detailed analyses of clinical symptoms, laboratory results, and biopsy specimens of patients with IgG4-RD, resulting in the establishment of comprehensive diagnostic criteria for IgG4-RD.

Results Although many patients with IgG4-RD have lesions in several organs, either synchronously or metachronously, and the pathological features of each organ differ, consensus has been reached on two diagnostic criteria for IgG4RD: (1) serum IgG4 concentration >135 mg/dl, and (2) >40% of IgG+ plasma cells being IgG4+ and >10 cells/high powered field of biopsy sample. Although the comprehensive diagnostic criteria are not sufficiently sensitive for the diagnosis of type 1 IgG4-related autoimmune pancreatitis (IgG4-related AIP), they are adequately sensitive for IgG4-related Mikulicz's disease (MD) and kidney disease (KD). In addition, the comprehensive diagnostic criteria, combined with organ-specific diagnostic criteria, have increased the sensitivity of diagnosis to 100% for IgG4-related MD, KD, and AIP.

Conclusion Our comprehensive diagnostic criteria for IgG4-RD are practically useful for general physicians and nonspecialists.

Keywords IgG4-related disease · Criteria · Mikulicz's disease · Autoimmune pancreatitis · Interstitial nephritis

Abbreviations

IgG4-RD	IgG4-related disease
MD	Mikulicz's disease
AIP	Autoimmune pancreatitis
KD	Kidney disease
TIN	Tubulointerstitial nephritis
SS	Sjögren's syndrome
MHLW	Japan Ministry of Health, Labor and Welfare Japan; familial multifocal fibrosclerosis
RPF	Retroperitoneal fibrosis
TIN	Tubulointerstitial nephritis
MOLPS	Multiorgan lymphoproliferative syndrome
SIPS	Systemic IgG4 plasmacytic syndrome

Introduction

IgG4-related disease (IgG4-RD) is a new emerging disease entity of unknown etiology with multiorgan involvement [1]. IgG4-RD has been found to affect the pancreas, bile duct, lacrimal glands, salivary glands, central nervous system, thyroid, lungs, liver, gastrointestinal tract, kidney, prostate, retroperitoneum, arteries, lymph nodes, skin, and breast. Therefore, IgG4-RD includes a wide variety of diseases, including Mikulicz's disease (MD) [2, 3], autoimmune pancreatitis (AIP) [4], hypophysitis, Riedel

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thyroiditis [5], interstitial pneumonitis [6, 7], interstitial nephritis [8, 9], prostatitis, lymphadenopathy [10, 11], retroperitoneal fibrosis [12, 13], inflammatory aortic aneurysm [14], and inflammatory pseudotumor. Although IgG4-RD is not rare and is clinically important, its clinical diagnostic criteria have not yet been established. Two study groups where thus organized by the Ministry of Health, Labor and Welfare (MHLW) Japan. One group, the Umehara team, chaired by Professor Umehara of Kanazawa Medical University, is seeking to establish diagnostic criteria for IgG4-RD; the second group, the Okazaki team, chaired by Professor Okazaki of Kansai Medical University, is seeking to understand the etiology and pathogenesis of IgG4-RD. These groups consist of physicians and researchers in various fields, including rheumatology, hematology, gastroenterology, nephrology, pulmonology, ophthalmology, odontology, pathology, statistics, and basic and molecular immunology from all over Japan, with 66 and 56 members of the Umehara and Okazaki teams, respectively.

Background for establishing diagnostic criteria for IgG4-RD

General concepts of IgG4-RD

Although the two groups independently analyzed the clinical features and conditions of IgG4-RD, they collaborated closely, which resulted in the following consensus: (1) IgG4-RD can occur in various organs, including the central nervous system, salivary glands, thyroid gland, lungs, pancreas, biliary duct, liver, gastrointestinal tract, kidneys, prostate gland, retroperitoneum, and lymph nodes, with clinical symptoms depending on lesion location. (2) IgG4-RD mainly affects middle-aged to elderly men; its clinical symptoms are relatively mild, and the condition usually comes to clinical attention due to organ swelling or damage. (3) Many patients with IgG4-RD can be treated effectively by steroid therapy. (4) Although the infiltration of IgG4+ cells and increased serum concentrations of IgG4 are characteristic of IgG4-RD, the severity of fibrosis is dependent on the individual organs involved. The common characteristics of these conditions include elevated serum IgG4 concentrations and tissue infiltration by IgG4+ plasma cells, accompanied by tissue fibrosis and sclerosis [1].

Naming of IgG4-related disease

Many terms have been used to describe IgG4-RD, including IgG4-related sclerosing disease [15], IgG4-related autoimmune disease [16], systemic IgG4 plasmacytic syndrome (SIPS) [17], and IgG4-related multiorgan lymphoproliferative syndrome (IgG4-MOLPS) [3]". The members of the Umehara and Okazaki teams carefully examined reports using these different nomenclatures and concluded that they referred to the same condition, and the two teams finally agreed to use a uniform nomenclature—IgG4-related disease (IgG4-RD)—for several reasons: (1) Although infiltration of IgG4+ cells and increased serum concentrations of IgG4 are characteristic of IgG4-RD, the severity of fibrosis is dependent on the individual organs involved. For example, storiform fibrosis is characteristic of IgG4-related autoimmune pancreatitis (IgG4-related AIP), IgG4-related retroperitoneal fibrosis (IgG4-related RPF), and IgG4-related tubulointerstitial nephritis (IgG4-related TIN), but is very seldom found in patients with IgG4-related MD and IgG4-related lymphadenopathy. (2) Although many patients with this IgG4-RD have lesions in several organs, either synchronously or metachronously, other patients show involvement of a single organ. (3) As there have been several reports describing patients with IgG4-associated conditions concomitant with malignant tumors, such as pancreatic and salivary carcinomas [18–21] and ocular adnexal lymphoma [22, 23], using the term systemic may lead to an incorrect diagnosis of an IgG4-related condition in a patient with malignant tumors in other organs [24].

Prevalence of IgG4-RD

It is difficult to ascertain the number of patients with IgG4-RD because the awareness of this disease is low and its diagnostic criteria have not yet been established. The Umehara team attempted to estimate the number of individuals with IgG4-RD throughout Japan by using as an example Ishikawa Prefecture, which contains 1.16 million people with little population inflow/outflow. The incidence of this disease throughout Japan was estimated to be 0.28–1.08/100,000, with 336–1,300 patients newly diagnosed per year and approximately 6,700–26,000 patients who developed IgG4-RD over the past 20 years [1]. In contrast, the Okazaki team attempted to estimate the

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incidence of IgG4-RD through a network of Japanese researchers in an AIP study; they reported that 8,000 patients throughout Japan had IgG4-RD.

Proposal of comprehensive diagnostic criteria for IgG4-RD

Concept of comprehensive diagnostic criteria for IgG4-RD

IgG4-RD may occur, either synchronously or metachronously, in a variety of organs throughout the body, including the pancreas, bile duct, lacrimal gland, salivary gland, thyroid, lung, liver, gastrointestinal tract, kidney, and retroperitoneum [1]. As clinical symptoms and pathological features depend on lesion location, it is probably impossible to establish criteria that include all patients with IgG4-RD. Detailed diagnostic criteria are needed for the involvement of each organ, including clinical symptoms, serological and histological findings, and radiological images. To date, diagnostic criteria for IgG4-related MD [25] (Table 1), IgG4-related AIP type 1 [26] (Table 2), and IgG4-related kidney disease (KD) [27] (Table 3) have been established. However, these organ-specific criteria are not suitable for the diagnosis of patients with involvement of other organs. In addition, organ-specific criteria may not be familiar to general clinicians and specialists in diseases of those organs, although all clinicians should become aware of this new disease entity and its diagnosis. Therefore, comprehensive diagnostic criteria are necessary for practical use and to differentiate among malignancies.

