

How to diagnose IgG4-related disease

We read with great interest the editorial by Fox and Fox¹ describing the use of serum immunoglobulin G4 (IgG4) concentrations as a marker for IgG4-related disease (IgG4-RD). IgG4-RD is a fascinating clinical entity including a wide variety of diseases, formerly diagnosed as Mikulicz's disease, autoimmune pancreatitis (AIP), interstitial nephritis, prostatitis and retroperitoneal fibrosis.²⁻³ However, universal criteria for IgG4-RD have not yet been established at present, making its diagnosis in some patients ambiguous leading to many IgG4-RD mimickers.

A 3-year investigation by the Japanese IgG4 team, organised by the Ministry of Health, Labour and Welfare (MHLW) of Japan, has reached a consensus, in that IgG4-RD can occur in various organs, with clinical symptoms depending on lesion location. Characteristics common to all forms of IgG4-RD include elevated serum IgG4 concentration and tissue infiltration by IgG4-positive plasma cells, accompanied by tissue fibrosis and sclerosis.² In 2011, the Japanese IgG4 team published comprehensive diagnostic (CD) criteria for IgG4-RD,⁴ with the major characteristics being serum IgG4 concentration >135 mg/dL, the infiltration of >10 IgG4+ cells per high-powered field (HPF) and an IgG4+/IgG+ cell ratio >40%. The cut-off of 135 mg/dL was based on receiver operating characteristic curves and its validity was confirmed in patients with AIP.⁵⁻⁶ Since then, serum IgG4 levels have been widely used as a reliable criterion for the diagnosis of IgG4-RD.⁴⁻⁶

However, Dr Fox mentioned drawbacks of using serum IgG4 levels in diagnosing IgG4-RD, citing studies reporting that the IgG4 cut-off >135 mg/dL had a low sensitivity and specificity for the diagnosis of IgG4-RD.⁷⁻⁸ As increased serum concentrations of IgG4 have been observed in several diseases with aberrant immunological condition unrelated to IgG4-RD, such as malignant tumours, autoimmune diseases especially rheumatoid arthritis and allergic diseases,⁹⁻¹⁰ increased IgG4 concentration is not a specific marker for IgG4-RD. In contrast, recent large cohort studies from the UK, Taiwan and Japan showed that serum IgG4 concentration >135 mg/dL had overall sensitivities of 82.8%, 86% and 88%, respectively, in diagnosing

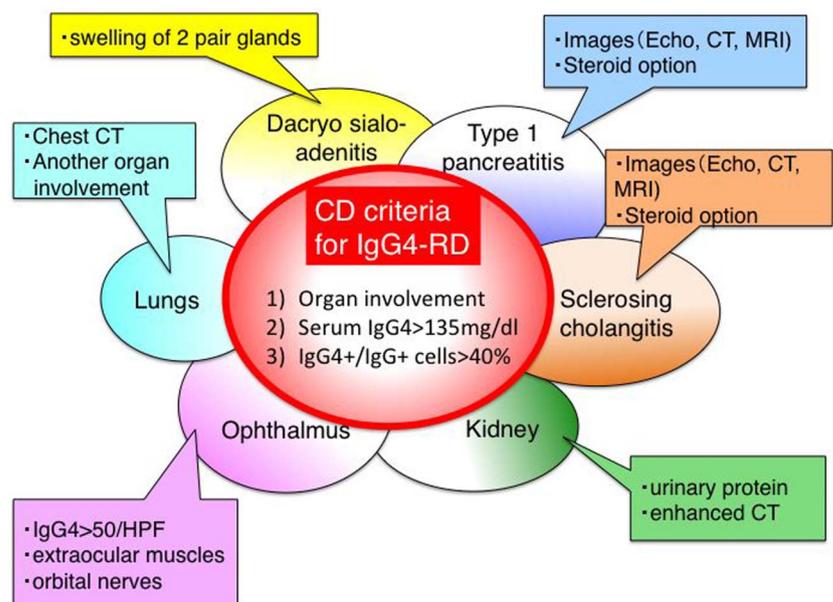
IgG4-RD.¹⁰⁻¹² As no universal criteria for IgG4-RD have been developed to date, three criteria such as international consensus diagnostic criteria for AIP,¹³ consensus statement on the pathology¹⁴ and CD criteria⁴ have been often used for diagnosis of IgG4-RD. Therefore, the sensitivity and specificity of specific markers may differ among studies that use different diagnostic criteria.

