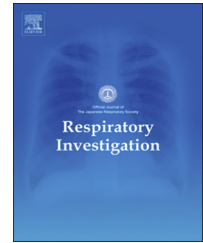




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Short Communication

Proposed diagnostic criteria for IgG4-related respiratory disease[☆]Shoko Matsui^{a,*}, Hiroshi Yamamoto^b, Seijiro Minamoto^c, Yuko Waseda^d,
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1. Background on the preparation of the diagnostic criteria

IgG4-related disease (IgG4-RD) [1] is a newly recognized systemic disease characterized by an elevated serum level of IgG4, infiltration of IgG4-positive plasma cells into affected lesions, and fibrosis. In 2011, comprehensive diagnostic criteria for IgG4-RD were proposed by the Study Group of Intractable Diseases from the Ministry of Health, Labor and Welfare, Japan (MHLW) [2], and these criteria have been gaining increasing acceptance.

The comprehensive diagnostic criteria [2] are highly convenient for diagnosing IgG4-RD and are based on findings common to multiple organs. However, because the field of

medicine has become increasingly specialized and subdivided, the Study Group at the MHLW has recognized the need for organ-specific diagnostic criteria focusing on the specific features of lesions in individual organs; organ-specific diagnostic criteria for the pancreas, kidney, and other sites of involvement have already been published [3,4].

Following the release of the comprehensive diagnostic criteria for IgG4-RD 2011 [2], an attempt was made by the subcommittee on IgG4-RD supported by the MHLW to prepare similar diagnostic criteria for lesions arising in the respiratory organs. The criteria for the respiratory organs were presented at a symposium at the 54th Annual Meeting of the Japanese Respiratory Society (2014), where the final diagnostic criteria

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Table 1 – Diagnostic criteria for IgG4-related respiratory disease.**A. Diagnostic factors****I. Chest imaging**

Imaging findings include any of the following intrathoracic lesions, such as hilar/mediastinal lymphadenopathy, bronchial wall/bronchovascular bundle thickening, interlobular septal wall thickening, nodular shadow, infiltrative shadow, pleural thickening and/or effusion.

II. Serology

Elevated serum IgG4 concentration of ≥ 135 mg/dl

III. Histology

Two or more of the following items are required from intrathoracic organ tissues.

a: ≥ 3 Items; b: 2 items

- (1) Marked lymphoplasmacytic cell infiltration into interstitium of peribronchovascular sheath, interlobular septal wall, and/or pleura.
- (2) IgG4/IgG-positive cell ratio $> 40\%$ and/or > 10 IgG4-positive cells/high power field.
- (3) Obliterative phlebitis or obliterative arteritis.
- (4) Storiform fibrosis or fibrosis consisting of proliferating spindle-shaped cells around infiltrating lymphocytes.

IV. Other organ involvement

The presence of lesions in the extrathoracic organs satisfying the diagnostic criteria of IgG4-related disease such as sclerosing dacryoadenitis/sialadenitis, autoimmune pancreatitis, IgG4-related sclerosing cholangitis, IgG4-related kidney disease, and retroperitoneal fibrosis.

V. Reference finding

Hypocomplementemia

B. Diagnosis

1. Definite diagnosis (definite): I+II+IIIa, or I+II+IIIb+IV
Histological definite diagnosis [definite (histological)]: I+all four items of III
2. Probable diagnosis (probable): I+II+IV, or I+II +IIIb+V
3. Possible diagnosis (possible): I+II+IIIb

C. Differential diagnosis

It is important to differentiate IgG4-related respiratory disease from the following diseases with similar features.

Castleman disease (plasma cell type), collagen-disease-related lung disease, granulomatosis with polyangiitis (Wegener granuloma), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), sarcoidosis, respiratory organs infection, Rosai–Dorfman disease, inflammatory myofibroblastic tumor, malignant lymphoma, lung cancer.

Table 2 – Diagnostic criteria of IgG4-related respiratory disease: appendix for Table 1.**1. Imaging findings**

- Hilar/mediastinal lymphadenopathy and bronchial wall/bronchovascular thickening are frequent findings.
- Lesions are found predominantly in the interstitium including the interlobular septa and pleura.
- Sometimes detected as an intrathoracic nodular, mass or infiltrative shadow.
- Since the imaging findings are non-specific, conditions noted in the Differential diagnosis, especially infection and malignancy, must be ruled out.

2. Clinical/test findings

- Presence or history of allergic conditions such as allergic rhinitis and bronchial asthma is sometimes noted.
- Hyper-IgG-emia, hyper-IgE-emia are frequently associated, while simultaneous elevation of serum IgA and IgM is rare.
- Antinuclear antibodies and/or rheumatoid factor positivity, and hypocomplementemia are sometimes found.
- No or only very mild findings of inflammation such as leukocytosis and CRP elevation.

3. Pathological findings

- Presence of fibrotic foci associated with marked lymphoplasmacytic cell infiltration into the tissues such as interstitium of peribronchovascular sheath, interlobular septal wall, pleura and contiguous alveolar septal wall.
- ‘Storiform fibrosis’ is the type of fibrosis typically seen, and consists of proliferating spindle-shaped cells associated with lymphoplasmacytic cell infiltration. The arrangement of these components is irregular and sometimes assumes a whirlpool-like pattern.
- Formation of mass lesions that appear to bury the alveolar spaces is sometimes observed because of the presence of marked cellular infiltration and fibrosis.
- Scattered eosinophil infiltrates are occasionally found, while neutrophil infiltrates and granulomas are usually not.
- For the pathological diagnosis, use of surgical biopsy specimens is desirable.

