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The Reclassification of Patients With Previously Diagnosed Eosinophilic Granulomatosis With Polyangiitis Based on the 2022 ACR/EULAR Criteria for Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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ABSTRACT. ***Objective.*** The American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) have proposed the 2022 classification criteria for eosinophilic granulomatosis with polyangiitis (EGPA). This study applied the 2022 ACR/EULAR criteria to Korean patients with previously diagnosed EGPA to investigate the concordance rate between the 2022 ACR/EULAR criteria and the old criteria for EGPA.

Methods. In total, 51 patients with EGPA who met the 1990 ACR criteria, the 2007 European Medicines Agency algorithm, and the 2012 Chapel Hill Consensus Conference definitions were reclassified based on the 2022 ACR/EULAR criteria.

Results. Of 51 patients, 44 (86.3%) were reclassified as having EGPA according to the 2022 ACR/EULAR criteria. Among the 7 patients who failed to meet the 2022 ACR/EULAR criteria, 3 patients were reclassified as having microscopic polyangiitis (MPA) and 1 was reclassified as having granulomatosis with polyangiitis (GPA) based on the 2022 ACR/EULAR criteria; as well, 3 patients were reclassified as having unclassifiable vasculitis. Moreover, 6 patients who met the 2022 ACR/EULAR criteria for EGPA simultaneously met the criteria for MPA based on the 2022 ACR/EULAR criteria for MPA, and 1 who met the criteria for EGPA simultaneously met the criteria for GPA based on the 2022 ACR/EULAR criteria for GPA.

Conclusion. The concordance rate between the 2022 ACR/EULAR criteria for EGPA and the old criteria was 86.3%. The most important factor in the failure to reclassify patients as having EGPA was the exclusion of nonfixed pulmonary infiltrates in the 1990 ACR criteria for EGPA. We cautiously suggest reconsidering nonfixed pulmonary infiltrates in cases reclassified as unclassifiable vasculitis. Further, additional classification strategies are needed for patients who simultaneously satisfy both antineutrophil cytoplasmic antibody–associated vasculitis subtypes.

Key Indexing Terms: 2007 EMA algorithm, 2012 CHCC definitions, 2022 ACR/EULAR criteria, concordance, eosinophilic granulomatosis with polyangiitis

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Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is a small-vessel vasculitis that is characterized by necrotizing vasculitis with few or no immune deposits. AAV includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). EGPA primarily induces necrotizing vasculitis in small-to-medium vessels in the respiratory tract and is often associated with asthma and peripheral eosinophilia.[1,2] Unlike other AAV subtypes such as MPA or GPA, EGPA consists of 3 phases: prodromal, eosinophilic, and vasculitic phases. The prodromal phase may precede the eosinophilic phase by months to years and exhibit upper respiratory tract symptoms, such as asthma, nasal polyps, and sinusitis, which are often observed in this phase. In the eosinophilic phase, lung, heart, and gastrointestinal manifestations are predominant, whereas in the vasculitic phase,

nerve, kidney, and skin manifestations are apparent, along with an improvement in asthma.[3]

In 1951, Churg and Strauss[4] first described the characteristics observed in 13 cases of EGPA through pathological findings obtained by autopsy. In 1984, Lanham and colleagues[5] reported the clinical findings of 16 cases of EGPA, including asthma, peripheral eosinophilia, and vasculitis. However, these 2 studies only described the clinical features of patients with EGPA but could not provide the well-structured classification criteria for EGPA.

In 1990, the American College of Rheumatology (ACR) proposed the first classification criteria for EGPA: the 1990 ACR criteria. The 1990 ACR criteria are composed of 6 items, which are listed in order of specificity, as follows: (1) eosinophilia > 10% (specificity 96.6%), (2) asthma (96.3%), (3) nonfixed pulmonary infiltrate (92.4%), (4) extravascular eosinophils (84.4%), (5) mono- or polyneuropathy (79.8%), and (6) paranasal sinus abnormality (79.3%). These criteria have been used most frequently thus far because the overall sensitivity and specificity are as high as 85.0% and 99.7%, respectively.[6]