Comprehensive diagnostic criteria for IgG4-RD

The comprehensive diagnostic criteria we have proposed for IgG4-RD (Table 4) consist of three parts: concept, diagnostic criteria, and explanatory notes. The concept clarifies the features characteristic of IgG4-RD, such as lesion location, symptoms, and prognosis. Diagnostic criteria are based on two major characteristics of IgG4-RD: increased serum concentrations of IgG4 and infiltration of IgG4+ cells. The cutoff value for serum IgG4 concentration, 135 mg/dl, was based on receiver operating characteristic (ROC) curves, and its validity was confirmed in patients with AIP [26, 28]. Although tissue biopsies are difficult to obtain from some organs, including the pancreas, retroperitoneum, and ocular cavity, histopathological examination is important. Because IgG4+ plasma cell infiltration has been reported in various diseases and clinical conditions, such as rheumatoid synovitis, inflammatory oral and skin lesions, and carcinomas with a peritumoral inflammatory response [29], pathological criteria should be rigorous. Histopathological findings of marked IgG4+ cell

Table 1 Diagnostic criteria for IgG4+ Mikulicz's disease [25] (approved by the Japanese Society for Sjögren's Syndrome, 2008)

1. Symmetrical swelling of at least two pairs of lachrymal, parotid, and 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
Differential diagnosis is necessary from other disorders, including sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer. Although the diagnostic criteria for Sjögren's syndrome (SS) may also include some patients with IgG4+ Mikulicz's disease, the clinicopathological conditions of patients with typical SS and IgG4+ Mikulicz's disease are different

Table 2 Clinical diagnostic criteria for autoimmune pancreatitis in Japan (2006) [26]

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular walls and diffuse or localized enlargement of the pancreas on imaging modalities, including abdominal ultrasound, computed tomography, and magnetic resonance imaging
2. High-serum F-globulin, IgG, or IgG4 concentration or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells to the periductal area, occasionally accompanied by lymphoid follicles in the pancreas
For diagnosis, criterion 1 must be present, together with criterion 2 and/or 3
However, it is necessary to exclude malignant diseases such as pancreatic and biliary cancers

Table 3 Diagnostic criteria for IgG4-related kidney disease [27]

1. Presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s) or decreased kidney function with either elevated serum IgG or IgE or hypocomplementemia
2. Abnormal renal radiologic findings:
   a. Multiple low-density lesions on enhanced computed tomography
   b. Diffuse kidney enlargement
   c. Hypovascular solitary mass in the kidney
   d. Hypertrophic lesion of the renal pelvic wall without irregularities of the renal pelvic surface
3. Elevated serum IgG4 level (>135 mg/dl)
4. Histological findings in the kidney:
   a. Dense lymphoplasmacytic infiltration by >10 IgG4+ plasma cells/high power field (HPF) and/or IgG4+/IgG+ plasma cells >40%
   b. Characteristic (sclero-) fibrosis surrounding nests of lymphocytes and/or plasma cells
5. Histological findings in extra-renal organ(s):
   Dense lymphoplasmacytic infiltration by >10 IgG4+ plasma cells/HPF and/or IgG4+/IgG+ plasma cells >40%

Definite:	1 + 3 + 4 a, b
	2 + 3 + 4 a, b
	2 + 3 + 5
	1 + 3 + 4 a + 5
Probable:	1 + 4 a, b
	2 + 4 a, b
	2 + 5
	3 + 4 a, (b)
Possible:	1 + 3
	2 + 3
	1 + 4 a
	2 + 4 a

Appendix:

1. Clinically and histologically, the following diseases should be excluded: Wegener's granulomatosis, Churg–Strauss syndrome, extramedullary plasmacytoma
2. Radiologically, the following diseases should be excluded: malignant lymphoma, urinary tract carcinomas, renal infarction, and pyelonephritis (rarely, Wegener's granulomatosis, sarcoidosis and metastatic carcinoma)

infiltration [>10 cells/high power field (HPF)] and an IgG4+/IgG+ cell ratio >40% are diagnostic of IgG4-RD. Explanatory notes describe clinical characteristics of IgG4-RD specific to each organ, as well as blood tests and pathologic findings, responses to steroids, and differential diagnoses.

Algorithm for diagnosing IgG4-RD

A diagnostic algorithm for IgG4-RD, using comprehensive diagnostic criteria combined with organ-specific criteria, is shown in Fig. 1. A diagnosis of IgG4-RD is definitive in patients with: (1) organ enlargement, mass or nodular lesions, or organ dysfunction; (2) a serum IgG4 concentration >135 mg/dl; and (3) histopathological findings of >10 IgG4 cells/HPF and an IgG4+/IgG+ cell ratio >40% (category 1). A diagnosis of IgG4-RD is possible in patients who fulfill criteria (1) and (2), but with negative results on histopathology or without histopathologic examination (category 2 and 3), whereas a diagnosis of IgG4-RD is probable in patients with organ involvement (1) and fulfilled histopathologic criteria, but without increased serum IgG4 concentration (2) (category 4). Patients with organ symptoms without satisfying serologic or histopathologic criteria are considered unlikely to have IgG4-RD (category 5 and 6). For patients in categories 2–5, organ-specific criteria for IgG4-RD could be applied, such as those for AIP [26], MD [25], and KD [27] associated with IgG4. Patients who fulfill the organ-specific criteria for IgG4-RD have a definite diagnosis of this disease (category 7).

Validation of comprehensive diagnostic criteria in previous reports of patients with IgG4-RD

To validate the comprehensive diagnostic criteria, we applied them to patients described in two studies of IgG4-related MD [3, 30], two of IgG4-related KD [9, 27], and

Table 4 Comprehensive diagnostic criteria for IgG4-related disease, 2011

I. Concept

IgG4-related disease (IgG4-RD) shows organ enlargement or nodular/hyperplastic lesions in various organs concurrently or metachronously, due to marked infiltration of lymphocytes and IgG4+ plasma cells, as well as fibrosis of unknown etiology. IgG4-RD affects various organs, including the pancreas, bile duct, lacrimal gland, salivary gland, central nervous system, thyroid, lung, liver, gastrointestinal tract, kidney, prostate, retroperitoneum, arteries, lymph nodes, skin, and breast. Although many patients with IgG4-RD have lesions in several organs, either synchronously or metachronously, others show involvement of a single organ. Clinical symptoms vary depending on the affected organ, and some patients may experience serious complications, such as obstruction or compression symptoms due to organomegaly or hypertrophy, and organ dysfunction caused by cellular infiltration or fibrosis. Steroid therapy is often effective

II. [Comprehensive clinical diagnostic criteria for IgG4-RD]

1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs

2. Hematological examination shows elevated serum IgG4 concentrations(≥135 mg/dl)

3. Histopathologic examination shows:

(1) Marked lymphocyte and plasmacyte infiltration and fibrosis.

(2) Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells > 40% and >10 IgG4+ plasma cells/HPF

Definite: 1) + 2) + 3)

Probable: 1) + 3)

Possible: 1) + 2)

However, it is important to differentiate IgG4-RD from malignant tumors of each organ (e.g. cancer, lymphoma) and similar diseases (e.g. Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, Churg–Strauss syndrome) by additional histopathological examination

Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4RD

III. Explanatory notes

1. The comprehensive diagnostic criteria are the minimal consensus to aid general practitioners and other nonspecialist physicians in the clinical diagnosis of IgG4-RD. For each affected organ, organ-specific diagnostic criteria established for IgG4-related Mikulicz's disease, IgG4-related autoimmune pancreatitis, and IgG4-related kidney disease, should be used concurrently

2. Concept:

The difference from multifocal fibrosclerosis is unclear although these diseases may be IgG4-RD. Many patients show multiple organ involvement and are characterized as having systemic disease, whereas other patients show involvement of a single organ

(a) Autoimmune pancreatitis, type 1 (IgG4-related autoimmune pancreatitis): This disease is synonymous with IgG4-related sclerosing pancreatitis/lymphoplasmacytic sclerosing pancreatitis (LPSP). It can be diagnosed using the clinical diagnostic criteria for autoimmune pancreatitis established by the Ministry of Health, Labor and Welfare, Japan Pancreas Society, in 2006 [26]

(b) IgG4-related sclerosing cholangitis: This disease is characterized by sclerotic changes with diffuse or localized stenosis in the intrahepatic/extrahepatic bile duct and gallbladder. Circumferential wall thickening is observed at the site of stenosis, with similar changes in areas without stenosis. Obstructive jaundice often develops, making it important to differentiate this condition from tumors, such as cholangiocarcinoma and pancreatic cancer, and from primary sclerosing cholangitis. It is also necessary to exclude secondary sclerosing cholangitis as an apparent cause

(c) IgG4-related lacrimal, orbital, and salivary-gland lesions: This condition includes IgG4-related Mikulicz's disease characterized by symmetrical (sometimes unilateral) swelling of any of the lacrimal, parotid, submandibular, sublingual glands, and some minor salivary glands. Nodular/infiltrative lesions may also occur in orbital tissue other than the lacrimal glands. IgG4-related Mikulicz's disease can be diagnosed by the organ-specific diagnostic criteria for IgG4-related Mikulicz's disease established by the Sjögren's Syndrome Study Group of Japan in 2008 [25]

(d) IgG4-related central nervous system lesions: These lesions include infundibular hypophysitis, hypertrophic pachymeningitis, and intracerebral inflammatory pseudotumor

Table 4 continued

(e) IgG4-related respiratory lesions: These lesions occur primarily in the interstitium, such as bronchovascular bundles, interlobular septum, alveolar septum, and pleura. They are frequently accompanied by mediastinal and hilar lymphadenopathy, along with X-ray evidence of a mass or infiltration of the lung. Some patients have asthma-like symptoms. It is important to differentiate these lesions from malignant tumors, sarcoidosis, collagen diseases of the lung, and infection

(f) IgG4-related renal lesions: Abnormal imaging findings include diffuse renal enlargement, multifocal contrast defects of the renal parenchyma, renal mass lesions, and pelvic wall thickening. Renal histology shows mainly interstitial nephritis, but glomerular lesions (e.g., membranous nephropathy), may also be present. IgG4-related tubulointerstitial nephritis can be diagnosed using the organ-specific diagnostic criteria for IgG4-related kidney disease [27]

