopathologic findings of kidney biopsy, with differential diagnosis made from imaging findings and histopathology of other involved organs.¹⁶ In these criteria, a steroid trial is not included because a needle biopsy of kidney tissue is a simple procedure compared with biopsy of other organs such as the pancreas.

Diagnosis of IgG4-related lymphadenopathy

Patients with IgG4-related lymphadenopathy might have been misdiagnosed as cases of lymphoma, especially angioimmunoblastic T-cell lymphoma, sarcoidosis or Castleman's disease before the IgG4 era. More aggressive chemotherapy used to be administered to such patients due to misdiagnosis.

Sato *et al.* classified IgG4-related lymphadenopathy into five patterns: 1) Castleman's disease-like morphology, 2) reactive follicular hyperplasia, 3) interfollicular plasmacytosis and immunoblastosis, 4) progressive transformation of germinal center-like, and 5) inflammatory pseudotumor-like morphology.⁴ They described IgG4⁺ plasma cells distributed in interfollicular areas in most cases, except pattern 4) cases where IgG4⁺ cells are present in the intragerminal center. Clinical differences among these classification patterns have not been established.

We should note that single-organ involvement of lymph node is quite rare in IgG4-related disease cases. In other words, if the patient has typical organ involvement, such as pancreas, lacrimal and salivary glands, or retroperitoneum, the diagnosis of IgG4-related lymphadenopathy seems to be reliable. However, lymph node-only cases seem to be problematic. In such cases, differential diagnosis, such as lymphoma, sarcoidosis, and Castleman's disease, must be determined carefully and definitively.

Similarly, single-organ involvement of lung, skin, blood vessel, joint, liver, thyroid, gastrointestinal tract, prostate, hypophysis, nerve, and so on is quite rare as well; thus, the same careful attention and approach are required.

Diagnosis of IgG4-related aortitis, periaortitis, and mediastinal and retroperitoneal fibrosis

Several IgG4-related aortic lesions have been reported,^{36,37} and cases involving inflammatory aortitis or aneurysm may include these conditions. Cases with typical organ involvement such as pancreas, and lacrimal and salivary glands are diagnosed easily; however, most cases of a single aortic lesion are difficult to diagnose before surgical resection. Aortic involvement varies, such as in subclinical cases found incidentally by ¹⁸FDG-PET, or typical aneurysm formation. The involved site ranges from ascending to descending aorta, their branches, and coronary arteries, among others. Furthermore, in some cases complicated by mediastinal and/

or retroperitoneal fibrosis, the borderline between aortic lesion and periaortic lesion is unclear.

The diagnostic criteria of IgG4-related aortitis and retroperitoneal fibrosis have not yet been established. The diagnosis of cases without typical organ involvement must be made carefully.

TREATMENT

General therapeutic concept

Some patients diagnosed with IgG4-RD may show spontaneous remission, and thus do not require treatment. Organ involvement may be determined using whole-body CT scans or ¹⁸FDG-PET-CT. Involved organs in patients with IgG4-RD strongly demonstrate ¹⁸FDG-avid lesions, similar to lymphomas, so this modality is recommended if possible.¹⁸⁻²⁰

Asymptomatic patients showing involvement of a single organ, such as a lacrimal or salivary gland, may be monitored without treatment. In contrast, patients with involvement of a major organ, such as the pancreas or kidney, should be treated as soon as possible because delaying treatment may cause irreversible fibrosis. Patients with aortic lesions that have progressed to aneurysm should undergo stent implantation prior to glucocorticoid treatment, thereby avoiding rupture. In contrast, patients with subclinical aortic lesions that can be detected only by ¹⁸FDG-PET are good candidates for early glucocorticoid treatment (Fig. 1). Stent implantation before starting glucocorticoid treatment is also recommended for patients with obstructive jaundice.

Glucocorticoid treatment

According to Japanese consensus criteria, the starting dose of prednisolone should be 0.5-0.6 mg/kg/day.^{2,3,7} This dose is reduced gradually in each patient, depending on the results of physical examination, laboratory data, and imaging modalities. Early discontinuation of glucocorticoid may result in disease recurrence, thus using a maintenance dose of 5 to 10 mg/day prednisolone for more than one year is recommended. Response to glucocorticoids should be confirmed by imaging modalities two to four weeks after starting treatment. A poor response at that time may indicate an initial misdiagnosis, suggesting that these patients require reassessment, including another biopsy.

Although treatment strategies for glucocorticoid-refractory patients have not yet been established, recurrence after withdrawal of glucocorticoids may be resolved by restarting or increasing glucocorticoids. Patients with glucocorticoid-resistant IgG4-RD may have been misdiagnosed or have true glucocorticoid-resistant IgG4-RD.

Several possibilities of misdiagnosis should be considered: 1) the initial diagnosis was incorrect; 2) the biopsy

specimen may have been compatible with IgG4-RD, while other sites may not; and 3) IgG4-RD may have undergone a histopathological transformation to another disorder, especially malignancy. Therefore, a glucocorticoid-resistant patient with IgG4-RD should be re-examined by imaging modalities and by taking additional biopsies. Alternative agents should not be attempted without reassessing the patient.

