Comprehensive Diagnostic Criteria for IgG4-Related Disease

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6.1 Introductory Remarks

IgG4-related disease (IgG4-RD) is a new disease concept first recognized in the twenty-first century [1, 2]. The condition is characterized by elevated serum IgG4 values and marked IgG4-positive plasma cell infiltration of affected lesions [1, 2]. The initial clue to its detection was contributed by Hamano et al. [3], who reported elevated serum IgG4 concentrations in patients with sclerosing pancreatitis. Following this observation, many additional reports on this disease, pertaining to clinical, pathology, radiological, and therapeutic aspects, have been supplied by investigators from Japan and beyond. IgG4-RD now attracts worldwide attention, and the formulation of a carefully considered disease concept and diagnostic criteria are both awaited eagerly.

Under the auspices of the Japanese Ministry of Health, Labor and Welfare, two research groups focusing on IgG4-RD have been organized. One is a group for research on the new disease entity of IgG4-related multiorgan lymphoproliferative syndrome (IgG4+MOLPS) (group leader: Hisanori Umehara, Department of Hematology & Immunology, Kanazawa Medical University, 66 members). The other is charged with establishing diagnostic and therapeutic approaches for IgG4-related systemic sclerosing diseases (group leader: Kazuichi Okazaki, Third Depatment of Internal Medicine, Kansai Medical University; 55 members).

Because IgG4-RD is a disease process that afflicts multiple organs, both groups are comprised of a versatile membership with representation of specialists from various clinical fields, pathologists, and basic investigators. These two cooperative groups have accomplished much in the field to date, including the achievement of a broad consensus on the disease name (IgG4-RD) and publication of a comprehensive set of diagnostic criteria. In this chapter, we outline these comprehensive diagnostic criteria for IgG4-RD [4].

6.2 Comprehensive Diagnostic Criteria for IgG4-RD

The establishment of diagnostic criteria for IgG4-RD was complicated by the fact that IgG4-RD is a truly multifaceted disorder that encompasses many conditions once considered to be separate but now recognized to overlap broadly. These conditions include autoimmune pancreatitis [5–8], Mikulicz's disease [9, 10], Riedel's thyroiditis [11], Küttner's tumor [11, 12], retroperitoneal fibrosis [13, 14], inflammatory pseudotumor [15], interstitial nephritis [16, 17], interstitial pneumonia [18, 19], and others [1] (Fig. 6.1). In addition, accurate pathology characterization is essential to the diagnosis, as IgG4-RD is often difficult to differentiate from immune-mediated conditions such as Sjögren's syndrome and granulomatosis with angiitis (formerly Wegener's) and from hematological conditions such as Castleman's disease and malignant lymphoma. These facts posed daunting challenges to the formulation of diagnostic criteria that are applicable potentially to all cases.

In approaching the task, an "All Japan IgG4 Team" comprised of representatives from both the Umehara and Okazaki groups was created to draft diagnostic criteria. The aims of this effort included:

1. Formulating criteria that would be useful not only to specialist clinicians devoted to the study of their respective organs but also to nonspecialist clinicians

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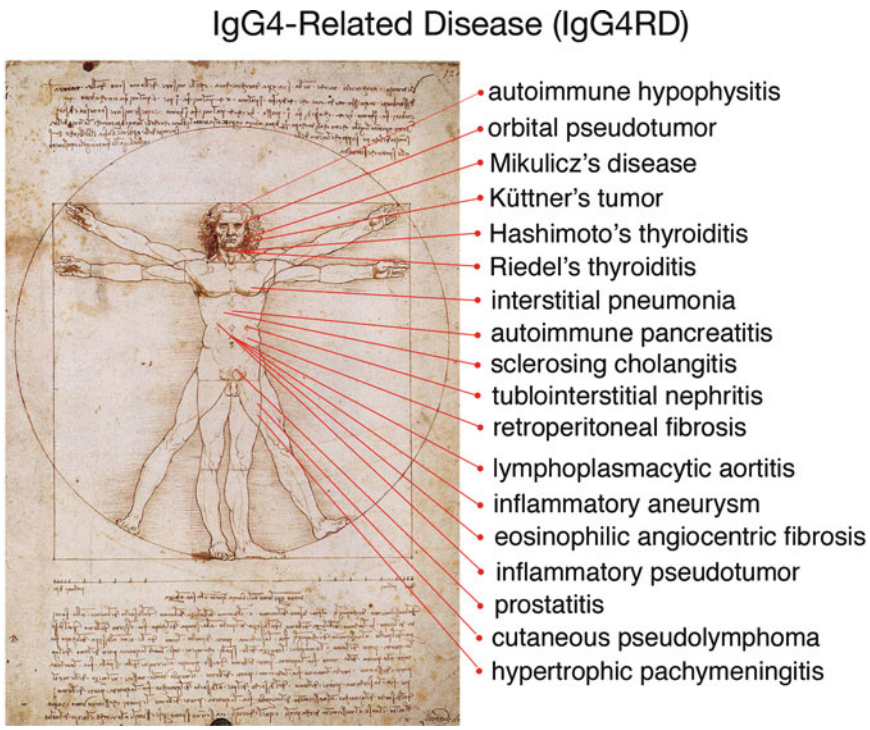

