Mod Rheumatol (2012) 22:21–30
DOI 10.1007/s10165-011-0571-z

ORIGINAL ARTICLE

Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011

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Received: 14 October 2011 / Accepted: 19 November 2011 / Published online: 5 January 2012

Abstract
Background IgG4-related disease (IgG4-RD) is a novel clinical disease entity characterized by elevated serum IgG4 concentration and tumefaction or tissue infiltration by IgG4+ plasma cells. Although IgG4-RD is not rare and is clinically important, its clinical diagnostic criteria have not been established. Comprehensive diagnostic criteria for IgG4-RD, including the involvement of various organs, are intended for the practical use of general physicians and nonspecialists.
Methods Two IgG4-RD study groups, the Umehara and Okazaki teams, were organized by the Ministry of Health, Labor and Welfare Japan. As IgG4-RD comprises a wide variety of diseases, these groups consist of physicians and researchers in various disciplines, including rheumatology, hematology, gastroenterology, nephrology, pulmonology, ophthalmology, odontology, pathology, statistics, and basic and molecular immunology throughout Japan, with 66 and 56 members of the Umehara and Okazaki teams, respectively. Collaborations of the two study groups involved

For the All Japan IgG4 team.

Professional collaborators of the All Japan G4 team are given in the Appendix.

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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).

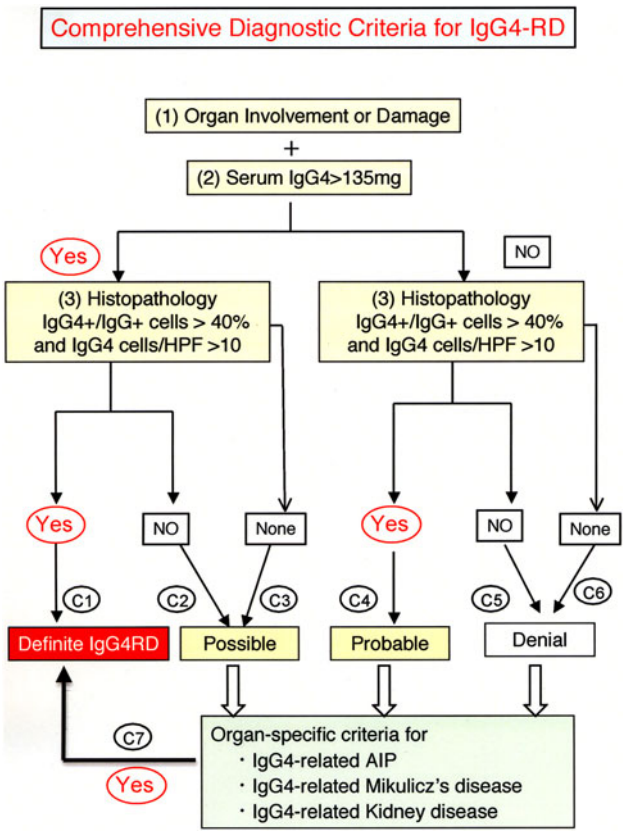

Fig. 1 Diagnostic algorithm performance for comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD) using comprehensive diagnostic criteria combined with organ-specific criteria. A diagnosis of IgG4-RD is definitive in patients with (*1*) organ enlargement, mass or nodular lesions, or organ 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.

Acknowledgments This work was supported by Intractable Diseases, the Health and Labor Sciences Research Grants from Ministry of Health, Labor and Welfare, Japan. We sincerely thank the many contributing researchers and collaborators who participated in the All Japan IgG4 team.

Conflict of interest None.

Appendix

The authors thank the many patients who participated in this registry. In addition to the listed authors, other professional collaborators of the All Japan G4 team in the Research Program for Intractable Disease by Ministry of Health, Labor and Welfare (MHLW) Japan, include: Atsushi Azumi (Kobe Kaisei Hospital); Keiji Kubo, and Hiroshi Yamamoto (Shinshu University); Daisuke Kawabata (Kyoto University); Seijiro Minamoto (Osaka Respiratory and Allergy Center); Susumu Nishiyama (Kurashiki Hospital); Kazuo Tsubota and Yoko Ogawa (Keio University); Shintaro Hirata (University of Occupational and Environmental Health); Tomoki Origuchi (Nagasaki University); Yasuharu Sato (Okayama University); Susumu Sugai (Kudou Hospital); Hiroki Takahashi (Sapporo Medical University); Hiroto Tsuboi (Tsukuba University); Dai Inoue, Masayuki Takahira and Yuko Waseda (Kanazawa University); Masaru Kojima (Dokkyo University School of Medicine); Norifumi Tsukamoto (Gunma University); Morio Matsumoto (Nishigunma National Hospital); Kayoko Murayama (Gunma Prefectural Cancer Center); Ritsuro Suzuki and Shigeru Ko (Nagoya University); Takahiro Nakazawa and Osamu Hasebe (Nagoya City University);

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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