(g) IgG4-related retroperitoneal fibrosis/periarterial lesions: This disease is characterized by thickening of the abdominal aortic adventitia and periurethral soft tissue, often accompanied by hydronephrosis or mass lesions. Periarteritis may occur around the aorta or relatively large branches and is evident as arterial wall thickening on radiological imaging. Magnetic resonance imaging (MRI) and positron emission tomography (PET) have been shown to be helpful for diagnosing retroperitoneal fibrosis in addition to X-ray, which may include CT scan. Biopsy is often inconclusive, making it difficult to differentiate this condition from secondary retroperitoneal fibrosis due to malignant tumors or infectious diseases

(h) Other tumefactive lesions: Proliferation of IgG4+ plasma cells and lymphocytes may accompany fibrosis. Including some conventional inflammatory pseudotumors, these lesions have been reported in the brain, orbit, lung, breast, liver, pancreas, retroperitoneum, kidney, and lymph nodes

IV. Blood test findings

1. Polyclonal serum γ-globulin, IgG, and IgE are often elevated, and hypocomplementemia may occur

2. Elevated IgG4 can also be seen in other diseases (e.g., atopic dermatitis, pemphigus, asthma, and multicentric Castleman's disease) and is therefore not specific to IgG4-RD

3. On rare occasions, serum IgG4 concentration may be elevated in patients with malignant tumors. However, patients with >270 mg/dl IgG4 are unlikely to have pancreatic cancer

4. In patients with single-organ involvement and serum IgG4 concentration <135 mg/dl, the IgG4+/IgG+ ratio may be helpful in making a diagnosis

5. At present, the significance of elevated IgG4 in the pathogenesis/pathophysiology of IgG4-RD is unknown

V. Histopathological findings

1. Storiform or swirling fibrosis or obliterative phlebitis are characteristic of IgG4-RD and may be important in its diagnosis

2. Eosinophilic infiltration often occurs, along with infiltration of IgG4+ cells

3. Reactive infiltration of IgG4+ cells and fibrosis may also occur, such as at the periphery of pancreatic cancers

VI. Imaging studies

IgG4-RD may occur, either synchronously or metachronously, in a variety of organs throughout the body, including the pancreas, bile duct, lacrimal gland, salivary gland, thyroid, lung, liver, gastrointestinal tract, kidney, and retroperitoneum. MRI and fluorodeoxyglucose (FDG)-PET have been shown to be helpful for detecting multiorgan involvements

VII. Steroids

1. Patients with malignant lymphoma or paraneoplastic lesions can sometimes be improved by steroid administration. Therefore, steroid trials should be strictly avoided

2. Efforts should be made to collect tissue samples for diagnosis. However, patients having disease in organs difficult to biopsy, such as pancreas, retroperitoneum, and pituitary, and who respond to steroids may possibly have IgG4-RD

3. In accordance with the guidelines for treatment of autoimmune pancreatitis, patients should be started on 0.5–0.6 mg/kg per day of prednisolone. If patients do not respond to the initial steroid therapy, the diagnosis should be reviewed

VIII. Diseases to be excluded or differentiated

1. To exclude malignancies (e.g., cancer, lymphoma) in involved organs, it is essential to determine histopathologically whether malignant cells are present

2. Similar diseases (e.g., Sjögren's syndrome, primary sclerosing cholangitis, multicentric Castleman's disease, idiopathic retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, Churg–Strauss syndrome) are diagnosed using the diagnostic criteria for each disease

3. Multicentric Castleman's disease is a hyper-interleukin (IL)-6 syndrome and is not included among the IgG4-RDs, even if the diagnostic criteria for IgG4-RD are fulfilled

three of IgG4-related AIP [31] (Table 5). The sensitivity of these criteria were comparatively good for diagnosing IgG4-related MD (83 and 70%) and KD (87 and 85%). In contrast, patients with IgG4-related AIP could not be diagnosed by the comprehensive diagnostic criteria (0% for definite, nearly 70% for possible, and 10–30% for unlikely) because biopsies could not be obtained from most of these patients. Application of organ-specific criteria to undiagnosed patients increased the sensitivity of diagnosis to 100%, even for patients with IgG4-related AIP (Table 5).

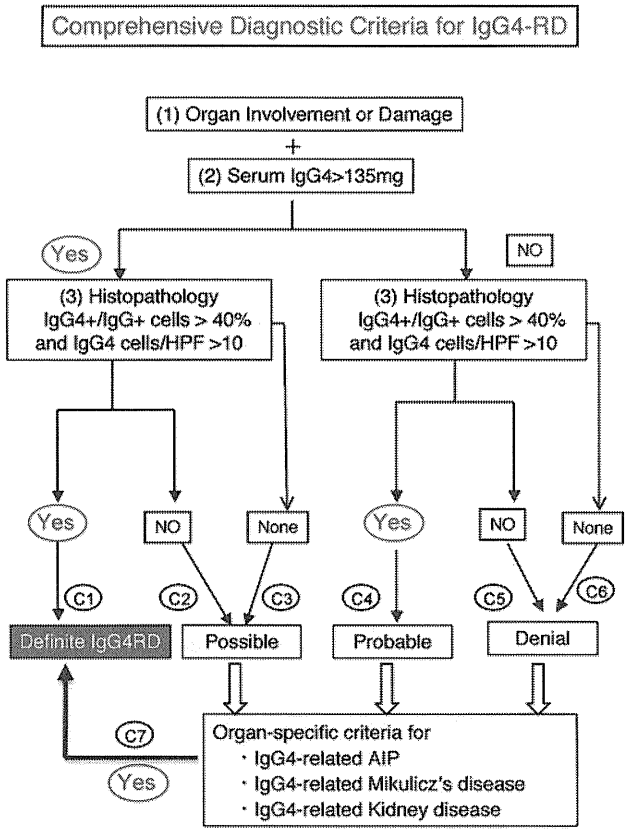

Fig. 1 Diagnostic algorithm performance for comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD) using comprehensive diagnostic criteria combined with organ-specific criteria. A diagnosis of IgG4-RD is definitive in patients with (*1*) organ enlargement, mass or nodular lesions, or organ dysfunction, (*2*) a serum IgG4 concentration >135 mg/dl, and (*3*) histopathological findings of >10 IgG4+ cells/HPF and an IgG4+/IgG+ cell ratio >40% (*C1*). A diagnosis of IgG4-RD is possible in patients who fulfill criteria (*1*) and (*2*), but with negative results on histopathology or without histopathologic examination (*C2*, *C3*), whereas a diagnosis of IgG4-RD is probable in patients with (*1*) organ involvement and (*2*) fulfilled histopathologic criteria, but without increased serum IgG4 concentration (*C4*). Patients with organ symptoms without satisfying the serologic or histopathologic criteria are considered unlikely to have IgG4-RD (*C5*, *C6*). For patients in C2–C6, organ-specific criteria for IgG4-related autoimmune pancreatitis (AIP), IgG4-related Mikulicz's disease (MD), and IgG4-related kidney disease (KD). Patients who fulfill the organ-specific criteria have a definite diagnosis of IgG4-RD (*C7*)

Discussion

Although there is increased interest in IgG4-RD, awareness of it remains low and diagnostic criteria have not yet been published. Therefore, IgG4-RD has often been misdiagnosed as a malignant tumor, lymphoma, Sjögren's syndrome, or other diseases despite the effectiveness of steroid therapy. As IgG4-RD affects various organs, its clinical symptoms vary, and each patient with IgG4-RD may visit specialists addressing organ-specific lesions. Organ-specific criteria have been established for IgG4-related AIP [26], MD [25] and KD [27], but these criteria are not suitable for diagnosing patients with other involved organs, and they are not familiar to general clinicians and nonspecialists. Comprehensive diagnostic criteria are therefore needed for practical use by such physicians. Although it is difficult to obtain tissue biopsy samples from some organs, including the pancreas, retroperitoneum, and brain, histopathologic examination is highly important to exclude malignancies [18–21] and other types of disease [29]. Indeed, most patients with IgG4-related AIP could be diagnosed without biopsy. The comprehensive diagnostic criteria for IgG4-RD have relatively low sensitivity in patients with IgG4-related AIP because of a lack of biopsy samples but were sufficiently sensitive for IgG4-related MD and KD. Patients who could not be diagnosed by the comprehensive diagnostic criteria could be diagnosed by organ-specific criteria, indicating the complementarity of comprehensive diagnostic criteria and organ-specific criteria for IgG4-RD.

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Conflict of interest None.