Fig. 6.1 IgG4-related disease (IgG4RD)

2. Devising diagnostic criteria that would be consistent for all organs
3. Succinctness
4. Sufficient emphasis on the need to exclude malignancy
5. Rationale for not recommending trials of glucocorticoid therapy for diagnostic purposes in possible IgG4-RD

We therefore proposed the first "comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011," attempting to encompass these concepts (Table 6.1) [4].

These criteria are comprised of three major items:

1. Single or multiple organs involved by diffuse or localized swelling, masses, nodules, and/or hypertrophic lesions
2. Elevated serum IgG4 levels(≥135 mg/dL)
3. Histopathological features that include
   - marked lymphocytic and plasma cell infiltration and fibrosis,
   - IgG4-positive plasma cell infiltration: IgG4/IgG-positive cell ratio ≥40 % and IgG4-positive plasma cells exceed 10/HPF

Patients can be classified into categories of definite, probable, or possible IgG4-RD, depending on how many of these diagnostic items are present.

The evaluation and diagnosis of patients with possible IgG4-RD requires the punctilious assessment of lesions in multiple organs, the interpretation of blood test findings, review of the pathology features (histopathology and immunostaining) and diagnostic imaging findings, judgment of the responsiveness to glucocorticoids, and exclusion of a lengthy list of potential mimickers (Table 6.1).

A variety of clues can be present in the blood. An elevated IgG4/IgG ratio (>8 %) in the blood may aid in the diagnosis in some cases even if the serum IgG4 concentration is <135 mg/dL, as is often the case – particularly in patients with single-organ disease. Patients with IgG4-RD typically demonstrate a polyclonal hypergammaglobulinemia with elevations of the total IgG concentration – IgG1 as well as IgG4 – though the IgG4 elevation is more impressive. The serum IgE concentration is also often elevated, and despite the putatively limited ability of IgG4 to fix complement and form immune complexes, hypocomplementemia is sometimes present, especially in those patients with renal disease.

The true role of IgG4 in the etiology and pathophysiology of IgG4 remains obscure. Elevations in serum IgG4 concentrations are by no means specific for IgG4-RD because the serum values can be elevated in a host of other diseases, as well, e.g., atopic dermatitis, pemphigus, bronchial asthma, and multicentric Castleman's disease. Increased serum IgG4 values are also reported in some patients with malignant tumors. The likelihood of pancreatic cancer, however, is low when IgG4 values are less than twice the upper limit of normal.

Histopathology is the key to the diagnosis of IgG4-RD. Characteristic histopathological findings include a swirling, "storiform" fibrosis and obliterative phlebitis. Neutrophilic infiltrates are not typical but can be observed occasionally in some organs such as the lung, where the biopsy may be taken from tissue bordering on mucosal surfaces.

Pancreatic cancer and other malignancies are sometimes associated with a reactive IgG4-positive plasma cell infiltration

Table 6.1 Comprehensive diagnostic criteria for IgG4-related disease, 2011 [4]

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-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

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 specialists and non-specialist 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

1. Autoimmune pancreatitis, Type I (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]

2. 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

3. 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, and 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]

4. IgG4-related central nervous system lesions

These lesions include infundibular hypophysitis, hypertrophic pachymeningitis, and intracerebral inflammatory pseudotumor

5. IgG4-related respiratory lesions

These lesions occur primarily in the interstitium, such as the 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

6. 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]

7. IgG4-related retroperitoneal fibrosis/periarterial lesions

This disease is characterized by thickening of the abdominal aortic adventitia and periuretheral 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. MRI and PET have been shown to be helpful for making diagnosis of retroperitoneal fibrosis in addition to CT. Biopsy is often not possible, making it difficult to differentiate this condition from secondary retroperitoneal fibrosis due to malignant tumors or infectious diseases

8. Other tumefactive lesions

Proliferation of IgG4-positive 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

(continued)

Table 6.1 (continued)

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 less than 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 is characteristic of IgG4-RD and may be important in its diagnosis 2. Eosinophilic infiltration often occurs, along with infiltration of IgG4- positive cells 3. Reactive infiltration of IgG4- positive 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 FDG -PET (fluorodeoxyglucose positron emission tomography) have been shown to be helpful for detecting multi-organ 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 the pancreas, retroperitoneum, and pituitary, and 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/day/ 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 the involved organs, it is essential to determine whether malignant cells are present histopathologically 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 IL-6 syndrome and is not included among the IgG4-related diseases even if the diagnostic criteria for IgG4-RD are fulfilled

and fibrosis in the peritumoral tissues. These findings represent a nonspecific, reactive phenomenon. High on the differential diagnosis of IgG4-RD, though, is malignancy, and thus it is essential to exclude malignant cells by careful histopathological evaluation and special marker studies as appropriate.

