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Clinical characteristics of patients with vasculitis positive for anti-neutrophil cytoplasmic antibody targeting both proteinase 3 and myeloperoxidase: a retrospective study

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA) may target proteinase 3 (PR3) or myeloperoxidase (MPO). Although a few patients with vasculitis have both MPO- and PR3-ANCA, the details of their clinical characteristics are not known. The objective of this study was to analyze the characteristics of patients with dual MPO- and PR3-ANCA-positive vasculitis. The medical records of patients with ANCA and vasculitis confirmed by biopsy were reviewed. The age at diagnosis, sex, and data on organ involvement of the kidney, lung, upper airways, skin, nervous system, and gastrointestinal tract were collected. Clinical variables were analyzed according to ANCA specificity. Of 85 patients with ANCA and vasculitis included in this study, 67 (78.8%) had MPO-ANCA, 10 (11.8%) had PR3-ANCA, and 8 (9.4%) had both MPO- and PR3-ANCA. Patients with MPO− PR3 + ANCA-associated vasculitis (AAV) were younger at diagnosis (median, 54.4 years; $p < 0.05$) than patients with MPO + PR3− AAV (67.0 years) or dual-ANCA AAV (MPO + PR3 +, 68.5 years). The initial glomerular filtration rate in patients with MPO + PR3− AAV (22.0 ml/min) was significantly lower than that in patients with MPO− PR3 + AAV (108.6 ml/min, $p < 0.05$), but was not different from that in dual-ANCA AAV patients (16.5 ml/min). Upper airway involvement also differed with ANCA type (MPO+ PR3−, 35.8% vs. MPO− PR3 +, 70.0% vs. MPO + PR3+, 75.0%, $p < 0.05$). The involvement of other organs did not differ according to ANCA type. Age at diagnosis, kidney involvement, and upper airway involvement were associated with ANCA type. Patients with dual-ANCA-positive vasculitis had considerably more kidney dysfunction than patients with MPO− PR3+ AAV. They also had more upper airway involvement than patients with MPO+ PR3− AAV.

Keywords Antibodies, antineutrophil cytoplasmic · Systemic vasculitis · Anti-neutrophil cytoplasmic antibody-associated vasculitis · Microscopic polyangiitis · Granulomatosis with polyangiitis

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are a group of clinical conditions in which inflammatory cell infiltration to small-to-medium blood vessels causes tissue necrosis. AAVs include three different syndromes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. GPA differs from MPA by the presence of necrotizing granulomatous inflammation. EGPA represents about 10–20% of patients with AAVs [2, 3]. It is treated as a separate entity by the latest published guidelines and has been in most clinical trials, as well [4].

Most patients with AAV have ANCAs against proteins present in the cytoplasmic granules of neutrophils. Their main antigenic targets were myeloperoxidase (MPO) and proteinase 3 (PR3) that were discovered almost 3 decades ago [5–7]. ANCA type according to target has been closely linked to clinical manifestations and treatment responses [8]. However, ANCA specificity does not correspond well with the clinical diagnosis of MPA or GPA. PR3-ANCAs are found in about two-thirds of patients with GPA and

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one-quarter of patients with MPA. Moreover, MPO-ANCAs are present in the majority of patients with MPA. They are also found in some patients with GPA defined by the 1994 Chapel Hill Consensus Conference (CHCC) [9]. Certain patients diagnosed with GPA or MPA can be negative for both types of ANCAs [10]. Furthermore, there have been several reports of dual-ANCA positivity (i.e., positive for both MPO- and PR3-ANCA) in AAV [9, 11–13].

However, in spite of the important role of ANCA type in their disease manifestation, there has been no detailed study on patients of AAV with dual-ANCA positivity. Therefore, the objective of this study was to investigate the clinical characteristics of patients with dual-ANCA positivity and analyzed the association between ANCA positivity and clinical manifestations.