Since this complex multisystem disease represented a single pathogenetic disorder manifesting in a variety of target organs, the diagnosis of IgG4-RD is largely based on biopsy results showing enhanced infiltration by IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis and moderate eosinophilia, all of which are frequently observed in the affected tissues of these patients.²⁻³ A high number of IgG4-positive plasma cells in tissue is a hallmark of IgG4-RD, even when serum IgG4 concentrations are below the cut-off level. The number of IgG4-positive plasma cells differ among organs, and consensus statement on the pathology emphasises tissue IgG4 cell counts in each organ for diagnosis of IgG4-RD.¹⁴ However, these counts should be supplemented by IgG4+/IgG+ plasma cell ratio of more than 40% to distinguish IgG4-RD.⁴

As stated by Fox and Fox,¹ IgG4-RD tends to be both underdiagnosed and overdiagnosed. Underdiagnosis is due to a lack of recognition of this disease, and overdiagnosis results from the well-intentioned enthusiasm of physicians and/or pathologists who recognise IgG4-RD and diagnose similar conditions as IgG4-RD. Therefore, simple and strict criteria are required in the diagnosis of patients with IgG4-RD. In this point, a definite diagnosis of IgG4-RD by CD criteria requires that patients satisfy all three diagnostic characteristics: clinical evidence, high (>135 mg/dL) serum IgG4 and pathological certification (>10 IgG4+ cells/HPF and IgG4+/IgG cell ratio >40%), although some patients may not satisfy these specific serological and/or histopathological criteria because of the difficulty of obtaining biopsies, and therefore cannot be diagnosed with definite IgG4-RD.⁴

To resolve this problem, several Japanese medical societies, including those for gastroenterology, pancreas, biliary tract, rheumatology, ophthalmology and respiratory, have published organ specific criteria for IgG4-RD.¹³⁻¹⁸ Each criterion contains organ-specific clinical symptom and characteristic radiological findings of IgG4-RD, even with steroidal trial in some

Figure 1 Combination of comprehensive diagnostic (CD) criteria and organ-specific criteria for diagnosing IgG4-related disease (IgG4-RD). HPF, high powered field; IgG4, immunoglobulin G4.



criteria. We recently published a paper describing the optimal method of diagnosing IgG4-RD, based on combinations of CD and organ-specific criteria¹⁹ (figure 1).

None of the diagnostic criteria have been approved to date by the American College of Rheumatology for reasons that include insufficient sensitivity and specificity, implications for billing and reimbursement, healthcare priorities and treatment implications for patients.²⁰ Physicians in every field of medicine, however, may encounter this new disease in daily practice, and proper diagnostic criteria are required immediately. Therefore, we believe that a careful and intensive judgement using combination of CD and organ-specific criteria is the current best way for diagnosis of IgG4-RD.

Hisanori Umehara,¹ Kazuichi Okazaki,² Mitsuhiro Kawano,³ Tsuneyo Mimori,⁴ Tsutomu Chiba⁵

¹Division of RA and Autoimmune Diseases, Nagahama City Hospital, Nagahama, Shiga, Japan

²Division of Gastroenterology and Hepatology, The Third Department of Internal Medicine, Kansai Medical University, Osaka, Japan

³Division of Rheumatology, Department of Internal Medicine, Graduate School of Medical Science, Kanazawa University, Ishikawa, Japan

⁴Department of Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

⁵Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Correspondence to Professor Hisanori Umehara, Division of Rheumatology and Immunology, Nagahama City Hospital, 313, Oinuicho Nagahama, Shiga 526-0043, Japan; umehara606@gmail.com

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