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REVIEW

Diagnostic criteria for IgG4-related ophthalmic disease

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Abstract Immunoglobulin G4 (IgG4)-related disease is a novel clinical entity characterized by infiltration of IgG4-immunopositive plasmacytes and elevated serum IgG4 concentration accompanied by enlargement of and masses in various organs, including the lacrimal gland, salivary gland, and pancreas. Recent studies have clarified that conditions previously diagnosed as Mikulicz disease as well as various types of lymphoplasmacytic infiltrative disorders of the ocular adnexa are consistent with a diagnosis of IgG4-related disease. Against this background, the diagnostic criteria for IgG4-related ophthalmic disease have recently been established, based on both the clinical and the histopathologic features of the ocular lesions. This article reviews these new criteria with reference to the comprehensive diagnostic criteria for IgG4-related disease for all systemic conditions reported in 2012.

Keywords IgG4 · Plasma cell · Lacrimal gland · Mikulicz disease

The members of the Japanese Study Group for IgG4-Related Ophthalmic Disease are mentioned in the "Appendix."

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Introduction

Immunoglobulin G4 (IgG4)-related disease is a collection of disorders of unknown etiology that are characterized by an infiltrate of IgG4-immunopositive plasmacytes accompanied by enlargement of and masses, nodules, or hypertrophic lesions in various organs of the body. The comprehensive diagnostic criteria for IgG4-related disease were reported in 2012 by the Research Program for Intractable Disease of the Ministry of Health, Labor, and Welfare (MHLW) Japan, All Japan IgG4 team (Table 1) [1]. The disorder, which used to be diagnosed as Mikulicz disease, involves symmetric enlargement of the bilateral lacrimal and salivary glands. Recent studies have found that most cases of Mikulicz disease are consistent with a diagnosis of IgG4-related disease. With this finding, ocular lesions related to IgG4 have attracted attention. However, in addition to the fact that the disorder is a relatively new disease entity, the various disease names used in the past to describe IgG4-related ocular lesions and the lack of definitive diagnostic criteria have created some confusion in the clinical setting as well as among professional bodies.

To address this situation, the ophthalmology committee composed of members of the Japanese Study Group for IgG4-Related Ophthalmic Disease in the Research Program for Intractable Disease (IgG4-related disease) of the Japanese Ministry of Health, Labor, and Welfare has taken the lead in developing diagnostic criteria for IgG4-related ophthalmic disease. This article reports on the background and criteria proposed by the group.

History of IgG4-related disease

IgG, one of the immunoglobulins in serum, is composed of four subclasses: IgG1–IgG4. Among these subclasses,

Table 1 Comprehensive diagnostic criteria for IgG4-related disease, 2011[a]

I. Concept

IgG4-related disease (IgG4-RD) shows organ enlargement or nodular/hyperplastic lesions in various organs concurrently or metachronously, owing 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 shows characteristic diffuse/localized swelling or masses in single or multiple organs

(2) Hematologic examination shows elevated serum IgG4 concentrations ($\geq$135 mg/dl)

(3) Histopathologic examination shows:

(i) Marked lymphocyte and plasmacyte infiltration and fibrosis

(ii) Infiltration of IgG4+ plasma cells: ratio of lgG4+ to IgG+ cells >40 % and >10 IgG4+ plasma cells/HPF

Definite: (1) + (2) + (3)

Probable: (1) + (3)

Possible: (1) + (2)

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

Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using the organ-specific diagnostic criteria for IgG4-RD

III. Explanatory notes

(1) The comprehensive diagnostic criteria are minimal consensus criteria 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 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 only 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

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

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

(e) 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, 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

(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 radiologic imaging. Magnetic resonance imaging (MRI) and positron emission tomography (PET) have been shown to be helpful for diagnosing retroperitoneal fibrosis in addition to X-rays, which may include CT scanning

Biopsy is often inconclusive, making it difficult to differentiate this condition from secondary retroperitoneal fibrosis due to malignant tumors or infectious diseases

Table 1 continued

(h) Other tumefactive lesions: Proliferation of IgG4+ plasmacytes 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 disease) and is therefore not specific to IgG4-RD

(3) On rare occasions, the 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+ to 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. Histopathologic 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 involvement

VII. Steroids

(1) 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 the disease in organs difficult to biopsy, such as the pancreas, retroperitoneum, and pituitary, and who respond to steroids may 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 the involved organs, it is essential to determine histopathologically whether malignant cells are present

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

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

[a] Adapted with permission from *Modern Rheumatology*

IgG4 constitutes only approximately 4 % of the total IgG. In 2001, Hamano et al. [2] reported abnormally high serum IgG4 levels in patients with autoimmune pancreatitis. Subsequent to their report, the association of IgG4 with various systemic diseases began to unfold. Apart from pancreatitis, cases showing enlargement or hypertrophy of various organs, such as the lacrimal gland (Fig. 1), salivary gland, hepatobiliary tract, and retroperitoneum, have been found to have elevated serum IgG4 levels. Subsequent studies gradually identified more characteristics of this group of diseases, such as marked infiltration of IgG4-positive plasmacytes and fibrosis in the local lesions, sometimes accompanied by follicular formation [3] (Fig. 2).

