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)

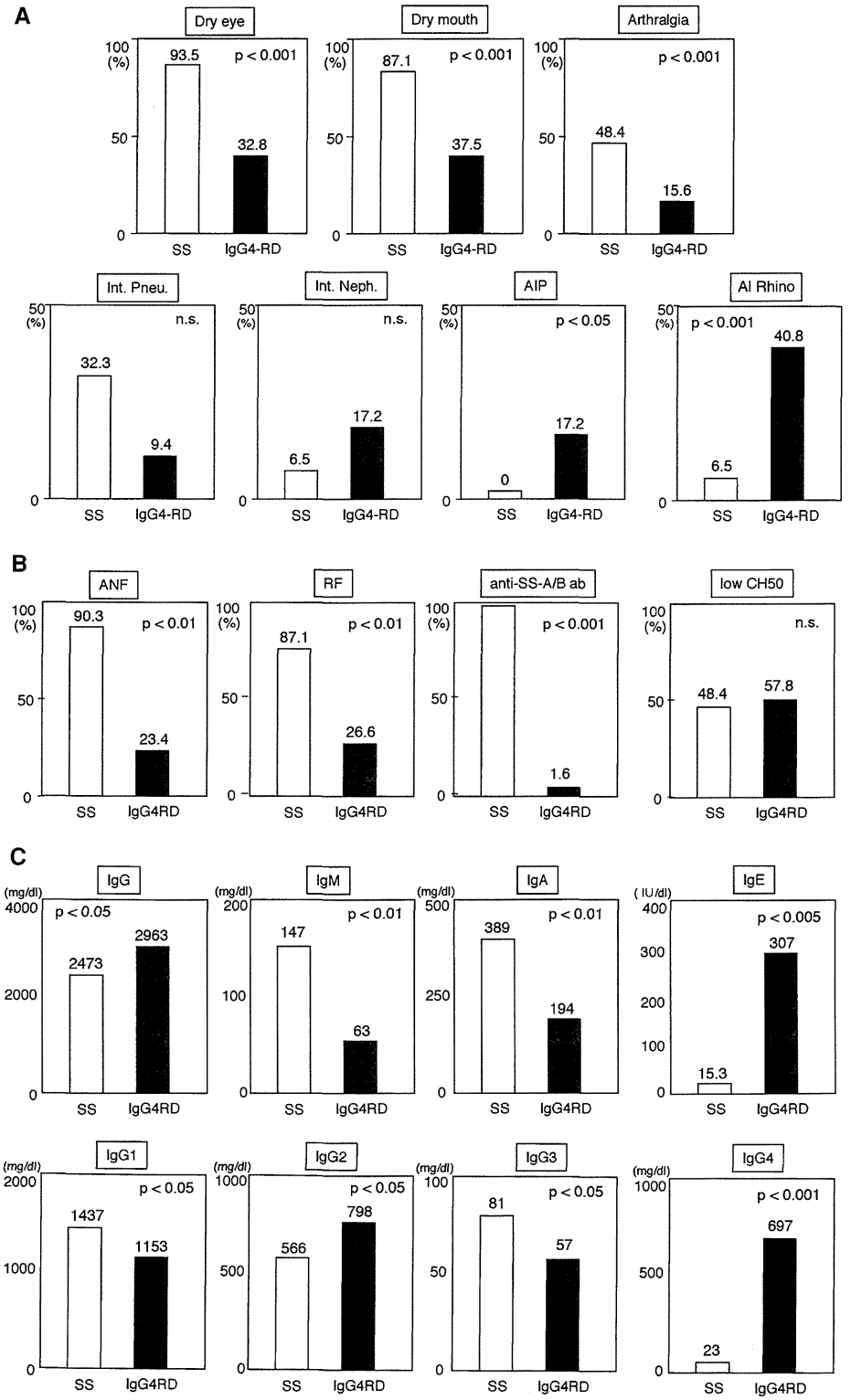

Fig. 4 Comparison of clinical symptoms and laboratory findings in IgG4RD and typical Sjögren's syndrome (*SS*) [29]. **a** Clinical symptoms, **b** immunological findings, and **c** subclasses of immunoglobulins and IgG observed in patients with IgG4RD ($n = 61$) and typical SS ($n = 31$). Data are expressed 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

