Respiratory lesions in IgG4-related disease: classification using 2019 American College of Rheumatology/European League Against Rheumatism criteria

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To the Editor:

In 2019, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) proposed classification criteria for IgG4-related disease (IgG4-RD) [1, 2]. IgG4-RD can cause fibroinflammatory lesions characterised by infiltration of abundant IgG4-positive plasma cells with fibrosis and an elevated serum IgG4 concentration [3–5]. Approximately 35% of patients with IgG4-RD present with intrathoracic lesions, including those involving the mediastinal lymph nodes, bronchial walls and peribronchovascular bundles [6–8]. To increase diagnostic sensitivity and specificity, we previously proposed diagnostic criteria for IgG4-related respiratory disease (IgG4-RRD) [9]. However, particularly for cases with isolated pulmonary lesions, the diagnosis of IgG4-RRD is sometimes difficult and requires multidisciplinary discussion (MDD) [10]. Additionally, we recently reported data for 16 patients with IgG4-positive interstitial pneumonia, which should be treated as a separate entity from conventional IgG4-RRD given the relative differences in disease behaviour and responses to glucocorticoid (GC) treatment [11].

This study aimed to identify potential problems in the current diagnosis for IgG4-RRD using the 2019 ACR/EULAR classification criteria by applying these criteria in patients with interstitial lung diseases (ILD) involving infiltration of IgG4-positive plasma cells.

We performed a secondary analysis of data from a retrospective study. Details of the study participants have been described previously [11]. Briefly, nationwide recruitment of patients was conducted from March to May 2019. All participants demonstrated ILD on chest high-resolution computed tomography (HRCT), elevated serum IgG4 concentrations ($\geqslant$135 mg·dL^{-1}), and infiltration of numerous IgG4-positive plasma cells (ratio of IgG4-positive/IgG-positive cells >40%; IgG4-positive cells >10 per high-power field) in specimens obtained *via* surgical lung biopsies. We reviewed the cases of 28 patients with suspected ILD involving IgG4-positive plasma cell infiltration from 17 institutions across Japan.

We reviewed clinical, radiological and histopathological data at diagnosis for each patient. The diagnostic gold standard for this study was the final diagnosis after expert MDD. Cases were classified as MDD definite-IgG4-RRD (d-IgG4-RRD) or mimickers. Thereafter, the included patients were assessed according to the 2019 ACR/EULAR classification criteria.

Briefly, a three-step classification process was proposed [1, 2]. First, entry criteria consisting of a potential IgG4-RD case involving at least one of the 11 possible organs were applied. Second, exclusion criteria comprising clinical, serological, radiological, and pathological items were applied. In this step, known diseases, such as multicentric Castleman disease, were excluded as specific disease exclusions. Additionally, cases exhibiting no objective response to GC treatment were excluded. Third, inclusion criteria comprising eight weighted domains addressing clinical, serological, radiological and pathological items were applied. If the total inclusion point score was $\geqslant$20, the case was classified as "IgG4-RD".

Shareable abstract (@ERSpublications)
In this study, ILDs involving IgG4-positive plasma cell infiltration were classified using the 2019 ACR/EULAR criteria. Most IgG4-positive interstitial pneumonia cases were excluded, suggesting the need for a unique treatment strategy. https://bit.ly/38GiUJM

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Continuous data are presented as the mean±standard deviation and were compared between groups using Mann–Whitney U-tests or unpaired t-tests. Categorical data are presented as numbers and compared using the $\chi 2$ test or Fisher's exact tests. Statistical significance was established at p-values<0.05.

Among the 28 cases included, seven were diagnosed as MDD d-IgG4-RRD. The other 21 cases were diagnosed as mimickers, including 16 cases of IgG4-positive interstitial pneumonia, three cases of multicentric Castleman disease, one case of rheumatoid arthritis-associated ILD, and one case of lung cancer.

There were no significant between-group differences in age at diagnosis (66.7±8.3 and 63.1±9.5 years, respectively), sex ratio (male: 6 and 16 patients, respectively) or smoking history (positive in 4 and 15, respectively).

On histopathological examination, patients with d-IgG4-RRD had a significantly higher incidence of obliterative phlebitis (4 and 3, respectively, p=0.043) and storiform fibrosis (3 and 0, respectively, p=0.011) than mimickers.