In 1994, the first International Chapel Hill Consensus Conference (CHCC) on the Nomenclature of Systemic Vasculitides—the 1994 CHCC definition—was held to specify the name and definition of systemic vasculitis.[1] In 2007, the European Medicines Agency (EMA) proposed a diagnostic tool using an algorithm for the classification of AAV—the 2007 EMA algorithm—which consisted of EGPA, GPA, MPA, polyarteritis nodosa, and unclassifiable vasculitis, in order. The 1990 ACR criteria for EGPA are applied as the first step of the 2007 EMA algorithm; if these criteria are met, the algorithm is terminated.[7] Thereafter, the understanding of vasculitis has advanced, and the tendency to not use eponyms in terminology has increased; the CHCC revised the names and definition of systemic vasculitis as appropriated in 2012—the 2012 CHCC definitions—and ANCA was first included in the eligibility criteria used in the MIRRA trial.[2,8]

In addition, the Diagnostic and Classification Criteria in Vasculitis study, which developed criteria for primary systemic vasculitis, proposed the ACR/European Alliance of Associations for Rheumatology (EULAR) provisional criteria for GPA at the ACR session in 2016. These criteria were primarily designed to distinguish GPA from EGPA by assigning differently weighted scores to 9 items. When a patient achieves a total score of ≥ 5, the patient may be classified preferentially as having GPA. A previous study applied these provisional criteria to Korean patients with AAV and reclassified 90.0% of patients with GPA, 5.6% of patients with MPA, and 3.3% of patients with EGPA as having GPA.[9] Moreover, that previous study confirmed the clinical significance of proteinase 3 (PR3)–ANCA to distinguish between GPA and EGPA.[9] However, these criteria had a limitation in that they had only aimed to differentiate GPA from EGPA and they were not officially published.

In March 2022, the ACR and EULAR suggested a new classification criteria for EGPA—the 2022 ACR/EULAR criteria—based on a differently weighted score system. These criteria consist of 7 items, and the classification of EGPA can be performed only when a total score of ≥ 6 is obtained.[10] Because it is a recent publication, no study has yet determined how many patients diagnosed with EGPA in Korea meet the 2022 ACR/EULAR criteria. Hence, our present study applied the 2022 ACR/EULAR criteria to Korean patients with previously diagnosed EGPA, based on the 1990 ACR criteria, 2007 EMA algorithm, and 2012 CHCC definitions, to determine the number of patients who could be reclassified as having EGPA.

METHODS

Patients. The term "a patient with previously diagnosed EGPA" was defined as one who was diagnosed with EGPA prior to this study. This study screened 53 patients with previously diagnosed EGPA who were enrolled in the Severance Hospital ANCA Associated Vasculitides (SHAVE) cohort. The SHAVE cohort, which was established in November 2016, is an observational cohort of Korean patients with AAV, according to the inclusion criteria described in previous studies.[11,12] The inclusion criteria were as follows:

1. Patients who were first classified or reclassified as having EGPA at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine and Severance Hospital.
2. Patients who fulfilled all of the 1990 ACR criteria, the 2007 EMA algorithm, and the 2012 CHCC definitions.[1,6,7]
3. Patients who had well-documented medical records that included the clinical, laboratory, radiologic, and histopathologic data to apply the 2022 ACR/EULAR criteria for EGPA.
4. Patients who did not have serious medical conditions, such as malignancies, infectious diseases requiring hospitalization, and other systemic diseases mimicking EGPA or confusing EGPA diagnosis.
5. Patients who had never been exposed to immunosuppressive drugs for the treatment of EGPA before EGPA diagnosis.
6. Patients who had been followed up for at least 3 months after EGPA diagnosis.

Of the 53 patients with previously diagnosed EGPA, 2 patients were excluded because they met only 3 of the 1990 ACR criteria for EGPA, although EGPA was highly suspected based on histopathologic features and asthmatic history. Finally, 51 patients with previously diagnosed EGPA were included in this study. Coexisting serious medical conditions and immunosuppressive drugs that were administered were identified using the International Classification of Diseases, 10th revision, and the Korean Drug Utilization Review system, respectively.