Appendix

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Table 5 Sensitivity for diagnosis by comprehensive diagnostic criteria for IgG4-RD

Main organ	Definite	Probable	Possible	Denial	References
Mikulicz (64)	53 (83%)	4 (6%)	7 (11%)	0 (0%)	Masaki et al. [3]
+OS criteria		4/4	7/7		
Total	64 (100%)				
Mikulicz (40)	28 (70%)	0 (0%)	12 (30%)	0 (0%)	Yamamoto et al. [30]
+OS criteria			12/12		
Total	40/40 (100%)				
Kidney (23)[a]	20 (87%)	0 (0%)	0 (0%)	3 (13%)	Saeki et al. [9]
+OS criteria				3/3	
Total	23 (100%)				
Kidney (41)[a]	35 (85%)	0 (0%)	3 (7%)	3 (7%)	Kawano et al. [27]
+OS criteria			3/3	3/3	
Total	41/41 (100%)				
AIP (60)	0 (0%)	0 (0%)	41 (68%)	19 (32%)	Takuma et al. [32]
+OS criteria			41/41	19/19	
Total	60 (100%)				
AIP (54)	0 (0%)	0 (0%)	42 (78%)	12 (22%)	Okazaki et al. [31]
+OS criteria			42/42	12/12	
Total	54 (100%)				
AIP (90)	0 (0%)	3 (3%)	70 (78%)	9 (10%)	Fujiwara et al. [33]
+OS criteria		3/3	70/70	9/9	
Total	90 (100%)				

OS criteria organ-specific criteria

[a] 10 patients were included both in Refs. [9, 27]

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REVIEW ARTICLE

A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details

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Abstract IgG4-related disease (IgG4RD) is a novel clinical disease entity characterized by elevated serum IgG4 concentration and tumefaction or tissue infiltration by IgG4-positive plasma cells. IgG4RD may be present in a certain proportion of patients with a wide variety of diseases, including Mikulicz's disease, autoimmune pancreatitis, hypophysitis, Riedel thyroiditis, interstitial pneumonitis, interstitial nephritis, prostatitis, lymphadenopathy, retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pseudotumor. Although IgG4RD forms a distinct, clinically independent disease category and is attracting strong attention as a new clinical entity, many questions and problems still remain to be elucidated, including its pathogenesis, the establishment of diagnostic criteria, and the role of IgG4. Here we describe the concept of IgG4RD and up-to-date information on this emerging disease entity.

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Keywords IgG4-related diseases · Mikulicz's disease · Sjögren's syndrome · Autoimmune pancreatitis · Castleman's disease

Abbreviations

IgG4RD	IgG4-related disease
MD	Mikulicz's disease
SS	Sjögren's syndrome
MHLW Japan	Ministry of Health, Labor and Welfare Japan
LPSP	Lymphoplasmacytic sclerosing pancreatitis
AIP	Autoimmune pancreatitis
FMF	Familial multifocal fibrosclerosis
ANA	Anti-nuclear antibody

Introduction

In 1892, Dr. Johann von Mikulicz, also known as Jan Mikulicz-Radecki, published a paper describing a patient with symmetrical swelling of the lachrymal, parotid, and submandibular glands, with massive infiltration of these glands by mononuclear cells [1]. Following reports describing similar patients, this condition was called Mikulicz's disease (MD). In contrast, patients with similar symptoms, but with diseases such as leukemia, malignant lymphoma, and sarcoidosis, were reported to have Mikulicz's syndrome [2]. In 1930, Dr. Henrik Sjögren, an ophthalmologist, published a paper describing a woman with rheumatoid arthritis accompanied by keratoconjunctivitis sicca and severe swelling of the parotid glands, a condition that has been recognized as Sjögren's syndrome (SS) [3]. In 1953, Morgan and Castleman examined 18 patients with MD and concluded that this condition is one manifestation of SS [4]. Since then, MD has attracted very little interest in western countries. In Japan, however, there have been many patients with MD, such that differences between MD and SS have been clarified [5–7]. For example, their gender distribution is quite different, in that MD occurs in both men and women, whereas SS occurs mainly in women. Second, patients with MD have relatively mild xerostomia and xerophthalmia, despite significant enlargement of their lachrymal and salivary glands. Further, MD is accompanied by more complications, such as autoimmune pancreatitis (AIP). Patients with MD show a better response to glucocorticoid therapy than patients with SS. Finally, it has become clear that MD is related to elevated serum IgG4 concentrations and infiltration of IgG4-positive cells [5–9].

Following the description of a patient with chronic pancreatitis due to an autoimmune mechanism [10], lymphoplasmacytic sclerosing pancreatitis (LPSP) was found to be a characteristic histopathological finding in patients with AIP [11]. These findings led to the concept of AIP, which has characteristics similar to those of other autoimmune diseases, such as hypergammaglobulinemia, the

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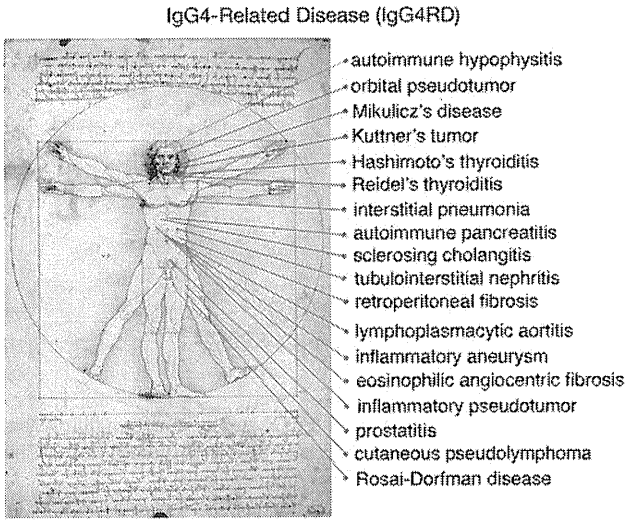


Fig. 1 IgG4-related conditions. Many diseases have been reported to be IgG4-related

presence of various autoantibodies, lymphocytic infiltration into pancreatic tissue, and good responsiveness to steroids [12]. Following a report showing elevated serum IgG4 concentrations in patients with AIP [13], the pancreatic research team of the Ministry of Health, Labor and Welfare Japan (MHLW Japan) showed that AIP was related to IgG4 [14].

IgG4-positive plasma cell infiltration has also been observed in patients with other conditions, including retroperitoneal and mediastinal fibrosis [15, 16], inflammatory pseudotumor of the lung and liver [17], Küttner tumor [18], and interstitial nephritis [19], indicating that these diseases and conditions collectively constitute a new disease concept, IgG4-related disease (Fig. 1). These findings have led to the organization of two study groups by MHLW Japan to analyze the condition of IgG4-related disease. These groups consist of doctors and researchers in various fields, including rheumatology, hematology, gastroenterology, nephrology, pulmonology, ophthalmology, odontology, pathology, statistics, and basic and molecular immunology, from all over Japan. One of these groups, chaired by Professor Umehara of Kanazawa Medical University, is seeking to establish diagnostic criteria for IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS), whereas the second group, chaired by Professor Okazaki of Kasai Medical University, is seeking to understand the etiology and pathogenesis of IgG4-related systemic disease.

Unification of different nomenclatures for IgG4-related disease (IgG4RD)

The concept of IgG4RD arose when elevated serum IgG4 concentrations were first reported in patients with sclerosing pancreatitis [13]. Autoimmune pancreatitis (AIP) is also associated with a variety of extrapancreatic lesions, including sclerosing cholangitis, sclerosing sialadenitis, and dacryoadenitis, resulting in the concept of IgG4-related systemic disease [20], also called IgG4-related autoimmune disease [21] or IgG4-related sclerosing disease [15]. The finding of elevated serum IgG4 and IgG4-positive plasma cell infiltration in MD suggested that MD was a systemic disease, which was called systemic IgG4 plasmacytic syndrome (SIPS) [22]. Further, a comparison of patients with MD and those with typical SS resulted in the formulation of a new clinical entity, IgG4+MOLPS [23]. Although many reports from Japan and other countries have described IgG4-related conditions under different names (Table 1), these may refer to the same condition, familial multifocal fibrosclerosis (FMF). Indeed, retroperitoneal fibrosis (RPF), mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may all be different manifestations of a single disease [24].