All 28 patients had clinical or radiological involvement of intrathoracic lesions, as well as pathological evidence of an inflammatory process accompanied by lymphoplasmacytic infiltration; therefore, they fulfilled the initial entry criteria. In the second step, two of seven patients with d-IgG4-RRD and 17 of the 21 mimickers met the exclusion criteria (figure 1). Among those with d-IgG4-RD, one was excluded due to positivity for antineutrophil cytoplasmic antibodies, while the other was excluded due to positivity for specific autoantibodies. Among mimickers, one, two, and two patients were excluded due to peripheral eosinophilia, fever and positivity for specific autoantibodies, respectively.

All 16 patients with IgG4-positive interstitial pneumonia had an inclusion criteria score ⩾20 points. However, 15 of these 16 patients were treated with GCs; nine demonstrated poor response to GC treatment

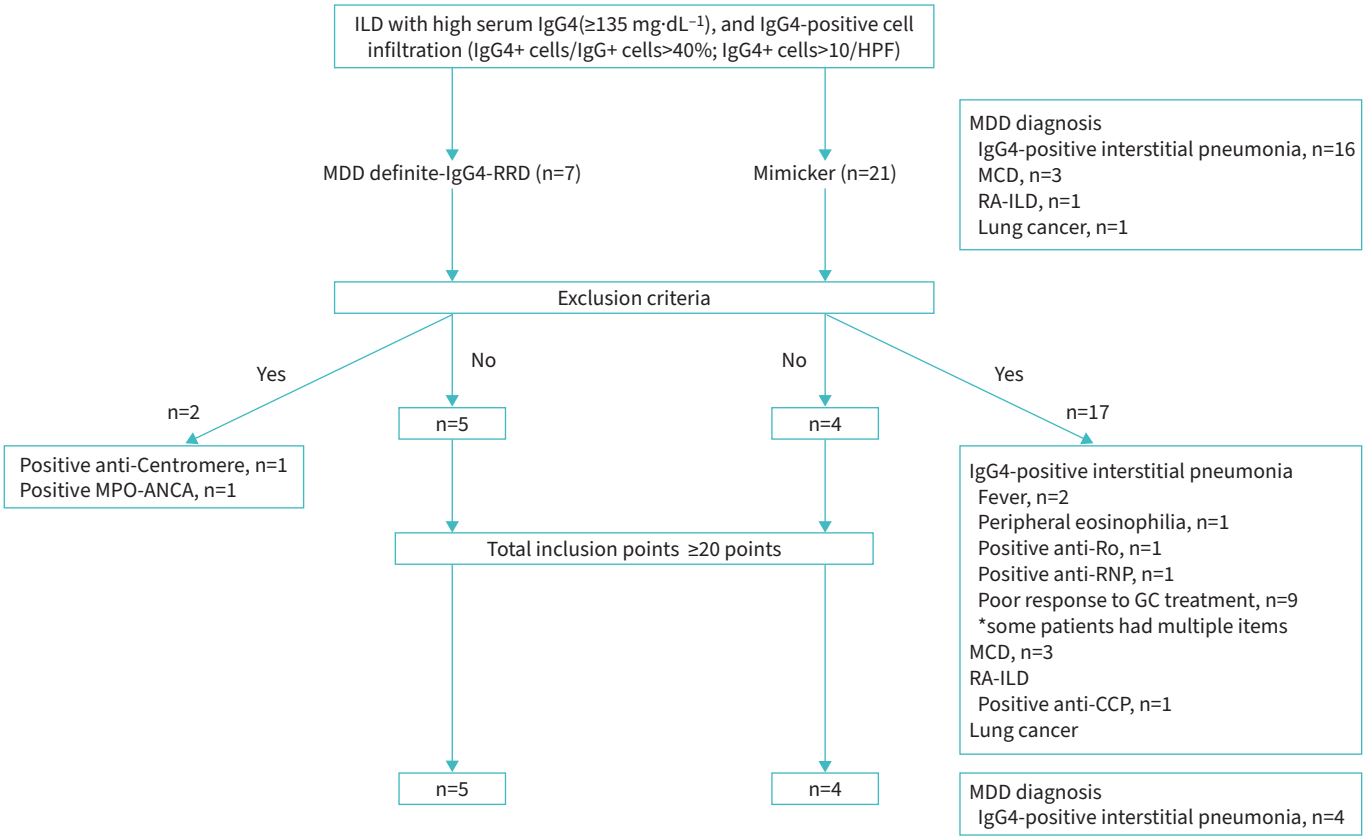

FIGURE 1 Performance of the 2019 ACR/EULAR classification criteria for IgG4-RD. ANCA: antineutrophil cytoplasmic antibody; GC: glucocorticoid; HPF: high-power field; IgG4-RRD: IgG4-related respiratory disease; ILD: interstitial lung disease; IP: interstitial pneumonia; MPO: myeloperoxidase; MCD: multicentric Castleman disease; MDD: multidisciplinary discussion.

and the remaining patients had residual reticular opacities and/or cystic lesions on HRCT. Furthermore, three patients died (two due to chronic respiratory failure and one due to acute exacerbation). Therefore, these patients were excluded in the second step.

All remaining patients with d-IgG4-RRD and mimickers had an inclusion criteria score ⩾20 points. Five IgG4-positive interstitial pneumonia cases were classified as IgG4-RD based on the 2019 ACR/EULAR classification score. The sensitivity, specificity, positive predictive value, and negative predictive value of the ACR/EULAR classification criteria were 71.4%, 81.0%, 55.6%, and 89.5%, respectively.

IgG4-RD typically affects the lungs [9, 10, 12], while IgG4-RRD presents with few respiratory symptoms [10]. Therefore, most patients with IgG4-RD exhibit incidental pulmonary lesions or abnormal lung shadows while examining extrathoracic IgG4-RD lesions.

Our results indicated that the 2019 ACR/EULAR classification criteria demonstrated excellent performance for patients with IgG4-RD exhibiting pulmonary lesions. However, other diseases, such as IgG4-positive interstitial pneumonia, were classified as IgG4-RD before GC treatment. In the 2019 ACR/EULAR classification criteria, the weights of certain inclusion criteria tended to be higher in the calculation of the inclusion score, especially for patients with multiple organ involvement and those with abundant infiltration of IgG4-positive plasma cells. Thus, it is important to exclude mimickers [1, 2, 5], but this is not easy in clinical practice, especially in patients with isolated pulmonary lesions [13, 14].