Clinical data and ANCA measurements. The clinical variables are shown in Table 1. The Birmingham Vasculitis Activity Score (BVAS) and the Five Factor Score (FFS) were collected as AAV-specific indices, and clinical manifestations were evaluated based on the 9 systemic categories of the BVAS.[13,14] Myeloperoxidase (MPO)-ANCA and PR3-ANCA were measured on the Phadia 250 analyzer using the novel, anchor-coated, highly sensitive immunoassay EliA (Thermo Fisher Scientific) and human native antigens. Immunoassays were used as the primary screening method for ANCA. However, when patients were found to be negative for ANCA by an antigen-specific assay but positive for perinuclear (P)-ANCA or cytoplasmic (C)-ANCA using an indirect immunofluorescence assay, they were considered to have MPO-ANCA or PR3-ANCA when AAV was strongly suspected based on the clinical and laboratory features.[11,15]

2022 ACR/EULAR criteria for EGPA. There are 2 entry requirements: the presence of small- or medium-vessel vasculitis and the exclusion of other diseases mimicking vasculitis. Differently weighted scores, as reported within parentheses below, are assigned to each criterion. The clinical criteria include obstructive airway disease (+3), nasal polyps (+3), and mononeuritis multiplex (+1). The laboratory and biopsy criteria include blood eosinophil count ≥ 1×10^9/L (+5), extravascular eosinophilic-predominant inflammation on biopsy (+2), PR3-ANCA (or C-ANCA) positivity (–3),

Table 1. Characteristics of patients with AAV with previously diagnosed EGPA at the time of the first classification.

	Values, N = 51
Demographic data	
Age, yrs, median (IQR)	53.7 (22.0)
Male sex	16 (31.4)
ANCA positivity	
MPO-ANCA (or P-ANCA) positivity	25 (49)
PR3-ANCA (or C-ANCA) positivity	5 (9.8)
Both ANCA positivity	3 (5.9)
ANCA negativity	24 (47.1)
AAV-specific indices, median (IQR)	
BVAS	13.0 (10.0)
FFS	1.0 (1.0)
Clinical manifestations at diagnosis	
General	17 (33.3)
Cutaneous	17 (33.3)
Muco-membranous or ocular	2 (3.9)
Otorhinolaryngological	41 (80.4)
Pulmonary	35 (68.6)
Cardiovascular	11 (21.6)
Gastrointestinal	5 (9.8)
Renal	14 (27.5)
Nervous systemic	30 (58.8)

Data are in n (%) unless otherwise indicated. AAV: antineutrophil cytoplasmic antibody–associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; BVAS: Birmingham Vasculitis Activity Score; C: cytoplasmic; EGPA: eosinophilic granulomatosis with polyangiitis; FFS: Five Factor Score; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3.

and hematuria (–1). When a total score of 6 or greater is achieved, the patient can be classified as having EGPA.[10]

Application of the 2022 ACR/EULAR criteria for MPA and GPA. When a patient with previously diagnosed EGPA was not reclassified as having EGPA, the 2022 ACR/EULAR criteria for MPA and GPA were further applied.[16,17] Moreover, when patients could not be reclassified as having MPA or GPA, they were reclassified as having unclassifiable vasculitis.

Statistical analyses. All statistical analyses were performed using SPSS Statistics for Windows (version 26; IBM Corp). Continuous variables were expressed as medians with IQRs, whereas categorical variables were expressed as numbers with percentages.

Ethics approval. This study was approved by the Institutional Review Board (IRB) of Severance Hospital, Seoul, Korea (IRB No. 4-2020-1071) and was conducted according to the principles of the Declaration of Helsinki. Given the retrospective design of the study and the use of anonymized patient data, the requirement for written informed consent was waived by the IRB.

RESULTS

Characteristics. The median age of the 51 patients with previously diagnosed EGPA was 53.7 years, and 16 of them were men. MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were detected in 25 (49%) and 5 (9.8%) patients, respectively. In total, 3 patients (5.9%) had both MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA). The median BVAS and FFS values were 13.0 and 1.0, respectively. The most common clinical manifestation was otorhinolaryngological (80.4%), followed by pulmonary (68.6%) and nervous systemic manifestations (58.8%; Table 1).