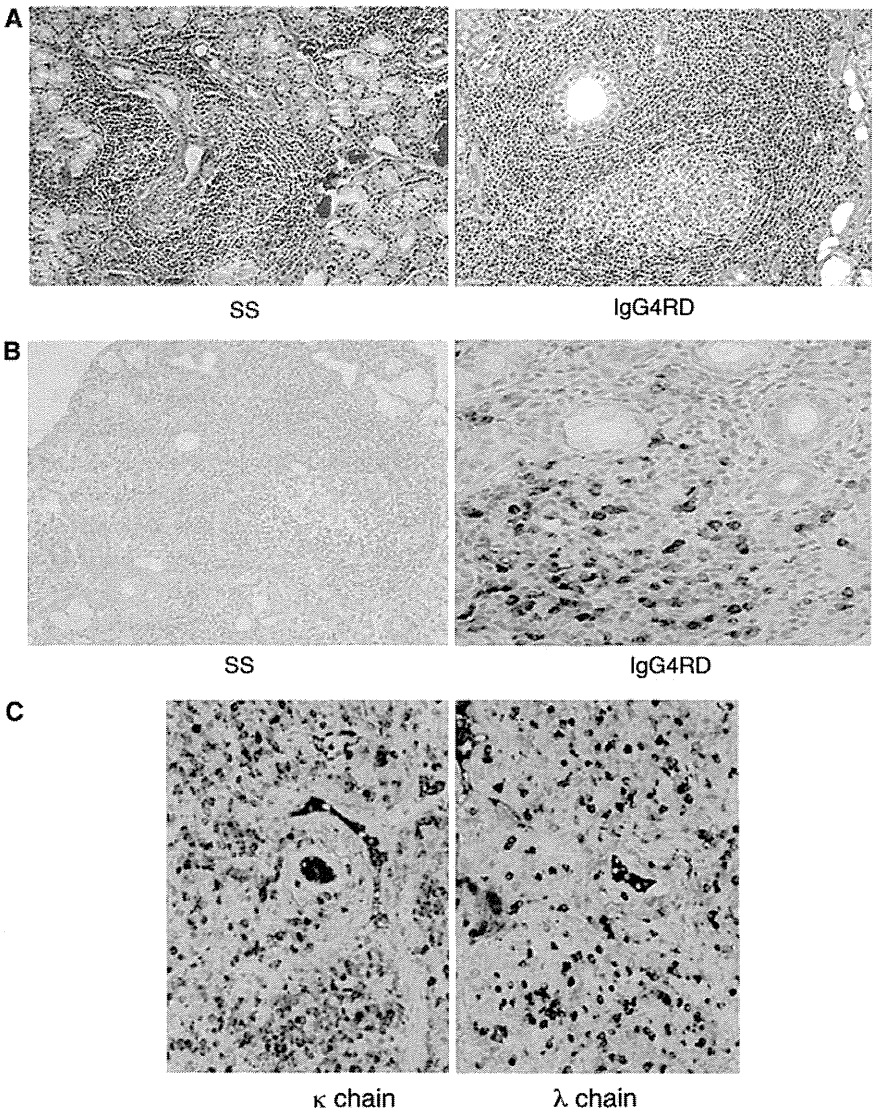

Fig. 5 Histopathological findings of minor labial salivary gland biopsies in patients with IgG4RD and typical SS. **a** Massive infiltration of lymphocytes and plasma cells was observed in patients with IgG4RD and those with typical SS (×200). IgG4RD, however, was characterized by lymphoid follicle formation 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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Review Article

Are Classification Criteria for IgG4-RD Now Possible? The Concept of IgG4-Related Disease and Proposal of Comprehensive Diagnostic Criteria in Japan

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Recent studies suggest simultaneous or metachronous lesions in multiorgans characterized by elevated serum levels of IgG4 and abundant infiltration of IgG4-positive plasma cells with various degrees of fibrosis. Two Japanese research committees for IgG4-RD, one from fibrosclerosis (Okazaki team) and the other from lymph proliferation (Umehara team) supported by the "Research Program for Intractable Disease" of the Ministry of Health, Labor, and Welfare of Japan, have agreed with the unified nomenclature as "IgG4-RD" and proposed the comprehensive diagnostic criteria (CDC) for IgG4-RD. Validation of the CDC demonstrated satisfactory sensitivity for the practical use of general physicians and nonspecialists but low sensitivity in the organs to be difficult in taking biopsy specimens such as type1 autoimmune pancreatitis (IgG4-related AIP), compared with IgG4-related sialadenitis/dacryoadenitis (Mikulicz's disease) and IgG4-related kidney disease. Although the diagnostic criteria covering all IgG4-RD are hard to be established, combination with the CDC and organ-specific diagnostic criteria should improve sensitivity.