Nonmalignant conditions can also bear strong resemblance to IgG4-RD. These include Sjögren's syndrome, primary sclerosing cholangitis, multicentric Castleman's disease [20], idiopathic retroperitoneal fibrosis, granulomatosis with polyangiitis (formerly Wegener's), sarcoidosis, and the Churg–Strauss syndrome [21]. Multicentric Castleman's disease occasionally manifests elevated serum IgG4 concentrations and IgG4-positive cell proliferation in tissues and can be difficult to distinguish from IgG4-RD. However, multicentric Castleman's disease is recognized to be a different disease.

Responses to glucocorticoids can be useful but imperfect indicators of IgG4-RD in cases in which it may be difficult to obtain diagnostic tissue, e.g., the pancreas, retroperitoneum, and pituitary gland. However, lymphoma and paraneoplastic lesions can also improve following glucocorticoid therapy, and so empiric steroid trials must not be undertaken lightly. For this reason, the response to glucocorticoid administration for diagnostic purposes has not been adopted in comprehensive diagnostic criteria for IgG4-RD, and the greatest possible effort must be made to obtain tissue samples to permit a histopathological diagnosis.

6.3 Algorithm for IgG4-RD Diagnosis

The diagnostic sensitivity of the comprehensive diagnostic criteria outlined above is not known for patients with lesions that are difficult to biopsy. To compensate for these limitations when applying these criteria in clinical practice, the use of detailed IgG4-RD organ-specific diagnostic criteria is helpful (Fig. 6.2). Diagnostic criteria for IgG4-related Mikulicz's disease and type 1 (IgG4-related) autoimmune pancreatitis have already been announced [22, 23]. Diagnostic criteria for IgG4-related kidney disease have also been created in collaboration with the Japan Kidney Society [24].

6.4 Concluding Remarks

Researchers in a variety of different fields from across the world have contributed to the acquisition and distribution of knowledge regarding IgG4-RD. With enhanced recognition of this entity, interest in IgG4-RD continues to grow. An IgG4-RD International Symposium was held in the context of the 20th Annual Meeting of the Japanese Society for Sjögren's syndrome (September 2011, Kanazawa, Japan), and an International Symposium for IgG4-RD was also held

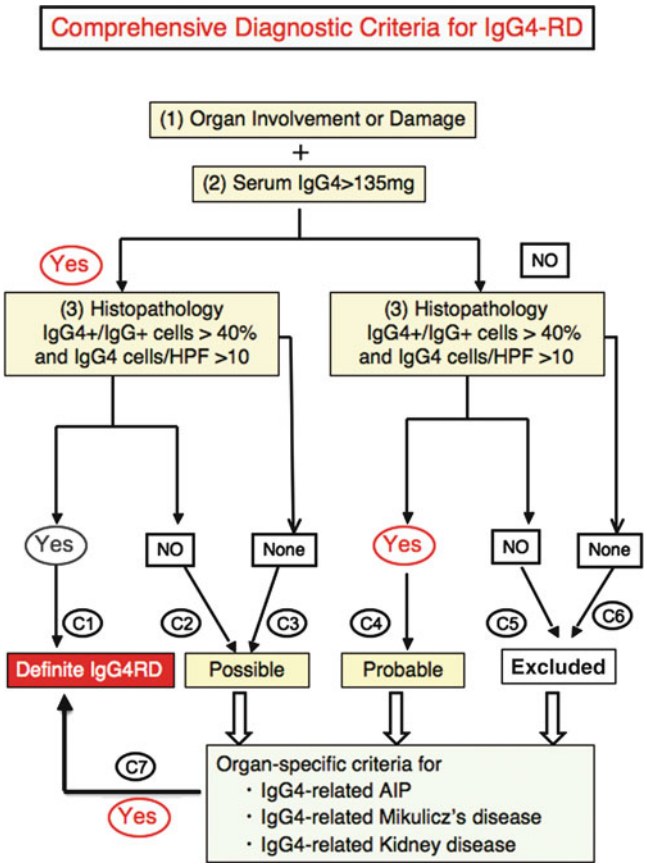

Fig. 6.2 Comprehensive diagnostic criteria for IgG4-RD

in the United States (October 2011, Boston). International consensus about nomenclature in each organ and pathology of IgG4-RD has been reached [25, 26]. As a next step, we must aim for broader recognition of IgG4-RD in daily clinical practice and promote the participation of larger numbers of physicians and other researchers in the investigation of this field.

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