Table 1 Nomenclatures of IgG-related conditions

IgG4-related autoimmune disease	Kamisawa [21]
IgG4-associated multifocal systemic fibrosis	van der Vliet [76]
IgG4-related systemic disease	Kamisawa [20]
IgG4-related sclerosing disease	Kamisawa [15]
Hyper-IgG4 disease	Neild [59]
IgG4-related disease (IgG4-RD)	Zen [77]
Systemic IgG4 plasmacytic syndrome (SIPS)	Yamamoto [22]
IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS)	Masaki [29]
IgG4-associated disease	Geyer [78]

The name "IgG4-related sclerosing disease" is mainly based on the swelling of fibrous organs, such as the pancreas and retroperitoneum, whereas "SIPS" and "IgG4+MOLPS" are based on lymphoplasmacytic proliferation in glands and swollen lymph nodes without fibrosis. Although many patients with this condition (i.e., IgG4-related sclerosing disease, etc.) have lesions in several organs, either synchronously or metachronously, other patients show involvement of only a single organ. At this point, it is unclear whether the pathogenetic mechanism of this disease is systemic or whether it consists of manifestations in individual organs. In addition, several reports have described patients with IgG4-associated conditions concomitant with malignant tumors such as pancreatic [25, 26] and salivary [27] carcinomas, and ocular adnexal lymphoma [28]. Therefore, using the term 'systemic' may lead to an incorrect diagnosis of an IgG4-related condition in a patient with malignant

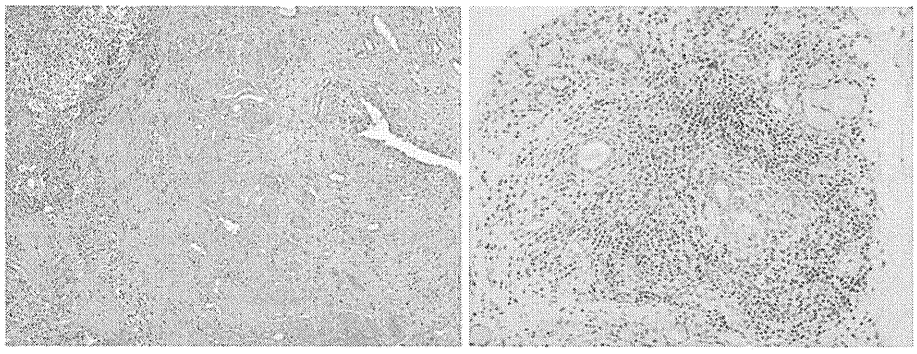


Fig. 2 Histopathology of IgG4-related disease (IgG4RD). IgG4RD is characterized histopathologically by the infiltration of IgG4-positive plasma cells and fibrosis. However, the severity of fibrosis is dependent on the individual organs involved. For example, storiform fibrosis and obliterative phlebitis are characteristic of retroperitoneal lesions, but are very seldom observed in salivary glands (×40)

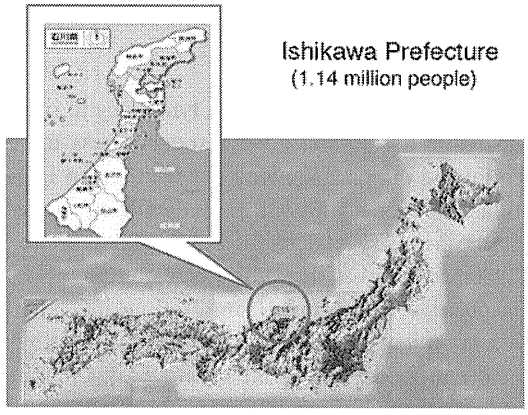
tumors in other organs. Based on these reasons, the members of the two MHLW Japan research teams agreed, at their second meeting in Kanazawa on February 11, 2010, to use the term "IgG4-related disease (IgG4RD)".

General concept of IgG4RD

After the unification of the disease name as IgG4RD, both MHLW Japan research teams have sought to determine its pathogenesis and to formulate diagnostic criteria. The two teams reached a consensus that IgG4RD can occur in various organs, including the central nervous system, salivary glands, thyroid gland, lungs, pancreas, biliary duct, liver, gastrointestinal tract, kidneys, prostate gland, retroperitoneum, and lymph nodes, but that clinical symptoms depend on the location of the lesion. IgG4RD mainly affects middle-aged to elderly men. Its clinical symptoms are relatively mild, and the condition usually comes to clinical attention due to organ swelling or damage. Many patients with IgG4RD are treated effectively by steroid therapy. Although the infiltration of IgG4-positive cells and increased serum concentrations of IgG4 are characteristic of IgG4RD, the severity of fibrosis is dependent on the individual organs involved. For example, storiform fibrosis and obliterative phlebitis are characteristic of pancreatic, biliary tract, and retroperitoneal lesions, but are very seldom found in salivary glands or lymph nodes (Fig. 2).

Prevalence of IgG4RD

It is difficult to ascertain the number of patients with IgG4RD because its diagnostic criteria have not yet been established, the awareness of this disease is low, and its symptoms vary. An attempt was made to estimate the number of individuals with IgG4RD throughout Japan by using as an example Ishikawa Prefecture, which has a population of 1.14 million people with little population inflow/outflow (Fig. 3). In Ishikawa Prefecture, there are



	KMU	KUH	total
2003	2	2	4
2004	0	1	1
2005	1	3	4
2006	1	3	4
2007	1	4	5
2008	1	3	4
2009	1	6	7
	7	22	29

Fig. 3 Prevalence of patients with IgG4RD. An attempt was made to estimate the number of individuals with IgG4RD throughout Japan by using as an example Ishikawa Prefecture (population 1.14 million people) with little population inflow/outflow. If all new patients with IgG4RD visit Kanazawa Medical University Hospital (*KMU*) or Kanazawa University Hospital (*KUH*), the incidence of this disease throughout Japan would be 0.28–1.08/100,000 population, with 336–1,300 patients newly diagnosed per year. If life expectancy after diagnosis is 20 years, then approximately 6,700–26,000 patients in Japan would have developed IgG4RD over the past 20 years. The *numbers in the table* represent the numbers of patients who visited KMU or KUH each year

two University Hospitals, Kanazawa Medical University Hospital (KMU) and Kanazawa University Hospital (KUH). Assuming that new patients with IgG4RD would visit one of these two hospitals, it was estimated that the incidence of this disease throughout Japan would be 0.28–1.08/100,000 population, with 336–1,300 patients newly diagnosed per year. Because the median age of onset of IgG4RD is 58 years and the clinical symptoms are relatively mild, with slow progression and good response to steroid therapy, life expectancy after diagnosis was estimated at 20 years. Thus, an estimated 6,700–26,000 individuals in Japan would have developed IgG4RD over the past 20 years.

Clinicopathological features of IgG4RD

Differences between IgG4-related MD and Sjögren's syndrome

Since elevated serum IgG4 was first reported in patients with MD [6], the members of the Japanese Society of Sjögren's Syndrome have assessed the clinical symptoms, laboratory findings, and detailed histopathology in patients with MD (characterized by symmetrical swelling of the lachrymal, submandibular, and parotid glands), nationwide, since 2004. Some patients did not show typical symptoms of MD such as swelling of the lachrymal, parotid, or submandibular glands but showed elevated serum IgG4 and other indices indicative of MD according to the criteria for the diagnosis of IgG4-related MD shown in Table 2 [8]. Sixty-four patients with MD or elevated serum IgG4 (>135 mg/dl) and characteristic histological findings were initially diagnosed with IgG4RD (formerly called IgG4+MOLPS) based on proposed guidelines for the diagnosis of IgG4RD (Table 3). A comparison of patients with IgG4RD and those with typical SS showed: (1) compared with SS patients, fewer patients with IgG4RD had symptoms of xerophthalmia, xerostomia, or arthralgia, whereas many had coexisting AIP, interstitial nephritis, allergic rhinitis, and/or bronchial asthma (Fig. 4a); (2) most patients with IgG4RD were negative for anti-SS-A and anti-SS-B antibodies, as well as for rheumatoid factor (RF) and anti-nuclear antibody (ANA) (Fig. 4b); (3) serum IgG4 and IgE concentrations were significantly higher in IgG4RD than in SS patients (Fig. 4c); and (4) steroid therapy was extremely effective in patients with IgG4RD but had limited effect in patients with SS [29].

The histopathological features of IgG4RD are unique, though both IgG4RD and SS show marked lymphocytic infiltration. IgG4RD is characterized by the formation of lymphoid follicles but lower levels of lymphocytic infiltration into the salivary ducts, such that their structure remains intact (Fig. 5a). Therefore, the absence of

Table 2 Diagnostic criteria of IgG4+ Mikulicz's disease [8] (approved by the Japanese Society for Sjögren's Syndrome 2008)

1. Symmetrical swelling of at least 2 pairs of lachrymal, parotid, or submandibular glands for at least 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
Differential diagnosis is necessary to distinguish IgG4+ Mikulicz's disease 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

Table 3 Guidelines for diagnosis of IgG4RD (proposed by the Research Program for Intractable Disease Ministry of Health, Labor and Welfare Japan, G4 team)

Clinical features highly suggestive of IgG4RD
1. Symmetrical swelling of lachrymal, parotid, or submandibular glands
2. Autoimmune pancreatitis
3. Inflammatory pseudotumor
4. Retroperitoneal fibrosis
5. Suspicion of Castleman's disease
Laboratory data highly suggestive of IgG4RD
1. Serum IgG4 >135 mg/dl
2. IgG4+ cells/IgG+ cells >40% in biopsy
Clinical features suggestive of IgG4RD
1. Unilateral swelling of at least one lachrymal, parotid, or submandibular gland
2. Orbital pseudotumor
3. Sclerosing cholangitis
4. Prostatitis
5. Hypertrophic pachymeningitis
6. Interstitial pneumonitis
7. Interstitial nephritis
8. Thyroiditis/hypo-function of thyroid
9. Hypophysitis
10. Inflammatory aneurysm
Laboratory data suggestive of IgG4RD
1. Hypergammaglobulinemia of unknown origin
2. Hypocomplementemia or existence of immune complex
3. Increase of IgE or eosinophils
4. Tumefactive lesions or lymph node swelling detected by gallium scan or fluoro-D-glucose positron emission tomography (FDG-PET)