1. Introduction

Recent studies have suggested simultaneous or metachronous lesions in multiorgans characterized by elevated serum levels of IgG4 and abundant infiltration of IgG4-positive plasma cells with various degrees of fibrosis, which lead us to propose the concept of a systemic disease [1, 4, 10, 23, 24]. However, there are many synonyms suggesting a systemic disease, such as IgG4-related autoimmune disease [1], IgG4-related sclerosing disease [4], IgG4-related plasmacytic syndrome (SIPS) [23], IgG4-related multiorgan lymphoproliferative syndrome (IgG4-MOLPS) [10], and systemic IgG4-related disease, all of which may refer to the same conditions [24, 25] (Table 1). To simplify these conditions, members of two Japanese research committees for IgG4-related disease, one from view of fibrosclerosis (Chaired by Prof. Okazaki) [24] and the other from lymph proliferation (Chaired by Professor. Umehara H) [25], both of which are supported by the "Research for Intractable Disease" Program from the Ministry of Health, Labor, and Welfare of Japan, have agreed with unification of different nomenclatures as "IgG4-related disease (IgG4-RD)" and proposed the comprehensive diagnostic criteria (CDC) for IgG4-RD [15]. As it still remains unclear whether pathogenetic mechanisms in each involved organ-are same or not, the term IgG4-RD was appointed as minimally reflecting these conditions to avoid misdiagnosis of malignancy as much as possible.

2. The Concept of IgG4-Related Disease

The two Japanese research committees independently analyzed the clinical features and conditions of IgG4-RD and finally resulted in the following consensus with close collaboration [15, 24, 25]. (1) Patients with IgG4-RD show

Table 1: Nomenclatures of IgG4-related conditions.

Nomenclature	Authors	(year)
IgG4-related autoimmune disease	Kamisawa et al. [1]	(2003)
IgG4-associated multifocal systemic fibrosis	van der Vliet and Perenboom [2]	(2004)
IgG4-related systemic disease	Kamisawa et al. [3]	(2004)
IgG4-related sclerosing disease	Kamisawa et al. [4–7]	(2006)
Hyper-IgG4 disease	Neild et al. [8]	(2006)
IgG4-related disease	Zen et al. [9]	(2007)
Systemic IgG4 plasmacytic syndrome (SIPS)	Masaki et al. [10]	(2009)
IgG4-related multiorgan Lymphoproliferative syndrome (IgG4-MOLPS)	Masaki et al. [10]	(2009)
IgG4-associated disease	Geyer et al. [11]	(2010)

diffuse/focal organ enlargement, with mass-forming or nodular/thickened lesions in various organs, including the central nervous system [26], lachrymal/salivary glands [10, 23], thyroid gland [27, 28], lungs [29], pancreas [30, 31], biliary duct [32], liver [33], gastrointestinal tract [34, 35], kidneys [36], prostate gland [37], retroperitoneum [38], skin [39], lymph nodes [5, 40, 41], and artery [42, 43]. These conditions are quite similar to multifocal idiopathic fibrosclerosis (MIF) [44]. (2) These multiorgan lesions may occur synchronously or metachronously, with the prominent infiltration of lymphocytes and IgG4-positive plasmacytes with fibrosis. (3) IgG4-RD mainly affects middle-aged to elderly men except for IgG4-related dacryoadenitis/sialadenitis. Although clinical symptoms depending on involved organs are relatively mild, some patients develop serious complications such as obstructive jaundice due to hepatic, gallbladder, or pancreatic lesions; hydronephrosis due to retroperitoneal fibrosis; respiratory symptoms due to pulmonary lesions. (4) Steroid treatment is effective in many patient with IgG4-RD. However, prognosis and risk factors of recurrence still remain unclear. (5) Although the infiltration of IgG4-positive cells and increased serum concentrations of IgG4 characteristic of IgG4-RD, 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 rarely observed in lachrymal/salivary glands or lymph nodes.