Frequencies of each criterion of the 2022 ACR/EULAR criteria for EGPA. Obstructive airway disease was the most frequently observed clinical criterion (90.2%), followed by mononeuritis multiplex (43.1%). Among the laboratory and biopsy criteria, eosinophilia was most commonly found (88.2%), followed by extravascular eosinophil-predominant inflammation (54.9%). In 17 patients, 1 point was deducted for the presence of hematuria, whereas 3 points were deducted in 5 patients for PR3-ANCA (or C-ANCA) positivity. Finally, 44 (86.3%) patients achieved a total score of ≥ 6, which reflects the concordance rate regarding the classification of EGPA between the 2022 ACR/EULAR criteria and the old criteria for EGPA (Table 2).

Total scores for the application of the 2022 ACR/EULAR criteria for EGPA. The highest total score of 14 was achieved in 2 patients. Among the 51 patients with previously diagnosed EGPA, 7 patients could not be reclassified as having EGPA according to the 2022 ACR/EULAR criteria for EGPA. In total, 3 patients with previously diagnosed EGPA received a total score of 5 points, 3 patients received 4 points, and 1 patient received 3 points (Table 3).

Itemized analysis of patients with previously diagnosed EGPA who failed to be reclassified as having EGPA. All 7 patients who did not meet the 2022 ACR/EULAR criteria for EGPA had obstructive airway disease but no nasal polyps. In total, 3 patients were deducted 1 point because of hematuria, and 2 patients were deducted 3 points because of PR3-ANCA (or C-ANCA) positivity. Because of their negative scores, these items had a critical negative effect on the reclassification of patients B, C, and D as having EGPA; for the remaining patients, the deduction of points was not a factor in the failure to satisfy reclassification. It is noteworthy that an important factor that prevented the reclassification to EGPA was the exclusion of nonfixed pulmonary infiltrates and paranasal sinus abnormality in the 1990 ACR criteria for EGPA (Table 4).

Table 2. Frequencies of each 2022 ACR/EULAR criterion for EGPA fulfilled by patients with previously diagnosed EGPA at the time of the first classification.

2022 ACR/EULAR criteria for EGPA	Score	N = 51
Clinical criteria		
Obstructive airway disease	+3	46 (90.2)
Nasal polyps	+3	8 (15.7)
Mononeuritis multiplex	+1	22 (43.1)
Laboratory, imaging, and biopsy criteria		
Serum eosinophil count ≥ 1000/μL	+5	45 (88.2)
Extravascular eosinophilic-predominant inflammation on biopsy	+2	28 (54.9)
PR3-ANCA (or C-ANCA) positivity	–3	5 (9.8)
Hematuria	–1	17 (33.3)
Total score for 7 items above	–	8.0 (3.0)
Patients with total score ≥ 6	–	44 (86.3)

Data are in n (%) unless otherewise indicated. ACR: American College of Rheumatology; ANCA: antineutrophil cytoplasmic antibody; C: cytoplasmic; EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European Alliance of Associations for Rheumatology; PR3: proteinase 3.

Table 3. Application of the 2022 ACR/EULAR criteria for EGPA to patients with previously diagnosed EGPA.

	Classification Criteria Score															
	0	1	2	3	4	5	6[a]	7	8	9	10	11	12	13	14	Total
Patients, n	0	0	0	1	3	3	4	5	10	7	8	5	1	2	2	51

[a] This is the cut-off of the total score for the classification of MPA based on the 2022 ACR/EULAR criteria for EGPA. ACR: American College of Rheumatology; EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European Alliance of Associations for Rheumatology; MPA: microscopic polyangiitis.

Table 4. Clinical manifestations of patients who were not reclassified as having EGPA based on the 2022 ACR/EULAR criteria for AAV.