In the field of ophthalmology, patients with symmetric enlargement of the lacrimal and salivary glands, who used to be diagnosed as having Mikulicz disease [4], were found to have abnormally high serum IgG4 levels [5]. Similar cases were subsequently confirmed by many facilities in Japan and other countries [6–12]. Earlier reports described IgG4-related disease involving the ocular adnexa as characterized by symmetrical and persistent swelling of the lacrimal and salivary glands as well as prominent infiltration of IgG4-expressing plasmacytes in those glands [5–8]. However, it is now known that IgG4-related ophthalmic lesions are not limited to the lacrimal glands but may also manifest diffusely in the orbit and in diverse ocular tissues such as the extraocular muscles, orbital nerve (trigeminal nerve branch), and eyelid [13]. In particular, enlargement of the infraorbital or supraorbital nerve, or both, is frequently observed in this disease [13–15].

Mikulicz disease was first reported in the 1880s [4]. Approximately 50 years later, when Sjögren syndrome was established as a disease entity, Mikulicz disease was

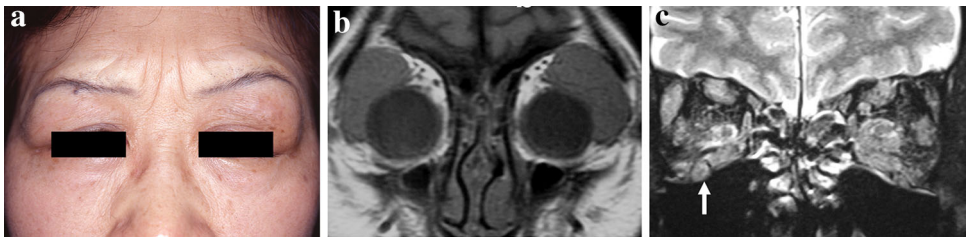

Fig. 1 Clinical findings of IgG4-related ophthalmic disease. **a** Typical IgG4-related ophthalmic disease showing symmetric enlargement of the bilateral lacrimal glands. **b** Coronal MRI (T1-weighted) depicts marked symmetric enlargement of the bilateral lacrimal glands. **c** Coronal MRI (T2-weighted) depicts moderate enlargement of the bilateral lacrimal glands and some extraocular muscles and marked enlargement of the infraorbital nerve (trigeminal nerve) (*arrow*)

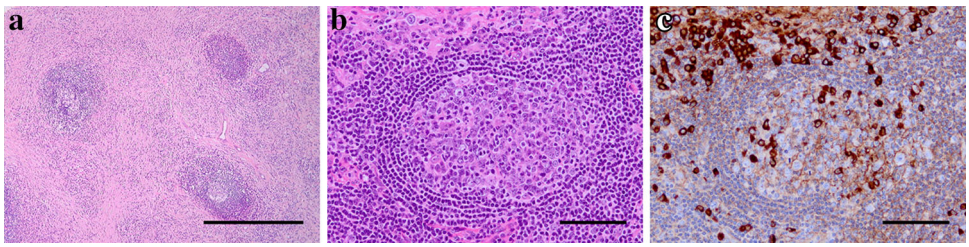

Fig. 2 Histopathologic findings of IgG4-related ophthalmic disease. **a** Lymphoplasmacytic infiltration accompanied by follicular formation and marked fibrosis. H&E staining. *Bar* = 500 μm. **b** Magnified image of a follicle with a germinal center. H&E staining. *Bar* = 100 μm. **c** Immunohistochemical staining showing many IgG4-positive cells. *Bar* = 100 μm

considered to be histopathologically equivalent to Sjögren syndrome [16]. However, the differences in the histopathology and lacrimal secretion of the two diseases had been pointed out [17] even before the concept of IgG4-related disease was established.

Names for IgG4-related ocular lesions

Various names have been employed to describe IgG4-related disease. In the field of ophthalmology, terms used include "ocular adnexal IgG4-related disease" [7], "IgG4+ chronic sclerosing dacryoadenitis" [18], "IgG4-related orbital inflammation" [19], "ocular adnexal IgG4-related disease" [20], "IgG4-related dacryoadenitis" [21], and "IgG4-related Mikulicz's disease" [22].

However, since 2012, following publication of the comprehensive diagnostic criteria for IgG4-related disease [1] in Japan, "IgG4-related ophthalmic disease" has been advocated as the standardized name for the ocular lesions of this disease.

Diagnostic criteria for IgG4-related ophthalmic disease, 2014

As described above, the comprehensive diagnostic criteria of IgG4-related disease for all systemic conditions were reported in 2012 [1]. However, other than for the kidney [23] and pancreas [24], the diagnostic criteria for individual organs are not well established. Against this background, the Study Group for IgG4-related Disease in the Intractable Disease Project supported by a grant from the Ministry of Health, Labor, and Welfare of Japan has played a central role in developing new diagnostic criteria for IgG4-related ophthalmic disease (Table 2). Essentially, the diagnostic criteria are based on the framework of the "Comprehensive Diagnostic Criteria for IgG4-related Disease 2011" (Table 1) [1], which was originally developed mainly for internal medicine, with emphasis given to the specific features of the ophthalmic lesions. In practice, diagnosis is classified as definitive, probable, or possible.