We recently proposed that clinical characteristics differ between IgG4-positive interstitial pneumonia and IgG4-RRD [11]. The most common findings on HRCT in patients with IgG4-positive interstitial pneumonia were ground-glass opacities, fine reticular opacities, and traction bronchiectasis [11]. On the other hand, typical findings on HRCT in patients with IgG4-RRD was thickening of the perilymphatic interstitium (bronchovascular bundle and interlobular septa) [10]. Moreover, even though the ground-glass opacities improved with GC treatment, the fine reticular opacities did not improve in most cases of IgG4-positive interstitial pneumonia. While most patients with IgG4-positive interstitial pneumonia demonstrated a poor response to GC treatment, most patients with IgG4-RRD demonstrated a good response to GC treatment and benign prognosis. Moreover, in some patients with IgG4-positive interstitial pneumonia, fibrosis eventually progressed despite the temporary effectiveness of GC treatment, and some of these patients died. Since most patients with IgG4-positive interstitial pneumonia were excluded according to the classification criteria, we believe that IgG4-positive interstitial pneumonia differs from IgG4-RD.

IgG4-RD status must be reconsidered when patients exhibit no objective response to GC treatment [1, 2, 5]. However, responsiveness to GC is not identified until the induction of treatment. Therefore, we advocate that IgG4-positive interstitial pneumonia should be excluded from IgG4-RRD at the time of diagnosis.

This study had several limitations, including its retrospective design and small sample size. However, we recruited patients from across Japan, all of whom underwent detailed clinical, radiological, and pathological assessments through MDD, suggesting high diagnostic reliability. Furthermore, the study cohort was mainly designed to assess patients with ILD, indicating possible selection bias.

In conclusion, the 2019 ACR/EULAR classification criteria for IgG4-RD excluded most cases of IgG4-positive interstitial pneumonia when used to assess ILD cases involving IgG4-positive plasma cell infiltration; thus, the current study highlights the need to remove this potentially lethal condition from the diagnostic criteria for IgG4-RRD. It also highlights the need for different management strategies prior to therapy initiation.

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