3. IgG4-Related Disease (IgG4-RD) as the Comprehensive Nomenclature [24, 25]

In addition to MIF, there are many synonyms, such as IgG4-related autoimmune disease [1], "IgG4-related sclerosing disease" [4], IgG4-related plasmacytic disease (SIPS) [23], and "IgG4 + sMOLPS" [10], all of which may refer to the same conditions. It has been debated which one is the most appropriate. Storiform fibrosis and obliterative phlebitis are characteristic of biliopancreatic, retroperitoneal, and renal lesions, but rarely observed in lachrymal/salivary glands and lymphnodes [24, 25]. Then, the nomenclature of "IgG4-related sclerosing disease" is mainly based on the fibrous swollen organs, whereas those of "IgG4-SIPS" and "IgG4-MOLPS" are based on lymphoplasmacytic proliferation and swollen lymph nodes without fibrosis [24, 25]. Although most patients have multiorgan lesions synchronously or metachronously, about 10–20% of the patients show a solitary organ involved without confirming other organ involvement [24, 25]. Therefore, it is unclear whether the pathogenetic mechanism is same among individual organs or not. In addition to IgG4-RD, IgG4-associate conditions such as high serum levels of IgG4 or abundant infiltration of IgG4-positive cells were reported in some patients with malignancy; pancreatic [6, 45], biliary [46] and salivary cancer [47], gastrointestinal sarcoma [48], and ocular adnexal lymphoma [49–51]. Therefore, the term "systemic" may lead us to misdiagnosis of other organ lesions showing IgG4-related conditions in cases of malignancy [51]. Based on these findings, the members of Umehara and Okazaki teams have agreed that the term "IgG4-related disease" is appointed as minimally accepting these conditions at this moment.

4. Comprehensive Diagnostic Criteria for IgG4-RD [15, 24, 25]

The patients with IgG-4-related disease show organ enlargement or nodular/hyperplastic lesions in organs in the entire body, synchronously or metachronously, due to the prominent infiltration and fibrosis of lymphocytes and plasmacytes; however, the causes of the disease are still not clear. The organs known to be affected include the central nervous system, lacrimal/salivary glands, thyroid gland, lungs, pancreas, biliary duct, liver, gastrointestinal tracts, kidneys, prostate gland, retroperitoneum, skin, arteries, and lymph nodes. Although it remains unclear whether this disease is the same as multifocal fibrosclerosis, that is a possibility. Clinical symptoms vary depending on the organ in which the lesions are located, which suggests that it is hard to establish criteria covering all patients with IgG4-RD. Therefore, specific diagnostic criteria are required for each involved organ such IgG4-related Mikulicz's disease (IgG4-related dacryoadenitis/sialadenitis [12] (Table 2), type 1 AIP (IgG4-related pancreatitis) [13] (Table 3), and IgG4-related kidney disease [14, 41] (Table 4). However, these organ-specific criteria do not cover other organs or are not familiar to general clinicians and specialists. Moreover, to avoid misdiagnosis of malignancy, all physicians have to know this emerging disease entity and can make a diagnosis of IgG4-RD. Therefore, the CDC for IgG4-RD, containing three major criteria (clinical, hematological and histopathological examinations), have been proposed for practical use of general physicians and nonspecialist [15] (Table 5). Although sensitivity of the CDC for definitive IgG4-RD is low in the organs to be difficult in taking biopsy specimens, it can detect possible cases of IgG4-RD. In the probable or possible cases, organ specific criteria should be used concurrently.

Table 2: Diagnostic criteria for IgG4+ Mikulicz's disease [12] (approved by the Japanese Society for Sjögren's Syndrome, 2008).

(1) Symmetrical swelling of at least 2 pairs of lachrymal, parotid, and submandibular glands continuing for more than 3 months,

(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.

(1) *Clinical Examination.* Physical examinations and imaging on US/CT/MRI can show the characteristic diffuse/localized swelling, masses, or thickness in single or multiple organs (Figure 1).

(2) *Immunological Examination*

(a) *Increase of Serum Levels of IgG4.* 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 autoimmune pancreatitis [7] (Table 6). In patients with single-organ involvement and serum IgG4 concentration less than 135 mg/dL, the IgG4/IgG ratio may be helpful in making a diagnosis.