The present criteria and the "Comprehensive Diagnostic Criteria for IgG4-related Disease 2011" [1] differ in several aspects. First, the ocular manifestations including enlargement of the lacrimal gland, trigeminal nerve (supraorbital and infraorbital nerves), extraocular muscle, and various ophthalmic tissues are described in more detail to reflect the involvement of various ocular tissues [13]. Second, in the ocular adnexa, fibrosis is not necessarily marked histopathologically. Third, a germinal center is frequently observed. Fourth, the criteria for an IgG4-positive plasma cell infiltrate is a ratio of IgG4-positive cells to IgG-positive cells of 40 % or above, or 50 or more cells per high-power field (×400). Fifth, the diseases requiring differentiation include Sjögren syndrome and diseases

Table 2 Diagnostic criteria for IgG4 related ophthalmic disease, 2014

(1) Imaging studies show enlargement of the lacrimal gland, trigeminal nerve, or extraocular muscle as well as masses, enlargement, or hypertrophic lesions in various ophthalmic tissues
(2) Histopathologic examination shows marked lymphocyte and plasmacyte infiltration, and sometimes fibrosis. A germinal center is frequently observed. IgG4+ plasmacytes are found and satisfy the following criteria: ratio of IgG4+ cells to IgG+ cells of 40 % or above, or more than 50 IgG4+ cells per high-power field (×400)
(3) Blood test shows elevated serum IgG4 (≥135 mg/dl)

Diagnosis is classified as "definitive" when (1), (2), and (3) are satisfied; "probable" when (1) and (2) are satisfied; and "possible" when (1) and (3) are satisfied

Table 3 Differential diagnosis of IgG4-related ophthalmic disease

Sjögren syndrome
Lymphoma
Sarcoidosis
Granulomatosis with polyangitis (Wegener granulomatosis)
Thyroid-related orbitopathy
Idiopathic orbital inflammation
Dacryoadenitis or orbital cellulitis caused by bacteria or fungi

Mucosa-associated lymphoid tissue (MALT) lymphoma may contain IgG4+ cells; therefore, careful differentiation is necessary

involving tumors or hypertrophic lesions in the ocular adnexa, such as lymphoma and sarcoidosis (Table 3). In addition, attention is drawn to the differentiation from mucosa-associated lymphoid tissue (MALT) lymphoma, which is the most common lymphoproliferative disease in the orbit. The relationship between IgG4-related disease and MALT lymphoma in the ocular adnexa has been reported [25–27] and should be discussed in the future.

Prevalence of IgG4-related ophthalmic disease

Not only is the entity of IgG4-related ophthalmic disease not well recognized and not widely known, the prevalence of the disease also remains unclear. According to a recent multicenter survey in Japan, among 1014 cases of orbital lymphoproliferative disease, MALT lymphoma had the highest prevalence (39.8 %), followed by IgG4-related ophthalmic disease (21.6 %) [28]. Together, these two diseases occupy over 60 % of all cases of lymphoproliferative disease in the orbit.

Among the ophthalmologic cases treated repeatedly with corticosteroids under a clinical diagnosis of "orbital pseudotumor," "inflammatory pseudotumor of the orbit," or "idiopathic orbital inflammation," the possibility exists that a considerable number are in fact IgG4-related ophthalmic disease. Furthermore, among other cases treated under a diagnosis of "orbital myositis," "orbital apex syndrome," "idiopathic optic neuropathy," or "posterior scleritis," some cases may be difficult to differentiate from IgG4-related ophthalmic disease.

Relationship with lesions in other organs

Although IgG4-related disease lesions may develop in various organs of the body as mentioned above, they do not necessarily occur synchronously in multiple organs. On the contrary, it is not uncommon to find no abnormalities in other organs at the time the ocular lesion is detected and diagnosed. On the other hand, a report has indicated that markedly elevated serum IgG4 (900 mg/dl or higher) is associated with a higher possibility of concurrent orbital and extraorbital lesions, such as in the salivary glands or lymph nodes [29].

Perspective

This review has introduced the diagnostic criteria for a new disease entity, IgG4-related ophthalmic disease. Further evaluation is expected to validate these criteria. In addition, attention has to be paid to the fact that the ocular symptoms of this disease are diverse and, in some cases, may seriously affect visual function.

This disease group is characterized by both temporal and spatial multiplicity of lesion onset and by relatively good response to systemic corticosteroids. However, the lesions may relapse repeatedly following tapering, and progression to a chronic state is not uncommon. On the basis of the diagnostic criteria described in this article, further studies are necessary to develop a classification system of severity specifically for ophthalmic lesions, considering also the clinical findings and the effect on visual function, as well as to establish treatment guidelines centering on corticosteroids. At the same time, through promotion of research on the pathogenesis of IgG4-related ophthalmic disease, elucidation of its etiology may be anticipated.

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Conflicts of interest H. Goto, None; M. Takahira, None; A. Azumi, None.

Appendix

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