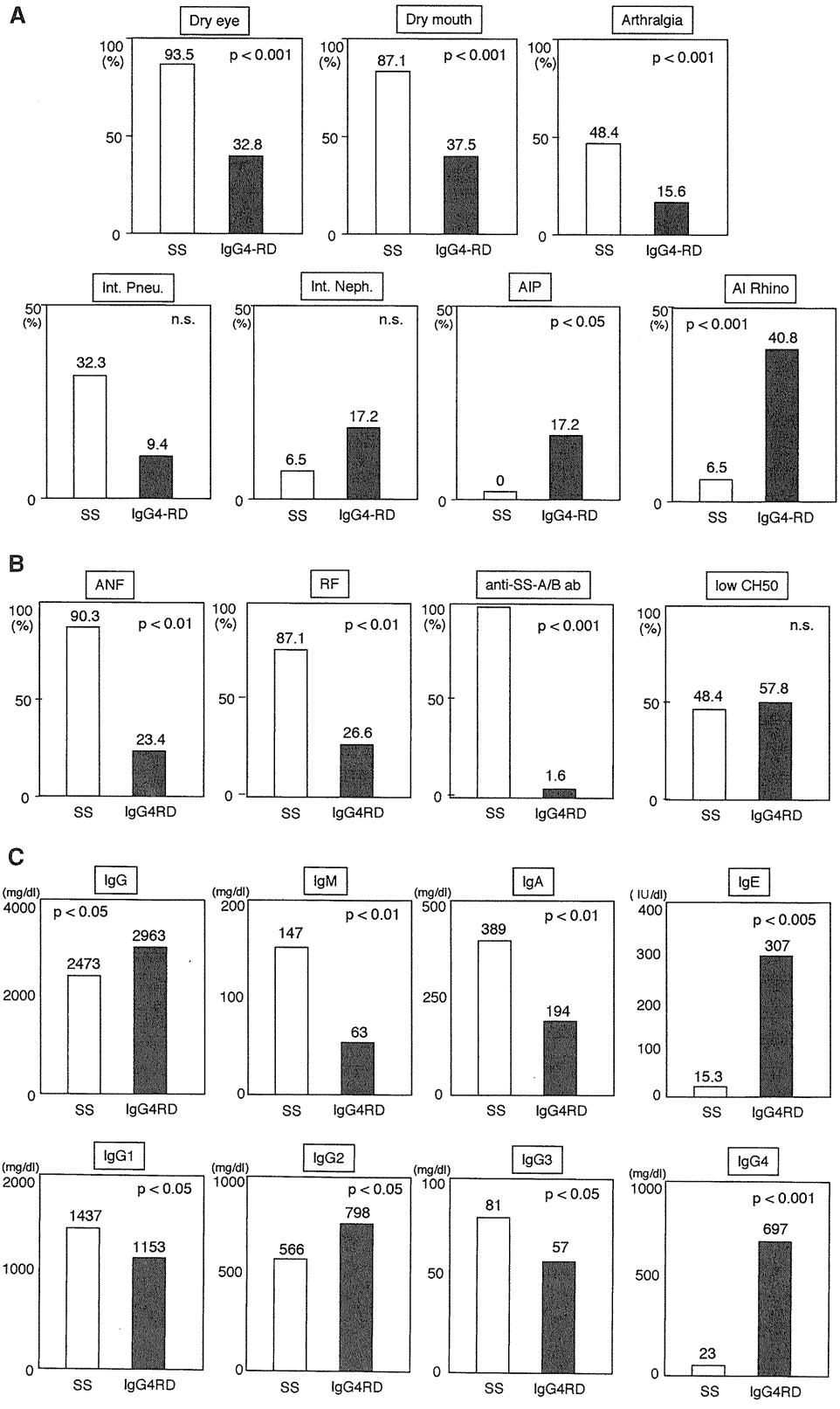


Fig. 4 Comparison of clinical symptoms and laboratory findings in IgG4RD and typical Sjögren's syndrome (*SS*) [29]. **a** Clinical symptoms, **b** immunological findings, and **c** subclasses of immunoglobulins and IgG observed in patients with IgG4RD ($n = 61$) and typical SS ($n = 31$). Data are expressed as percentages. *P* values are for comparisons of IgG4RD with typical SS. Patients with typical SS fulfilled both Japanese and European SS criteria and were positive for both anti-SSA/Ro and anti-SSB/La antibodies

lymphoepithelial lesions in patients with IgG4RD, in contrast to SS, may explain the lower rate of dryness in the former, despite the marked swelling of lachrymal and salivary glands. The most important difference between IgG4RD and SS is that the former is characterized by marked infiltration of IgG4-positive plasma cells, with a

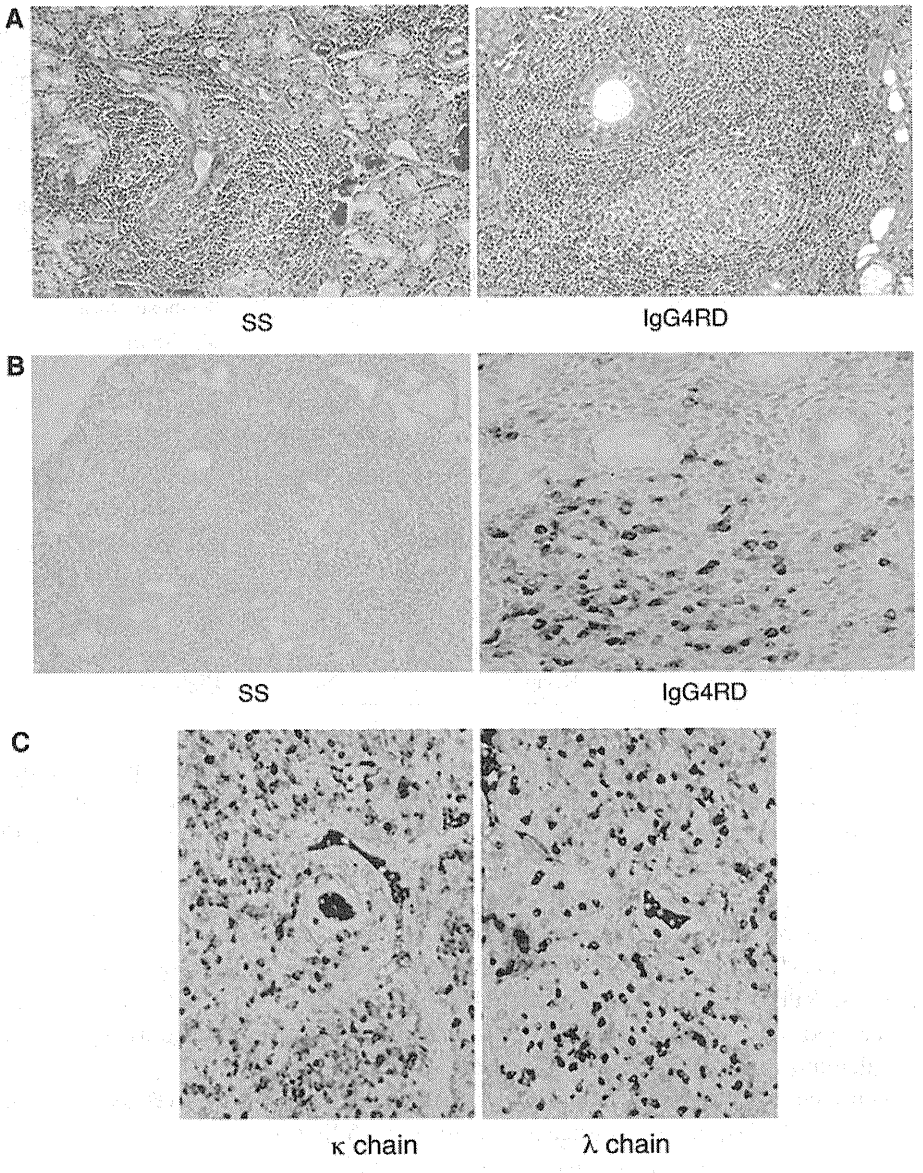


Fig. 5 Histopathological findings of minor labial salivary gland biopsies in patients with IgG4RD and typical SS. **a** Massive infiltration of lymphocytes and plasma cells was observed in patients with IgG4RD and those with typical SS (×200). IgG4RD, however, was characterized by lymphoid follicle formation but ducts were intact without lymphocytic infiltration. H&E staining. **b** IgG4RD showed scattered IgG4+ plasma cells in the periphery of the follicles (×200), whereas typical SS showed few or no IgG4+ cells. IgG4 immunostaining. **c** Staining for immunoglobulin κ- and λ-chains (×200)

ratio of IgG4-positive to IgG-positive cells of >40%, a finding almost never seen in patients with SS (Fig. 5b). Moreover, most patients with IgG4RD show polyclonal B-cell proliferation, with equal staining for immunoglobulin κ- and λ-chains (Fig. 5c). Thus, despite their similarities in organ involvement, IgG4-MD and SS are quite different conditions, with distinct clinical and pathological characteristics [7–9, 22, 29–31].