However, elevated IgG4 may be also observed in other diseases (e.g., atopic dermatitis, pemphigus, asthma, and multicentric Castleman's disease), especially in about 10% of malignancy, which suggests that high serum IgG4 is not necessarily specific marker of IgG4-RD [6]. Although a high cutoff value with >270 mg/dL of IgG4 increases specificity but decreased sensitivity of IgG4-RD differing from pancreatic cancer [45]. Therefore, at present, the significance of elevated IgG4 in the pathogenesis/pathophysiology of IgG4-RD still remains unknown.

(b) *Other Immunological Markers.* In addition to increased serum levels of IgG4, high serum levels of polyclonal γ-globulin, IgG, and IgE are often, and hypocomplementemia may occur [52]. As these markers are less sensitive for IgG4-RD, they are not included as a diagnostic criterion.

(3) *Histopathologic Examination.* Although tissue biopsies are difficult to obtain from some organs, including the pancreas, retroperitoneum and ocular cavity, histopathological examination is important.

(a) *Marked Lymphocyte and Plasmacyte Infiltration and Fibrosis.* Storiform or swirling fibrosis or obliterative phlebitis is Characteristic of IgG4-RD and may be important in its diagnosis.

(b) *Infiltration of IgG4-Positive Plasma Cells.* IgG4/IgG-positive cells more than 40% [53] or 50% [12] have been reported in lymphnodes of the patients with IgG4-RD. On the other hand, more than 10 IgG4-positive plasma cells are recommended that in diagnosis of type 1 AIP [13]. Based on these findings, the CDC for IgG4-RD recommend both the ratio of IgG4/IgG-positive cells >40% and infiltration of >10 IgG4-positive plasma cells/HPF for the definitive diagnosis [15]. Eosinophilic infiltration is often observed along with infiltration of IgG4-positive cells. It is noted that reactive infiltration of IgG4-positive cells and fibrosis may be observed in various diseases and clinical conditions, such as rheumatoid synovitis, inflammatory oral and skin lesions, and around cancer. However, it is noted that some additional immune-mediated conditions with increased serum interleukin-6 (IL-6) such as multicentric Castleman's disease may show elevated serum IgG4 and/or IgG4+/IgG+ plasma cell ratios >40%.

(4) *Prohibition of Facile Steroid Treatment in the CDC for IgG4-RD.* Patients with malignant lymphoma or paraneoplastic lesions can sometimes be improved by steroid administration. Therefore, steroid trials should be strictly avoided. Efforts should be made to collect tissue samples for diagnosis. However, patients having disease in organs difficult to biopsy, such as the pancreas, retroperitoneum, and pituitary, and respond to steroids may possibly have IgG4-RD. In accordance with the guidelines for treatment of autoimmune pancreatitis, patients should be started on 0.5-0.6 mg/kg/day/prednisolone. If patients do not respond to the initial steroid therapy, the diagnosis should be reviewed again.

(5) *Diseases to be Excluded or Differentiated*

(a) *Malignancies (e.g., Cancer, Lymphoma).* In cases of malignancy in the involved organs, it is essential to determine whether malignant cells are present histopathologically.

(b) *Similar Diseases.* Other similar benign diseases including Sjögren's syndrome, primary sclerosing cholangitis, multicentric Castleman's disease, idiopathic retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, and Churg-Strauss syndrome should be differentially diagnosed using the diagnostic criteria for each disease. It is noted that multicentric Castleman's disease, one of hyper IL-6 syndromes should be excluded from IgG4-RD, even if the CDC for IgG4-RD are fulfilled.

Table 3: International Consensus Diagnostic Criteria (ICDC) for autoimmune pancreatitis [13].