Materials and methods

Patients

The patients with ANCA-associated systemic vasculitides, diagnosed from 1997 to 2016 in the Chungnam National University Hospital and Chungbuk National University Hospital, were searched using ICD codes as follows: M301(Churg–Strauss syndrome, eosinophilic granulomatosis with polyangiitis), M313 (Wegener's granulomatosis, granulomatosis with polyangiitis), M317 (microscopic polyangiitis), and N085 (glomerular disorders in systemic connective tissue disorders). Only patients with vasculitis confirmed by biopsy were included. Clinical diagnoses were reviewed using the CHCC definitions [1]. Patients were classified as having EGPA if they had systemic vasculitis with necrotizing granulomatous inflammation and extravascular eosinophils in a biopsy specimen, that associated with asthma and eosinophilia in the peripheral blood. Patients were classified as having GPA if they had systemic necrotizing vasculitis with granulomatous inflammation in a biopsy specimen or clinical involvement of the upper respiratory tract with purulent/bloody nasal discharge, sinusitis, or otitis media, or involvement of lower respiratory tract with nodules, cavitary lesions, or infiltrates, which are strongly suggestive of granulomatous disease. Patients were classified as having MPA if they had systemic vasculitis without granuloma in a biopsy specimen and the absence of clinical signs suggestive of GPA.

Data collection

From medical records of patients, age at diagnosis, sex, and the involvement of kidney, lung, upper airway (nose/sinus/ear), skin, peripheral nervous system, central nervous system, and gastrointestinal tract were collected. Clinical manifestations of upper respiratory tract involvement included bloody nasal discharge, sinusitis, subglottic stenosis, otomastoiditis, or hearing loss. Skin manifestations included palpable purpura, ulcers, or rashes confirmed by biopsy. Eye manifestations were retinal vasculitis, uveitis, episcleritis, scleritis, conjunctivitis, or orbital mass. Central nervous system involvement included hemorrhage, infarct or brain lesions confirmed by computed tomography or magnetic resonance imaging. Peripheral nervous system involvement included peripheral nerve abnormalities confirmed by nerve conduction studies. Cardiac dysfunction associated with vasculitis or gastrointestinal lesion confirmed by biopsy was also included. The following laboratory values were collected: PR3-ANCA, MPO-ANCA, initial creatinine, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Only results of PR3-ANCA and MPO-ANCA measured by enzyme-linked immunosorbent assay were included. Remission was defined as a score of zero using Birmingham Vasculitis Activity Score version 3.0 while receiving corticosteroid therapy or immunosuppressive therapy [14]. This study was approved by the Institutional Review Board of each medical center and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, Illinois, USA). For categorical variables, the significance of differences across the groups was analyzed by the χ^2 test or Fisher's exact test. Continuous variables are expressed as mean ± standard deviation or median [range] and were analyzed using the Kruskal–Wallis test and Mann–Whitney test. The p value of < 0.05 was considered to indicate statistical significance.

Results

Patient characteristics

A total of 85 patients with AAV were included in this study. Their baseline characteristics are summarized in Table 1 according to clinical diagnosis. Among these 85 patients, 26 had GPA, 54 had MPA, and 5 had EGPA. Their mean (± SD) age was 52.1 (± 14.9) years. Diagnosis of clinical syndromes was related to ANCA type. All the patients with MPA were MPO-ANCA positive and a few of them were also PR3-ANCA positive. However, the patients with GPA were positive for either PR3-ANCA or MPO-ANCA. EGPA patients were exclusively MPO-ANCA positive. The majority of patients with MPA were diagnosed by renal biopsy (88.9%), whereas most GPA patients were diagnosed by renal (42.3%) or upper airway biopsy (42.3%).