True glucocorticoid resistance can consist of 1) refractoriness to primary glucocorticoid treatment, 2) recurrence at a relatively high glucocorticoid dose while tapering, 3) recurrence after complete discontinuation of glucocorticoid, and 4) intolerance to glucocorticoid, including patients with severe diabetes mellitus (DM) or osteoporosis. Alternative treatments should be considered only for patients with true glucocorticoid resistance.

Most patients with DM before glucocorticoid treatment may experience exacerbation of DM symptoms during glucocorticoid treatment and require insulin treatment transiently. Furthermore, some patients without DM or pancreatic lesion may have subclinical pancreatic lesions and develop DM after glucocorticoid treatment is started. These patients should therefore be hospitalized for a short period of time and be monitored by a DM specialist at the start of glucocorticoid treatment. However, the presence of DM is not a contraindication for glucocorticoid treatment. Patients with DM due to a clinical or subclinical pancreatic lesion may recover pancreatic function and glucose tolerance as a result of early glucocorticoid treatment.

Other immunomodulatory agents

Alternative drugs should be considered only for patients truly refractory to glucocorticoids. Other drugs reported to be effective include azathioprine, methotrexate, mizoribine,³⁸ mycophenolate mofetil, cyclophosphamide, cyclosporine, bortezomib,³⁹ and rituximab.⁴⁰⁻⁴⁴ However, their relative effectiveness and appropriateness have not yet been established.

Rituximab

Rituximab is frequently used in western countries, especially the USA. In one trial, ten patients with glucocorticoid-refractory IgG4-RD were treated with 1 g of rituximab on days 1 and 15⁴³ and assessed using IgG4-RD responder

index.⁴⁴ Except for one patient with a fibrosis lesion due to Riedel thyroiditis, the other nine experienced improvements and were able to discontinue treatment with prednisolone and/or other anti-rheumatic drugs. Although serum IgG4 levels were reduced in these patients, four relapsed symptomatically or showed an increase in serum IgG4 level, requiring retreatment with rituximab. In that study, the glucocorticoid maintenance period was too short, with complete discontinuation after 2-3 months. Therefore, glucocorticoid refractoriness in these patients did not correspond to glucocorticoid refractoriness in Japanese patients with IgG4-RD.

The primary etiology of IgG4-RD has not yet been determined. The increased populations of lymphocytes and plasma cells are usually polyclonal,⁴⁵ suggesting that these increases are not etiologic, but are due to other types of stimulation. Therefore, an effective treatment mechanism has not yet been established completely, and the rationale for treatment remains unclear.

A few trials have analyzed rituximab in the treatment of patients with glucocorticoid-refractory IgG4-RD. Japanese physicians should therefore be careful in using this agent, especially without reassessing diagnosis. Moreover, Japanese health insurance plans do not cover rituximab for patients with IgG4-RD at present.

Treatment study

Although glucocorticoid treatment is effective for patients with IgG4-RD, treatment regimens have not yet been standardized. The starting dose, method of tapering, and maintenance dose and duration must therefore be established. We performed a prospective phase II trial to establish a standard glucocorticoid treatment regimen for patients with IgG4-RD (UMIN: 000002311) (Table 1).

In that trial, the initial dose of prednisolone was 0.6 mg/kg body weight per day. Every 2 weeks, the dose was reduced by 10%. The maintenance dose was 10 mg/day for at least three months. The subsequent maintenance dose and the need for continued prednisolone treatment were determined for each individual patient, on the basis of the results of physical examination, laboratory data, and imaging modalities. The trial that we performed enrolled patients who fulfilled the CDC for IgG4-RD, as established by the Japanese IgG4-RD research group. It included patients who fulfilled serum and

Table 1. Phase II prospective treatment study for IgG4⁺ MOLPS (UMIN: R000002820): The All Japan, Ministry of Health, Labor, and Welfare (MHLW) IgG4 Team

Starting dose	prednisolone 0.6 mg/kg/day
Tapering	10% every 2 weeks
Maintenance	10 mg/day at least 3 months: The subsequent maintenance dose was determined by each physician, according to each patient's needs, based on physical examination, laboratory data, and imaging modalities.

pathological criteria according to differential diagnoses. The primary study endpoint was the complete remission rate at 1 year. Secondary endpoints included the maintenance dose of prednisolone, the relapse rate, and adverse events. We had assumed enrollment of 57 patients over 5 years, but enrollment rates were higher, with 61 patients registered over 4 years. Registration was subsequently closed. We are collecting data and will publish the results soon.

Although evidence for glucocorticoid treatment has not yet been established, second-line treatment is being examined in the USA. The phase I/II Massachusetts General Hospital and Mayo Clinic intergroup trial of rituximab for patients with glucocorticoid-resistant IgG4-RD is currently ongoing (<http://clinicaltrials.gov/show/NCT01584388>). That trial is enrolling patients with IgG4-related retroperitoneal fibrosis, AIP, sialadenitis, and pseudotumor. These patients will be treated with two doses of 1 g of rituximab, on days 1 and 15, followed by evaluation of treatment response and safety.

Despite the importance of this trial, health insurance limitations prevent the use of rituximab in Japan. A prospective trial in Japan must be performed prior to using rituximab to treat patients with IgG4-RD.

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CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

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