IgG4-related Küttner tumor

Küttner tumor, a unilateral sclerosing sialadenitis, is an IgG4RD [18]. A common feature of MD and Küttner tumor is that both manifest sialadenitis, as in IgG4RD. Histologically, Küttner tumors are very severe fibrous sclerotic lesions containing IgG4-positive plasma cells [32]. In contrast, fibrosis tends to be less severe in MD, although fibrosis in MD is frequently not examined extensively, because MD is generally diagnosed by the biopsy of minor labial salivary glands. Therefore, at present, it is difficult to set a strict boundary between MD and Küttner tumor.

IgG4-related autoimmune pancreatitis (IgG4-related AIP)

Recent studies have suggested that AIP manifests as two distinct subtypes, called types 1 and 2 (Table 4) [33]. Clinically, type 1 AIP seems to be the pancreatic manifestation of IgG4RD, characterized by: (1) mild abdominal symptoms, usually without acute attacks of pancreatitis; (2) occasional occurrence of obstructive jaundice; (3) increased serum gammaglobulin, IgG, and/or IgG4 concentrations; (4) presence of autoantibodies; (5) diffuse enlargement of the pancreas with a capsule-like low-density rim; (6)

Table 4 Subtypes of autoimmune pancreatitis (AIP) [33]

Subtype of AIP other nomenclatures	Type 1 AIP without GEL IgG4-related, LPSP	Type 2 AIP with GEL IgG4-unrelated IDCP
Prevalence	Asia > USA, Europe	Europe > USA > Asia
Age	High age	Younger
Gender	Male ≫ female	Male = female (NS)
Symptoms	Often obstructive jaundice	Often obstructive jaundice
Jaundice	Rare abdominal pain	Abdominal pain like acute pancreatitis
Pancreas images	Swelling/diffuse	Swelling/diffuse
	Segmental/focal	Segmental/focal
	Mass-forming	Mass-forming
Serology	High serum IgG	Normal IgG
	High serum IgG4	Normal IgG4
	Auto antibodies (+)	Auto antibodies (−)
Other organ involvement (OOI)	Sclerosing cholangitis	Unrelated to OOI
	Sclerosing sialadenitis	
	Retroperitoneal fibrosis	
	Other characteristics	
Ulcerative colitis	Rare	Often
Steroid response	Responsive	Responsive
Relapse	High rate	Rare

GEL, granulocyte epithelial lesion; *LPSP*, lymphoplasmacytic sclerosing pancreatitis; *IDCP*, idiopathic duct-centric chronic pancreatitis; *NS*, not significant

irregular narrowing of the pancreatic duct (sclerosing pancreatitis on endoscopic retrograde cholangiopancreatography [ERCP] images); (7) lymphocyte and IgG4-positive plasmacyte infiltration and fibrosis, and obliterative phlebitis; (8) occasional association with extrapancreatic lesions, such as sclerosing cholangitis similar to primary sclerosing cholangitis (PSC), sclerosing cholecystitis, sclerosing sialoadenitis, RPF, interstitial renal tubular disorders, enlarged celiac and hilar lymph nodes, chronic thyroiditis, and pseudotumor of the pancreas, liver, or lung; and (9) responsiveness to steroid therapy. Older males with IgG-related AIP often have obstructive jaundice, with both pancreatic and extrapancreatic manifestations responding to steroid therapy [12–15, 21, 33, 34].

Histological examination by American and European pathologists of the resected pancreases of patients with chronic non-alcoholic pancreatitis revealed another histopathological pattern, called idiopathic duct-centric pancreatitis (IDCP) or AIP with granulocytic epithelial lesions (GELs), later called type 2 AIP [35, 36]. Type 2 AIP is characterized primarily by these GELs, often accompanied by destruction and obliteration of the pancreatic duct [36]. Patients with type 2 AIP show swelling of the pancreas, but no or very few IgG4-positive plasma cells. Type 2 AIP has different clinicopathological features than type 1 AIP. Type 2 AIP shows no elevations in serum IgG4 or IgG, no autoantibodies, and no involvement of other organs, except for inflammatory bowel disease. Inflammatory bowel disease has been observed in approximately 30% of patients with type 2 AIP. Although type 1, or IgG4-related, AIP (LPSP type) often occurs in older men and is accompanied by a variety of extrapancreatic lesions, type 2, or neutrophil-related pancreatitis (IDCP/GEL type), has no gender bias, younger age at onset (often <40 years), and is frequently associated with inflammatory bowel disease. Thus, after a worldwide debate over the diagnostic criteria for AIP, IgG4-related pancreatitis has been defined as type 1 (LPSP type) and neutrophil-related pancreatitis has been defined as type 2 (IDCP/GEL type) [34].

IgG4-related sclerosing cholangitis (IgG4-related SC)

Extrapancreatic bile duct lesions are frequently associated with AIP. For example, 73% of patients with AIP have shown wall thickening or sclerosing changes in extrapancreatic bile ducts on endoscopic ultrasonography (EUS) and intraductal ultrasonography (IDUS), though only 26% of patients with AIP demonstrated sclerosing changes by ERCP [37]. However, many individuals without AIP have shown IgG4-related SC with isolated biliary tract involvement [38, 39]. In IgG4-related SC, stenosis is usually observed in the lower part of the common bile duct. The cholangiographic appearance of stenosis in the intrahepatic or hilar hepatic bile duct is very similar to that observed in PSC [40], a progressive disease of unknown etiology that ultimately results in liver cirrhosis. IgG4-related SC is associated with older age, male predominance, obstructive jaundice, weight loss, and abdominal discomfort [40]. Although steroid therapy has shown mixed results in patients with PSC, IgG4-related SC

responds dramatically to steroid therapy, as does IgG4RD [41]. The histopathological features of IgG4-related SC are similar to those of AIP and include diffuse plasmacytic infiltration, marked interstitial fibrosis with a focal storiform-like pattern, and obliterative phlebitis.

IgG4-related kidney disease (IgG4-related KD)

The kidney is a frequent target organ in IgG4RD, with tubulointerstitial nephritis (TIN) and fibrosis and abundant IgG4-positive plasma cell infiltration being diagnostically important histopathological features of this disease [42–44]. Recently, the clinicopathological features of 23 patients with IgG4-related TIN were reported to be quite uniform and similar to those observed in patients with IgG4-AIP, including high serum concentrations of IgG4 and IgE, hypocomplementemia, and TIN with infiltration of large numbers of IgG4-positive plasma cells plus fibrosis [45].

Kidney diseases in IgG4RD include conditions other than renal parenchymal lesions, such as hydronephrosis associated with RPF and tumors of the renal pelvis and urethra. However, IgG4-related TIN is considered to be representative of IgG4 renal parenchymal lesions [19]. Compared with other types of interstitial nephritis, IgG4-related TIN is often associated with extrarenal lesions, such as pancreatitis, sialadenitis, and lymphadenitis, and a high incidence of hypocomplementemia [46]. Imaging often shows heterogeneous shadows in the kidneys, such as a mass or multiple nodules (findings that are not observed in other types of interstitial nephritis). Histopathologically, the renal tubulointerstitium shows the infiltration of many lymphocytes and plasmacytes, as well as fibrosis, and IgG4 immunostaining shows a number of IgG4-positive plasma cells [47]. Although many studies have found no significant changes in the glomeruli, others have reported an association with glomerular lesions, including membranous nephropathy [46]. In the near future, the Japanese Kidney Society expects to develop diagnostic criteria for IgG4-related KD.

IgG4-related pulmonary diseases (IgG4-related PD)

IgG4-related PD has been described as inflammatory pseudotumor, interstitial pneumonitis, organizing pneumonia, and lymphomatoid granulomatosis [48]. Most (81%) patients with IgG4-related PD have been reported to be men, with a median age at diagnosis of 69 years [48], features similar to those of IgG4RD. Some patients present initially with respiratory symptoms, such as dry cough or dyspnea, whereas 75% of patients are asymptomatic and the disease is found incidentally by abnormal shadows on chest X-rays. Although IgG4-related PD is associated with a variety of radiologic abnormalities [49], diffuse lymphoplasmacytic infiltration has been observed in all lesions, with irregular fibrosis and obliterative vascular changes being more common in solid areas [48]. Hilar and pancreatic accumulation of gallium-67 has been reported as characteristic of the active stage of AIP when serum IgG4 concentrations are high [50].

Radiographically, IgG4-related PD can be divided into two types, inflammatory pseudotumors and interstitial pneumonitis. Inflammatory pseudotumors have been described as nodular or mass lesions, or infiltration, and are characterized by radiating reticular shadows surrounding the tumor. Interstitial pneumonitis presents in most patients with reticular shadows, ground-glass opacity, and interstitial fibrosis in both lower lung fields [17].