Table 1 Baseline characteristics of the patients

Characteristics	GPA ($n=26$)	MPA ($n=54$)	EGPA ($n=5$)	p[a]
Male, *n* (%)	15 (58%)	22 (41%)	2 (40%)	0.364
Age, median [range]	60.0 [23–81]	67.5 [25–86]	70.0 [66–73]	0.043[b,c]
MPO-ANCA positive, *n* (%)	16 (61.5%)	54 (100.0%)	5 (100.0%)	< 0.001
PR3-ANCA positive, *n* (%)	12 (46.2%)	6 (11.1%)	0	0.002
Hematuria, *n* (%)	17 (65.4%)	52 (96.3%)	4 (80.0%)	0.001
Proteinuria, *n* (%)	12 (46.2%)	49 (90.7%)	1 (20.0%)	< 0.001
Initial serum Cr, mg/dL, median [range]	0.93 [0.48–11.38]	3.79 [0.51–16.50]	0.71 [0.60–2.01]	< 0.001[b,c,d]
Initial GFR, ml/min/1.73 m^2 median [range]	81.5 [5.6–180.0]	15.8 [2.3–125.2]	104 [26.3–119.0]	< 0.001[b,c,d]
Hemodialysis ever, *n* (%)	3 (11.5%)	31 (57.4%)	0	< 0.001
Lung involvement, *n* (%)	18 (69.2%)	30 (55.6%)	4 (80.0%)	0.392
Mass/nodule, *n* (%)	13 (50.0%)	10 (18.5%)	1 (20.0%)	0.011
Hemorrhage, *n* (%)	2 (7.7%)	12 (22.2%)	1 (20.0%)	0.195
ILD/fibrosis, *n* (%)	8 (30.8%)	14 (25.9%)	2 (40.0%)	0.723
Infiltrate, *n* (%)	1 (3.8%)	2 (3.7%)	0	1.000
Endobronchial, *n* (%)	0	0	1 (20.0%)	0.059
Pleural effusion, *n* (%)	2 (40.0%)	3 (5.6%)	0	0.749
Upper airway involvement, *n* (%)	21 (80.8%)	13 (24.1%)	3 (60.0%)	< 0.001
Skin involvement, *n* (%)	5 (19.2%)	8 (14.8%)	2 (40.0%)	0.339
Neurologic involvement, *n* (%)	11 (42.3%)	13 (24.1%)	3 (60.0%)	0.097
CNS, *n* (%)	5 (19.2%)	5 (9.3%)	1 (20.0%)	0.311
PNS, *n* (%)	7 (26.9%)	11 (20.4%)	2 (40.0%)	0.440
Eye involvement, *n* (%)	6 (23.1%)	3 (5.6%)	0	0.070
Retina vasculitis, *n* (%)	0	1 (1.9%)	0	1.000
Uveitis, *n* (%)	2 (7.7%)	1 (1.9%)	0	0.372
Scleritis, *n* (%)	5 (19.2%)	1 (1.9%)	0	0.022
Conjunctivitis, *n* (%)	1 (3.8%)	0	0	0.365
Orbital mass, *n* (%)	2 (7.7%)	0	0	0.206
Heart involvement, *n* (%)	0	13 (24.1%)	0	0.009
GI involvement, *n* (%)	2 (7.7%)	4 (7.4%)	0	1.000

GPA granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *MPO* myeloperoxidase, *ANCA* anti-neutrophil cytoplasmic antibody, *PR3* proteinase 3, *Cr* creatinine, *GFR* glomerular filtration rate, *ILD* interstitial lung disease, *CNS* central nervous system, *PNS* peripheral nervous system, *GI* gastrointestinal

[a]All p values were calculated by the χ^2 test or Fisher's exact test for comparison of the three groups except age, initial serum Cr, and initial GFR

[b]By Kruskal–Wallis test for comparison of the three groups

[c]GPA vs. MPA, $p<0.05$ by post hoc Mann–Whitney U tests

[d]MPA vs. EGPA, $p<0.05$ by post hoc Mann–Whitney U tests

Clinical manifestations of patients with dual-ANCA positivity

The characteristics of the study patients according to ANCA specificity are shown in Table 2. Among 85 patients with AAV, only 8 (9.4%) patients had both MPO and PR3 ANCA. Five patients were males. Clinical diagnoses were MPA in 6 patients and GPA in 2 patients. All patients with dual-ANCA (MPO+ PR3+) had kidney involvement. The initial serum creatinine levels and glomerular filtration rates were different between the ANCA groups (both $p<0.05$ by Kruskal–Wallis test). The initial serum creatinine level was higher in patients with only MPO-ANCA (MPO+ PR3−, 2.47 [0.51, 16.50] mg/dl) and those with dual ANCA (4.29 [0.66, 13.50] mg/dl) than in patients with only PR3-ANCA (MPO− PR3+, 0.74 [0.48, 1.71] mg/dl, both $p<0.05$ by post hoc Mann–Whitney test). The initial glomerular filtration rate in patients with MPO+ PR3− AAV (22.0 [2.3, 125.2] ml/min) was lower than that in patients with MPO− PR3+ AAV (108.6 [42.7, 180.0] ml/min, $p<0.001$ by post hoc Mann–Whitney test), but was not significantly different from that in patients with dual ANCA (16.5 [3.4,