4. Extra-thoracic organ lesions

- Extra-thoracic organ lesions are those that satisfy the established organ-specific diagnostic criteria (pancreas, bile duct, or kidney), or pathological findings such as prominent IgG4-positive lymphoplasmacytic cell infiltration and fibrosis consistent with the characteristic (organ-specific) clinical and imaging findings (lacrima gland, salivary gland, or retroperitoneum).

were prepared after discussion and agreement by all members present. In this report, we outline these criteria.

2. Guidelines for IgG4-related respiratory disease

2.1. Nomenclature of respiratory tract lesions

At the International Symposium on IgG4-RD held in Boston in 2011, two separate names were adopted for the respiratory tract lesions of IgG4-related disease: ‘IgG4-related lung disease’ and ‘IgG4-related pleural disease’ [5]. However, since a subsequent report that respiratory tract lesions are typically interstitial lesions [6], the Ministry of Health group decided to refer to lesions of both the intrathoracic respiratory organs

and auxiliary structures collectively as ‘IgG4-related respiratory disease (IgG4-RRD)’.

2.2. The diagnostic criteria for IgG4-RRD

The diagnostic criteria for IgG4-RRD are listed in Table 1. Some commentary has been added (Table 2) to enhance the understanding of chest imaging, clinical/laboratory results, and pathological findings of these diagnostic criteria. An algorithm has also been prepared to concretely illustrate the process whereby the diagnosis is reached (Fig. 1).

3. Summary

The diagnostic criteria of IgG4-RRD are outlined. We hope for further consideration and acceptance of the criteria.

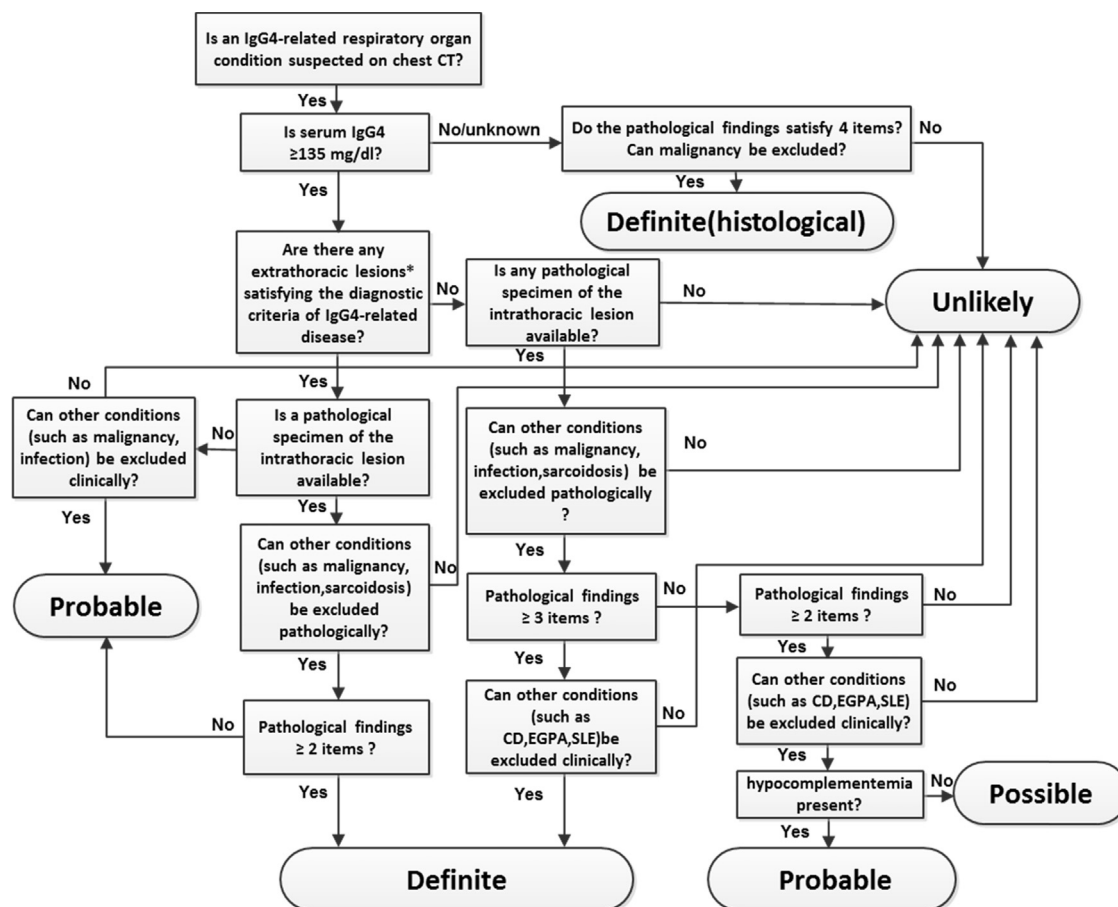


Fig. 1 – Diagnostic algorithm. CD: Castleman disease (plasma cell type) EGPA: eosinophilic granulomatosis with polyangiitis SLE: systemic lupus erythematosus *sclerosing dacryoadenitis· sialadenitis, autoimmune pancreatitis, IgG4-related sclerosing cholangitis, IgG4-related kidney disease, retroperitoneal fibrosis.

Conflict of interest

None of the authors have any relevant conflicts of interest to report.

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