Diagnosis	Primary basic for diagnosis	Imaging Evidence	Collateral evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1 H)
	Imaging	Typical	Any non-D level 1/level 2
		Indeterminate	Two or more from level 1 (+level 2 D*)
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or level 1 D + level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H + Rt
*Level 2 D is counted as level 1 in this setting.			
	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical†): segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
S	Serology	IgG4, >2× upper limit of normal value a or b	IgG4, 1-2× upper limit of normal value a or b
OOI	Other organ involvement		
		(a) Histology of extrapancreatic organs:	(a) Histology of extrapancreatic organs including endoscopic biopsies of bile duct‡:
		any three of the following:	both of the following:
		(1) marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration;	(1) marked lymphoplasmacytic infiltration without granulocytic infiltration;
		(2) storiform fibrosis;	(2) abundant (>10 cells/HPF) IgG4-positive cells.
		(3) obliterative phlebitis;	
		(4) abundant (>10 cells/HPF) IgG4-positive cells.	
		(b) Typical radiological evidence	(b) Physical or radiological evidence:
		at least one of the following:	at least one of the following:
		(1) segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture;	(1) symmetrically enlarged salivary/lachrymal glands;
		(2) retroperitoneal fibrosis;	(2) radiological evidence of renal involvement described in association with AIP.
H	Histology of the pancreas	LPSP (core biopsy/resection):	LPSP (core biopsy):
		at least 3 of the following:	any 2 of the following:
		(1) periductal lymphoplasmacytic infiltrate without granulocytic infiltration;	(1) periductal lymphoplasmacytic infiltrate without granulocytic infiltration;
		(2) obliterative phlebitis;	(2) obliterative phlebitis;
		(3) storiform fibrosis;	(3) storiform fibrosis;
		(4) abundant (>10 cells HPF) IgG4-positive cells.	(4) abundant (>10 cells/HPF) IgG4-positive cells.
			Diagnostic steroid trial
Response to steroid (Rt)*	Rapid (≤2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations		

Table 4: Diagnostic criteria for IgG4-related kidney disease [14].

(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-positive plasma cells/high power field (HPF) and/or IgG4+/IgG+ positive plasma cells > 40%;

(b) characteristic (sclero-) fibrosis surrounding nests of lymphocytes and/or plasma cells;

(5) Histological findings in extrarenal organ(s):

dense lymphoplasmacytic infiltration by >10 IgG4-positive plasma cells/HPF and/or IgG4/IgG-positive 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, and extramedullary plasmacytoma.

(2) Radiologically, the following diseases should be excluded:
Malignant lymphoma, urinary tract carcinomas, renal infarction, and pyelonephritis.

(Rarely, Wegener's granulomatosis, sarcoidosisand metastatic carcinoma)

Table 5: Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011 [15].

[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-positive 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.

[Comprehensive clinical diagnostic criteria for IgG4-RD, 2011]

(1) Clinical examination shows 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-positive plasma cells: ratio of IgG4/IgG positive cells > 40% and > 10 IgG4-positive 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, and 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.

Table 6: Sensitivity and specificity of serum levels of IgG4 in patients with type 1 AIP.

	Cut-off	Sensitivity		Specificity	
	mg/dL	n	Median/(range)	n	(vs cancer)
Japan	135				
Okazaki et al. [16]		71	80% 410 (3–3670)	101	98%
Okazaki et al. [17]		52	73% 505 (43–1540)		NS
Kawa et al. [18]		64	92% 618 (8–2855)	80	98%
Korea	135				
Choi et al. [19]		30	73% 473 (10–1764)	76	99%
USA	140				
Ghazale et al. [20]		45	76% 550 (16–2890)	135	90%
Raina et al. [21]		26	44% (8–825)	NS	
Italy	135				
	(focal)	55	66% 267		NS
Frulloni et al. [22]	(diffuse)	32	27% 78		

Table 7: Validation of a combination of CDC and organ-specific criteria for type 1 AIP.

Compared with pancreas cancer, the sensitivity of comprehensive criteria for definite/probable AIP was 0%, but 78% for possible AIP, and specificity was 100% in any groups. Although it is hard to take an enough size of specimen in diagnosis of AIP malignancy can be usually denied by EUS-FNA. Therefore, the CDC are enough for detecting possible AIP, but not for definite/probable AIP.				
AIP (n = 60) PaCa (n = 17) Total (n = 77)	JPS 2006	ICDC for type 1 AIP	CDC for IgG4-RD	
Diagnosis of AIP	Definite AIP	Definite/probable AIP	Definite/probable AIP	Possible
sensitivity	70%	97%	0%	78%
specificity	100%	100%	100%	100%
PPV	100%	100%	0%	100%
NPV	49%	8%	100%	57%
accuracy	77%	95%	22%	83%

PaCa: pancreas cancer, PPV: positive predictive value, NPV: negative predictive value.