Table 2 Clinical manifestations according to ANCA positivity

Characteristics	MPO + PR3− ($n=67$)	MPO − PR3+ ($n=10$)	MPO + PR3+ ($n=8$)	p[a]
Male, *n* (%)	29 (43.3%)	5 (50.0%)	5 (62.5%)	0.545
Age, median [range]	67.0 [25, 86]	54.4 [23, 67]	68.5 [47, 76]	0.001[b,c]
Clinical diagnosis				< 0.001
GPA, *n* (%)	14 (20.9%)	10 (100.0%)	2 (25.0%)	
MPA, *n* (%)	48 (71.6%)	0	6 (75.0%)	
EGPA, *n* (%)	5 (7.5%)	0	0	
Hematuria, *n* (%)	60 (89.6%)	5 (50.0%)	8 (100.0%)	0.007
Proteinuria, *n* (%)	52 (77.6%)	2 (20.0%)	8 (100.0%)	<0.001
Initial serum Cr, mg/dL, median [range]	2.47 [0.51, 16.50]	0.74 [0.48, 1.71]	4.29 [0.66, 13.50]	0.001[b,c]
Initial GFR, ml/min/1.73 m^2, median [range]	22.0 [2.3, 125.2]	108.6 [42.7, 180.6]	16.5 [3.4, 129.0]	< 0.001[b,c]
Hemodialysis ever, *n* (%)	28 (41.8%)	1 (10.0%)	5 (62.5%)	0.051
Kidney involvement by biopsy, *n* (%)	50 (74.6%)	2 (20.0%)	8 (100.0%)	< 0.001
Lung involvement, *n* (%)	40 (59.7%)	6 (60.0%)	6 (75.0%)	0.791
Mass/nodule, *n* (%)	18 (26.9%)	5 (50.0%)	1 (12.5%)	0.231
Hemorrhage, *n* (%)	13 (19.4%)	1 (10.0%)	1 (12.5%)	0.880
ILD/fibrosis, *n* (%)	17 (25.4%)	3 (30.0%)	4 (50.0%)	0.314
Infiltrate, *n* (%)	3 (4.5%)	0	0	1.000
Endobronchial, *n* (%)	1 (1.5%)	0	0	1.000
Pleural effusion, *n* (%)	3 (4.5%)	1 (10.0%)	1 (12.5%)	0.285
Upper airway involvement, *n* (%)	24 (35.8%)	7 (70.0%)	6 (75.0%)	0.021[d]
Skin involvement, *n* (%)	12 (17.9%)	3 (30.0%)	0	0.307
Neurologic involvement, *n* (%)	20 (29.9%)	2 (20.0%)	5 (62.5%)	0.160.
CNS, *n* (%)	8 (11.9%)	0	3 (37.5%)	0.078
PNS, *n* (%)	16 (23.9%)	2 (20.0%)	2 (25.0%)	1.000
Eye involvement, *n* (%)	5 (7.5%)	3 (30.0%)	1 (12.5%)	0.074
Retinal vasculitis, *n* (%)	1 (1.5%)	0	0	1.000
Uveitis, *n* (%)	2 (3.0%)	1 (10.0%)	0	0.515
Scleritis, *n* (%)	3 (4.5%)	2 (20.0%)	1 (12.5%)	0.106
Conjunctivitis, *n* (%)	0	1 (10.0%)	0	0.212
Orbital mass, *n* (%)	1 (1.5%)	1 (10.0%)	0	0.381
Heart involvement, *n* (%)	11 (16.4%)	0	2 (25.0%)	0.293
GI involvement, *n* (%)	5 (7.5%)	1 (10.0%)	0	0.772
Remission at 12 week, *n* (%)	38 (56.7%)	6 (60.0%)	3 (37.5%)	0.338
Death at 12 week, *n* (%)	4 (6.0%)	0	1 (12.5%)	0.472
Remission at 1 year, *n* (%)	41 (61.2%)	8 (80.0%)	4 (50.0%)	0.682
Death at 1 year, *n* (%)	8 (11.9%)	0	2 (25.0%)	0.236