Patient	Detailed Descriptions (and Scores) of Patients Who Failed to be Reclassified as EGPA Based on the 2022 ACR/EULAR Criteria for EGPA (decisive clues for previously diagnosed EGPA)	Scores Based on the 2022 ACR/EULAR Criteria for EGPA	Final Classification Based on the 2022 ACR/EULAR Criteria for AAV
A	Obstructive airway disease (+3); extravascular eosinophilic inflammation on biopsy (+2) (asthma, nonfixed pulmonary infiltrates, sinusitis, and extravascular eosinophils on biopsy)	5	Unclassifiable vasculitis
B	Obstructive airway disease (+3); serum eosinophil count ≥ 1000/μL (+5); PR3-ANCA positive (−3) (asthma, peripheral eosinophilia, nonfixed pulmonary infiltrates, and sinusitis)	5	Unclassifiable vasculitis
C	Obstructive airway disease (+3); mononeuritis multiplex (+1); extravascular eosinophilic inflammation on biopsy (+2); hematuria (−1) (asthma, mononeuritis multiplex, nonfixed pulmonary infiltrates, and extravascular eosinophils on biopsy)	5	MPA
D	Obstructive airway disease (+3); serum eosinophil count ≥ 1000/μL (+5); PR3-ANCA positive (−3); hematuria (−1) (asthma, peripheral eosinophilia, nonfixed pulmonary infiltrates, and sinusitis)	4	Unclassifiable vasculitis
E	Obstructive airway disease (+3); mononeuritis multiplex (+1) (asthma, mononeuritis multiplex, nonfixed pulmonary infiltrates, and sinusitis)	4	MPA
F	Obstructive airway disease (+3); mononeuritis multiplex (+1) (asthma, mononeuritis multiplex, nonfixed pulmonary infiltrates, and sinusitis)	4	GPA
G	Obstructive airway disease (+3); mononeuritis multiplex (+1); hematuria (−1) (asthma, mononeuritis multiplex, nonfixed pulmonary infiltrates, and sinusitis)	3	MPA

AAV: antineutrophil cytoplasmic antibody–associated vasculitis; ACR: American College of Rheumatology; ANCA: antineutrophil cytoplasmic antibody; EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European Alliance of Associations for Rheumatology; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; PR3: proteinase 3.

Itemized analysis of applying the 2022 ACR/EULAR criteria for MPA and GPA to patients who failed to be reclassified as having EGPA. We attempted to apply the ACR/EULAR criteria for MPA and GPA to patients who failed to be reclassified as having EGPA, and found that 3 were reclassified as having MPA and 1 was reclassified as having GPA. Based on the 2022 ACR/EULAR criteria for MPA, patients C and E received a total score of 9 because of MPO-ANCA (or P-ANCA) positivity (+6) and pauci-immune glomerulonephritis on biopsy (+3). Patient G obtained a total score of 9 because of MPO-ANCA (or P-ANCA) positivity (+6) and interstitial lung disease (+3). In addition, based on the 2022 ACR/EULAR criteria for GPA, patient F obtained a total score of 7 because of nasal involvement (+3), cartilaginous involvement (ie, subglottic stenosis; +2), pulmonary nodule and cavitation (+2), paranasal sinusitis (+1), and MPO-ANCA (or P-ANCA) positivity (−1). However, the remaining patients did not meet the ACR/EULAR criteria for MPA, GPA, or EGPA, and were finally reclassified as having unclassifiable vasculitis (Supplementary Table S1, available with the online version of this article).

Itemized analysis of patients who were reclassified as having both EGPA and MPA or both EGPA and GPA. Among the 44 patients reclassified as having EGPA, 6 fulfilled the ACR/EULAR criteria for MPA simultaneously. All patients achieved a score of +6 because of MPO-ANCA (or P-ANCA) positivity but received a score of −4 because of peripheral eosinophilia. None of the patients were positive for PR3-ANCA (or C-ANCA). Nevertheless, they could be reclassified as having MPA because of the presence of fibrosis or interstitial lung disease on chest imaging (+3) and/or pauci-immune glomerulonephritis on biopsy (+3). Meanwhile, 1 patient who was reclassified as having EGPA met the ACR/EULAR criteria for GPA simultaneously. The patient received positive scores for nasal involvement (+3), conductive or sensorineural hearing loss (+1), PR3-ANCA (or C-ANCA) positivity (+5), and paranasal sinusitis (+1), but they received negative scores for MPO-ANCA (or P-ANCA) positivity (−1) and peripheral eosinophilia (−4). Finally, the patient obtained a total score of 6, which is the cut-off value (Supplementary Table S2, available with the online version of this article).