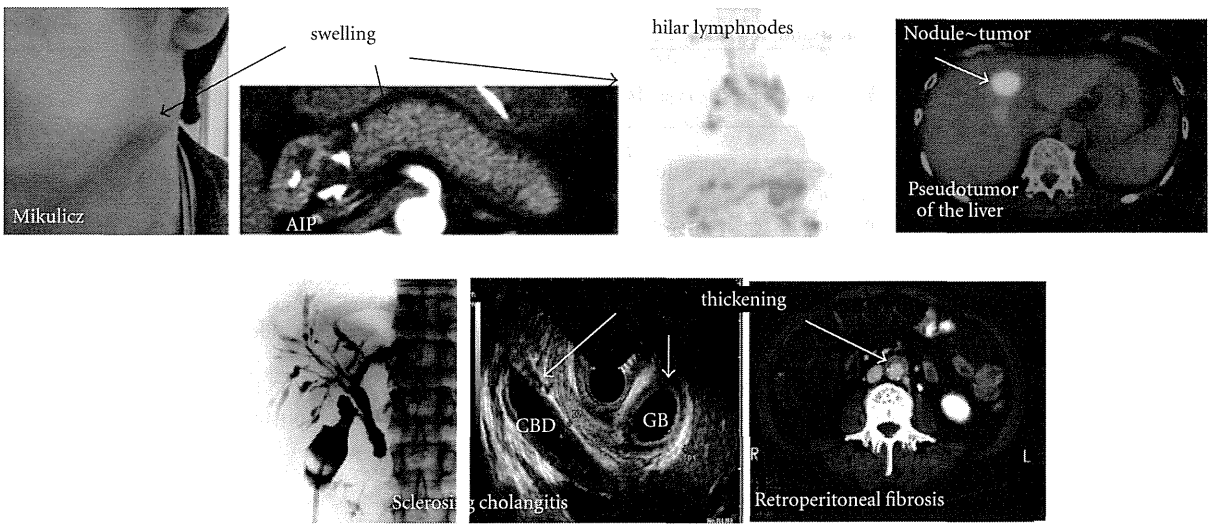

Figure 1: Clinical findings of IgG4-related disease. Physical examinations and imaging on US/CT/MRI can show the characteristic diffuse/localized swelling, masses, or thickness in single or multiple organs.