Histopathologically, inflammatory pseudotumor is a plasma cell granuloma, with infiltration mainly by plasma cells and lymphocytes, irregular fibrosis, lymphoid follicle formation, findings of interstitial pneumonitis at the periphery of the nodule, obliterating phlebitis and arteritis, and eosinophilic infiltration [17]. Interstitial pneumonitis is characterized by thickening of the alveolar septa due to infiltration by plasma cells and lymphocytes, and by diffuse fibrosis. Histopathologically, interstitial pneumonitis often shows a pattern previously classified as non-specific interstitial pneumonia (NSIP) [51]. The diagnostic criteria for IgG4-related PD are now under consideration by the Japanese Respiratory Association.

IgG4-related Hashimoto's thyroiditis (IgG4-related HT)

Hashimoto's thyroiditis (HT) has been considered a well-defined clinicopathological entity, characterized by the presence of goiter and serum thyroid autoantibodies. Recently, a unique subtype of HT was described, characterized by the presence of prominent fibrosis such as storiform fibrosis and swirling fibrosis, numerous IgG4-positive plasma cells, and elevated serum IgG4 [52], and called IgG4-related HT [53]. Among 23 patients with HT who underwent total thyroidectomy, 14 cases (60.8%) were IgG4-related HT, but there were no significant differences in positivity for thyroid and microsome tests between IgG4-related HT and non-IgG4 HT [54].

Riedel's thyroiditis was first described in 1896 in two patients with hard goiter and tracheal compressive symptoms. One-third of patients with Riedel's thyroiditis have multifocal fibrosclerosis, including sclerosing cholangitis, salivary gland fibrosis, RPF, or fibrotic orbital pseudotumor. Therefore, despite the lack of immunohistochemical staining for IgG4, certain proportions of Riedel's thyroiditis were considered a type of IgG4RD. Although one patient with IgG4RD showed involvement of the lachrymal gland and pulmonary and biliary tracts as well as Riedel's

thyroiditis [32], it is still unclear whether Riedel's thyroiditis is a type of IgG4RD.

IgG4-related lymphadenopathy and Castleman's disease

Concomitant lymphadenopathy is common in patients with IgG4RD, and there have been several reports dealing with the morphological and immunohistological findings of lymph node lesions [55–57]. Although IgG4-related lymphadenopathy is occasionally characterized by systemic lymphadenopathy, polyclonal hyperimmunoglobulinemia, especially elevated IgG and IgE concentrations, and positivity for various autoantibodies, patients with IgG4RD with generalized lymphadenopathy should only be evaluated for lymphoma, sarcoidosis, multicentric Castleman's disease, and other malignancies.

IgG4-related lymphadenopathy can be characterized into five histological subtypes: Castleman's disease-like morphology (type I), reactive follicular hyperplasia (type II), interfollicular plasmacytosis and immunoblastosis (type III), progressive transformation of germinal center-like (type IV), and inflammatory pseudotumor-like morphology (type V) [57]. In addition, IgG4-related lymphadenopathy can be classified into two types based on the infiltrative patterns of IgG4-positive cells: interfollicular plasmacytosis (types I, II, III, and V) and intragerminal center plasmacytosis (type IV). Patients with systemic IgG4-related lymphadenopathy were significantly older (68.8 vs. 43.3 years) and had significantly lower C-reactive protein (0.29 vs. 8.71 mg/dl) and interleukin (IL)-6 (8.45 vs. 34.82 pg/ml) concentrations than patients with multicentric Castleman's disease [56].

IgG4-related retroperitoneal fibrosis (IgG4-related RPF)

RPF is a chronic inflammatory condition with marked fibrosis in retroperitoneal tissue. In patients with advanced RPF a retroperitoneal mass covers the abdominal aorta and compresses the ureters, leading to urinary obstruction. Its etiology is unknown, but it has many causes, including infection, radiation, drugs, malignant tumor, and trauma. Three patients with RPF and elevated serum IgG4 have been described [58], and the histology of all 12 patients with RPF was reported to be similar to that seen in AIP, including fibrosis, intense inflammatory cell infiltration with plasma cells, venulitis, and obliterative arteritis [59]. Of 17 patients with RPF, 10 had both elevated serum IgG4 and histopathological features typical of IgG4RD, suggesting that RPF could be categorized as IgG4-related [60]. However, in RPF, fibrosis gradually progresses during chronic inflammation, with lymphocyte infiltration predominant during the early stages and a fibroinflammatory process occurring later. Therefore, determining the stage of illness seems important for diagnosis and prediction of response to steroid treatment [61].

IgG4-related aortitis

There have been several recent reports of inflammatory aneurysms in the abdominal or thoracic aorta [62–64]. For example, 40% of inflammatory abdominal aortic aneurysms (AAAs) were IgG4RD, with elevated IgG4 in serum and abundant infiltration of IgG4+ plasma cells and obliterative phlebitis [62]. These findings suggested that inflammatory AAAs can be classified into 2 groups: IgG4-related and IgG4-unrelated [62]. Although IgG4RD shows good response to steroid therapy, treatment with the anti-CD20 monoclonal antibody, rituximab, may result not only in clinical improvement, but in the tapering or discontinuation of steroids or other drugs [65].

Pathogenesis and pathophysiology of IgG4RD

At present, the pathogenetic mechanism and underlying immunological abnormalities in IgG4RD remain unclear. The elevated serum IgG4 concentration and tissue infiltration of IgG4-positive plasma cells are characteristic features of IgG4RD. Because IgG4 antibodies are dynamic molecules that can exchange Fab arms by swapping a heavy chain and attached light chain, IgG4 can form bi-specific antibodies, as well as functioning as a monovalent molecule [66, 67]. These properties may protect against type I allergy by inhibiting IgE functions, and may prevent type II and III allergy by blocking the Fc-mediated effector functions of IgG1 and inhibiting the formation of large immune complexes. The predominant expression of IgG4 under conditions of chronic antigen exposure is compatible with the clinical features of IgG4RD, including its slow progression and relatively weak immune response.

Some autoantibodies, including those to pancreatic trypsin inhibitor (PSTI), lactoferrin (LF), and carbonic anhydrase (CA), have been detected in patients with IgG4RD, especially in those with IgG4-related AIP [34]. Although IgG4 from the patients was able to bind the normal epithelia of the pancreatic ducts, gallbladder, and salivary gland ducts [68], IgG4-type autoantibodies have not been detected in patients with IgG4RD.

Aberrant immunological findings have been observed in patients with IgG4RD. For example, the Th2-dominant immune response and the production of Th2-type cytokines, such as IL-4, IL-5, IL-10, and IL-13, are increased [69–71]. Furthermore, the numbers of regulatory T cells (Treg) expressing CD4+CD25+Foxp3 are significantly higher in the affected tissues and peripheral blood of

patients with IgG4RD than the numbers in patients with autoimmune and nonautoimmune diseases [72–74]. Overexpression of the regulatory cytokines IL-10 and transforming growth factor β (TGF-β) has also been reported in patients with IgG4RD [74, 75]. IL-10 and TGF-β have potent activities in directing B cells to produce IgG4 and induce fibroplasia, respectively. IL-4, IL-5, and IL-13 are important for class switching to IgE production and eosinophil migration. Therefore, abnormalities in the production of these cytokines may be involved in the pathogenesis of IgG4RD.

Perspectives on IgG4RD

Although IgG4RD is a novel clinical entity, it is not a rare disease. Despite the effectiveness of steroid therapy, for IgG4RD, the condition has often been misdiagnosed as a malignant tumor, lymphoma, Sjögren's syndrome, or other diseases. To date, the clinical diagnostic criteria for IgG4RD have not been established. Because IgG4RD may occur in a variety of organs throughout the body, comprehensive discussions with the cooperation of many clinicians from various specialized fields is needed to establish uniform diagnostic criteria. At present, the diagnostic criteria for IgG4-MD (Table 2) [8] and those for IgG4-AIP type 1 (Table 5) [14] have been established.

Consensus has been reached on two diagnostic criteria for IgG4RD: (1) serum IgG4 concentration >135 mg/dl, and (2) >40% of IgG-positive plasma cells being IgG4-positive. The MHLW Japan team has proposed guidelines for the diagnosis of IgG4RD; these are shown in Table 3. The formulation of organ-specific (i.e., kidney and pulmonary) diagnostic criteria for IgG4RD requires cooperation with the relevant societies. Although IgG4RD responds well to steroid therapy, recurrence and relapse occur following the early reduction or withdrawal of prednisone. Therefore, it is necessary to develop treatment guidelines to establish initial doses of steroids, tapering procedures, and maintenance doses. The MHLW Japan team is currently pursuing a "Prospective study for creating IgG4-related disease treatment guidelines", and unified clinical guidelines are expected in the near future.

Table 5 Clinical diagnostic criteria of autoimmune pancreatitis; revised proposal in Japan (2006) [79]

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas on imaging modalities, such as abdominal ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI)
2. High-serum F-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 into the periductal area, with occasional lymphoid follicles in the pancreas

For diagnosis, criterion 1 must be present, together with criteria 2 and/or 3

However, it is necessary to exclude malignant diseases such as pancreatic and biliary cancers

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Conflict of interest None.

Appendix

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