DISCUSSION

This study investigated the number of patients who could be reclassified as having EGPA by the 2022 ACR/EULAR criteria among Korean patients with previously diagnosed EGPA according to the 1990 ACR criteria, 2007 EMA algorithm, and 2012 CHCC definitions. Our findings include the following. First, 44 out of 51 (86.3%) patients were reclassified as having EGPA, and 7 patients could not be reclassified as having EGPA based on the 2022 ACR/EULAR criteria for EGPA. Second, PR3-ANCA (or C-ANCA) positivity and hematuria, to which negative scores were assigned, had a critical negative effect on the reclassification. Further, an important factor in the failure to reclassify patients as having EGPA was the exclusion of nonfixed pulmonary infiltrates and paranasal sinus abnormality in the 1990 ACR criteria for EGPA. Third, when the ACR/EULAR criteria for MPA and GPA were applied to patients who were not reclassified as having EGPA, 3 patients were reclassified as having MPA and 1 was reclassified as having GPA. The remaining patients did not meet the 2022 ACR/EULAR criteria for MPA, GPA, or EGPA, and were finally reclassified as having unclassifiable vasculitis. Fourth, among the 44 patients who were reclassified as having EGPA, 6 patients were also reclassified as having MPA. In addition, 1 patient with EGPA also met the ACR/EULAR criteria for GPA.

The biggest difference between the 1990 ACR criteria and the 2022 ACR/EULAR criteria for EGPA is that 2 items—nonfixed pulmonary infiltrates and paranasal sinus abnormality—were deleted (Supplementary Table S3, available with the online version of this article). Paranasal sinus abnormality is currently included only in the 2022 ACR/EULAR criteria for GPA. Since the 2007 EMA algorithm also indicated that chronic sinusitis is a GPA surrogate marker, and a considerable number of patients with asthma have allergic rhinitis and paranasal sinusitis, paranasal sinus abnormality may not be a sufficiently specific symptom to suggest EGPA.[7,18] However, nonfixed pulmonary infiltrates could be a predictive marker for EGPA because they are rarely observed in patients with MPA and GPA. In the 1990 ACR criteria for EGPA, the sensitivity of nonfixed pulmonary infiltrates was only 40.0%, but the specificity was as high as 92.4%.[6] Moreover, in the 2022 ACR/EULAR criteria for EGPA, the entry requirement specifies that the criteria should be applied after excluding infectious pulmonary infiltrates mimicking AAV.[10] For these reasons, we would like to argue that migratory and rapidly changing pulmonary infiltrates indicate the eosinophilic phase of EGPA.[19]

The 2022 ACR/EULAR classification criteria are designed to identify homogenous patients for inclusion in clinical studies; therefore, excluding ambiguous items from the classification might be appropriate because it is difficult to define nonfixed pulmonary infiltrates. Since the patients included in this study were diagnosed with EGPA through a clinical practice and not for clinical trial purposes, the diagnosis criteria may differ from the classification criteria for identifying homogenous patients. In this study, all 7 patients who could not be reclassified as having EGPA based on the 2022 ACR/EULAR criteria clearly exhibited nonfixed and rapidly migratory pulmonary infiltrates at the first classification. All of these patients had asthma, and all but 1 had peripheral eosinophilia or mononeuritis multiplex, ensuring that the initial diagnosis was correct. The sensitivity of the 2022 ACR/EULAR criteria for EGPA was 84.9%, which was lower than that of the 2022 ACR/EULAR criteria for GPA or MPA. We believe that excluding the nonfixed pulmonary infiltrates item is a factor that lowers the sensitivity. Although the purpose of the classification criteria is to identify homogenous patients for clinical studies, EGPA is a rare disease and it is important to register as many patients as possible. Therefore, we suggest that the addition of nonfixed and rapidly migratory pulmonary infiltrates to the 2022 ACR/EULAR criteria for EGPA should be reconsidered carefully.