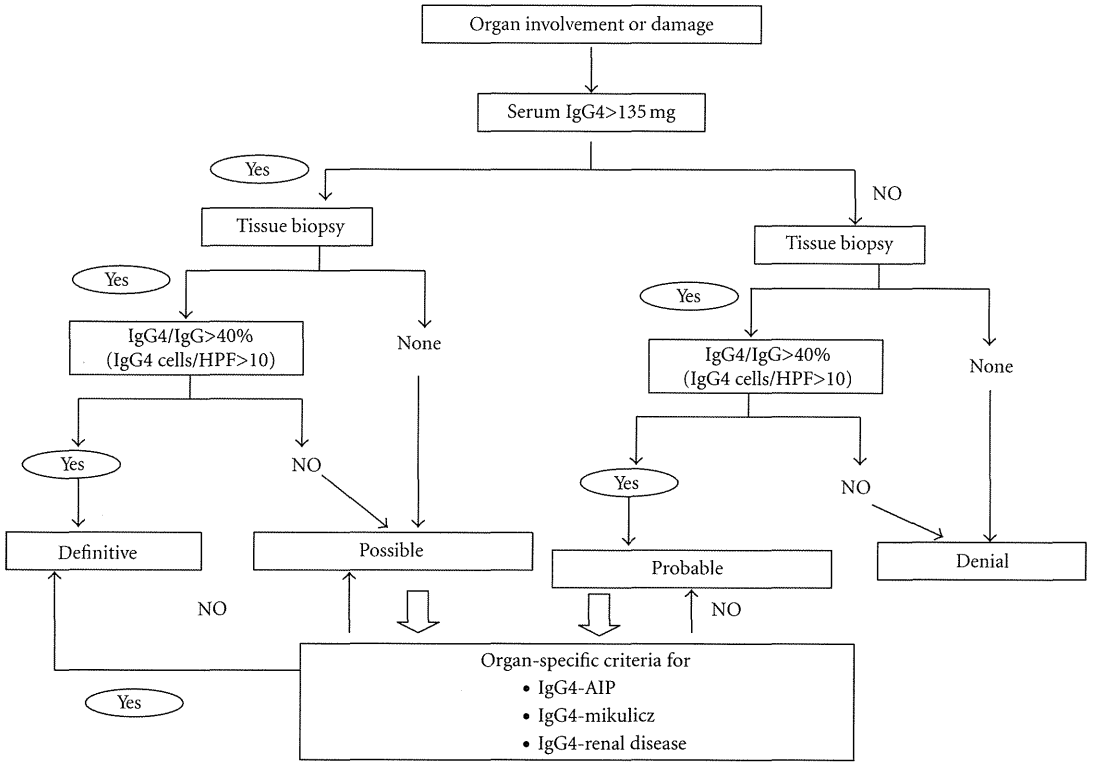

FIGURE 2: Diagnostic algorithm for IgG4-RD in Japan.

5. Sensitivity and Specificity of the CDC Criteria and Diagnostic Algorithm for IgG4-RD

The sensitivity of CDC for definitive/probable IgG4-RD is satisfactory in IgG4-related MD [12] and IgG4-related KD [14], but not in type 1 AIP [6, 13]. The major reason of low sensitivity in type 1 AIP is that enough biopsy samples of the pancreas are not easily obtained in most of these patients. In addition, endoscopic ultrasonography (EUS), guide fine needle aspiration (FNA), is available in a few of institutes in Japan, for examples only 16 of 226 (7%) board member institutes in Kink district of Japan Gastroenterological Endoscopy Society (JGES). On the other hand, the sensitivity of the CDC for possible IgG4-RD is satisfactory in type 1 AIP (Table 7). In contrast, patients with type 1 AIP could not be diagnosed by the comprehensive diagnostic criteria (0%) for definite, because biopsies could not be obtained from most of these patients. Therefore, combination of the CDC and organ-specific criteria should increase the sensitivity of diagnosis, even in the possible cases of IgG4-RD.

Based on these findings, a diagnostic algorithm for IgG4-RD in combination with the CDC and other organ-specific criteria has been proposed, although they have a limitation to the utility of the criteria proposed [15] (Figure 2). In patients with (a) organ enlargement, mass or nodular lesions, or organ dysfunction, performing of both (b) measurement of serum IgG4 and (c) tissue biopsy is recommended. In the cases with >135 mg/dL of IgG4, diagnostic histopathological findings of >10 IgG4 cells/HPF and an IgG4/IgG cell ratio >40 can diagnose them as definitive AIP. In possible or probable cases fulfilling criterion (a) with (b), or (c), organ-specific criteria for each disease should be applied. 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, and Churg-Strauss syndrome) by additional histopathological examination. Future studies including other organ diseases similar to IgG4-RD are needed to establish the diagnostic efficacy of CDC.

6. Conclusion

"All Japan Research Team for IgG4-RD" unified the nomenclatures as "IgG4-related disease (IgG4-RD)" and proposed the comprehensive diagnostic criteria (CDC) for IgG4-RD. The CDC for IgG4-RD was made for the practical use and for general physicians to differentiate IgG4-RD from malignancy or similar diseases as much as possible. Although sensitivity of the CDC for definitive IgG4-RD is low in the organs to

be difficult in taking biopsy specimens, it can detect possible cases of IgG4-RD. In the probable or possible cases, organ-specific criteria should be used concurrently.

Authors' Contribution

K. Okazaki and H. Umehara declare that they equally contributed to this work.

Disclosure

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SPECIAL ARTICLE

Recommendations for the Nomenclature of IgG4-Related Disease and Its Individual Organ System Manifestations

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Introduction

During the first decade of this century, recognition of a multi–organ system disease known as IgG4-related disease has grown. Serum IgG4 elevation (in some patients) and tissue infiltration with IgG4-positive plasma cells (in essentially all patients) (1–3) are common threads that connect a variety of seemingly disparate conditions observed previously in multiple organs (4). A highly characteristic histopathology and immunohistochemical staining pattern are found in the involved organs (5–7). Japanese investigators recently agreed on the name "IgG4-related disease" for this multifocal disorder (7).

An International Symposium on IgG4-Related

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