Since the 2007 EMA algorithm applied the criteria to patients in the order of EGPA, GPA, MPA, polyarteritis nodosa, and unclassifiable vasculitis, there have been no cases of classification into 2 AAV subtypes.[7] However, if the 2022 ACR criteria for AAV are applied to patients simultaneously, several cases can be classified into 2 AAV subtypes, as seen in the results of this study. Hence, it is questionable as to which subtype should be focused on for managing patients who are classified as having MPA or GPA along with EGPA. This is because the treatment strategy for EGPA is different from that for MPA or GPA.[8,20,21] Therefore, we believe that the principle as to the order of applying the 2022 ACR/EULAR criteria for AAV and initiating the treatment strategy should be established. Here, we provide the following 3 clinical examples. First, the classification order may be determined in a top-down format in the same order as in the 2007 EMA algorithm.[7] Second, because the treatment strategy for MPA and GPA is stronger than that for EGPA, the treatment order may be determined from MPA and GPA to EGPA.[20] Third, among patients classified as having both EGPA and active severe MPA or GPA, the treatment strategy for active severe MPA and GPA should be considered first. However, among patients classified as having both EGPA and active nonsevere MPA or GPA simultaneously, the treatment strategy for active nonsevere EGPA, which includes mepolizumab, may be considered in addition to that for active nonsevere MPA and GPA.[8,20] It is important to quickly establish a common opinion among experts regarding this topic.

In addition, for research purposes, when it is important to recruit homogenous patients and increase the specificity, we suggest that excluding patients who meet more than 1 criterion may be appropriate. In our study population, 6 patients met the criteria for both EGPA and MPA and 1 patient met the criteria for both EGPA and GPA, based on the 2022 ACR/EULAR criteria for AAV. Of the 6 patients who met the criteria for both EGPA and MPA, 5 patients were positive for MPO-ANCA and their kidney biopsies showed pauci-immune glomerulonephritis, suggesting the possibility of MPA. However, all these patients also had asthma and peripheral eosinophilia, which is specific for EGPA. Similarly, the patient who met the criteria for both EGPA and GPA showed nasal involvement as well as hearing loss and was PR3-ANCA positive, suggesting the possibility of GPA. However, this patient also had asthma, nasal polyps, and peripheral eosinophilia, which is a specific finding for EGPA.

Therefore, either diagnosis is considered reasonable in clinical practice. However, for research purposes, these patients constitute a factor in reducing the specificity. A consensus of additional expert opinions should be reached.

This study had a number of strengths. The merit of this study was that it applied the 2022 ACR/EULAR criteria for AAV to patients with previously diagnosed EGPA and that it investigated the concordance rate between the 2022 ACR/EULAR criteria and the old criteria in a well-structured cohort. In addition, we identified patients with unclassifiable vasculitis and those with 2 subtypes of AAV, and we suggested strategies for AAV classification and treatment.

This study also had several limitations. Although there were few interobserver variations and selection biases, the number of patients with EGPA was small because this was a single-center, prospective, observational cohort study, and validation in a separate group could not be done. Further, since there was no separate control group in this study and patients with EGPA who did not meet the 1990 ACR criteria were not included, the sensitivity and specificity of the 2022 ACR/EULAR criteria could not be analyzed. A retrospective study design may also reduce the reliability of the results of the present study. However, since all of the patients were first classified as having EGPA in the same hospital by the same 3 rheumatologists, it is believed that the clinical, laboratory, radiologic, and histopathologic data used in applying the 2022 ACR/EULAR criteria for MPA, GPA, and EGPA could be reliable. Last, the follow-up period of patients who were reclassified as having unclassifiable vasculitis was not long enough to confirm that they could be differentiated into AAV subtypes. A future prospective study with a larger number of patients and a longer follow-up period will overcome these limitations and provide sequential and more reliable information on the reclassification and alteration of AAV subtypes.

In conclusion, among the 51 patients previously diagnosed with EGPA, 86.3% were reclassified as having EGPA based on the 2022 ACR/EULAR criteria for EGPA. Although 5.9% and 2.0% of patients were reclassified as having MPA and GPA, respectively, 5.9% of them were reclassified as having unclassifiable vasculitis. Moreover, 11.8% of the patients were reclassified as having both EGPA and MPA simultaneously, and 2% were classified as having EGPA and GPA simultaneously. We suggest that nonfixed pulmonary infiltrates be reconsidered in cases reclassified as unclassifiable vasculitis, and we further highlight the need for diagnostic and therapeutic strategies for patients with 2 AAV subtypes.

DATA AVAILABILITY

The authors will provide raw data upon request to the corresponding author.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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