ANCA anti-neutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *PR3* proteinase 3, *GPA* granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *Cr* creatinine, *GFR* glomerular filtration rate, *ILD* interstitial lung disease, *CNS* central nervous system, *PNS* peripheral nervous system, *GI* gastrointestinal

[a]All p values were calculated by χ^2 test or Fisher's exact test for comparison of the three groups except age, initial serum Cr, and initial GFR

[b]By Kruskal–Wallis test for comparison of three groups

[c]MPO + PR3− vs. MPO-PR3+, $p<0.05$ by post hoc Mann–Whitney U tests

[d]MPO + PR3 − vs. MPO + PR3 +, $p<0.05$ by post hoc one-sided Fisher's exact test

129.0] ml/min, $p=0.354$ by post hoc Mann–Whitney test). The initial glomerular filtration rate in patients with dual-ANCA (MPO+ PR3+) AAV was also significantly lower than that in patients with MPO− PR3+ AAV ($p=0.004$ by post hoc Mann–Whitney test). Upper airway involvement differed according to ANCA specificity (MPO + PR3−, 35.8% vs. MPO− PR3 +, 70.0% vs. dual ANCA, 75%; p = 0.021 by Fisher's exact test). Upper airway lesions were

present in a higher proportion of patients with dual ANCA than in those with MPO + PR3 − AAV ($p = 0.045$, by one-sided Fisher' exact test). Lung, skin, nervous system, and eye involvement did not differ among patients with dual- or single-ANCA positivity.

MPO-ANCA-positive versus MPO-ANCA-negative vasculitis patients

Patients with MPO-ANCA ($n = 75$, 67.0 [25–86] years) were associated with older age at diagnosis than patients without MPO-ANCA ($n = 10$, 54.5 [23–67] years, $p < 0.001$ by Mann–Whitney test). The initial serum creatinine level in patients with MPO-ANCA (2.49 [0.51–16.50] mg/dl) was higher than that in patients without MPO-ANCA (0.74 [0.48–1.71] mg/dl, $p < 0.001$ by Mann–Whitney test). The initial GFR also was lower in patients with MPO-ANCA (22.0 [2.3–129.0] ml/min) than in patients without MPO-ANCA (108.6 [42.7–180.0] ml/min, $p < 0.001$ by Mann–Whitney test). Among the MPO-ANCA-positive patients, the proportion of those having hematuria (90.7%) or proteinuria (80.0%) and those who had ever started hemodialysis (44.0%) was significantly higher than that in MPO-ANCA-negative patients (hematuria, 50.0%, $p = 0.004$; proteinuria, 20.0%, $p < 0.001$; hemodialysis ever, 10%, $p = 0.045$). The proportion of lung, upper airway, skin, nervous system, eye, heart, or gastrointestinal tract involvement did not differ between MPO-ANCA-positive and MPO-ANCA-negative patients. There were five deaths at 12 weeks, five (6.7%) among patients with MPO-ANCA and none among the patients without MPO-ANCA. There were 10 deaths at 1 year, 10 (13.3%) among the patients with MPO-ANCA and none among the patients without MPO-ANCA. The number of deaths at 12 weeks and at 1 year was not different between the MPO-ANCA-positive and MPO-ANCA-negative patients.

PR3-ANCA-positive versus PR3-ANCA-negative vasculitis patients

Clinical diagnosis of GPA was predominant in patients with PR3-ANCA (66.7%). Regarding the relationship between PR3-ANCA and clinical manifestations, PR3 positivity was associated with younger age at diagnosis (59.5 [23–76] years, with PR3-ANCA vs. 67.0 [25–86] years, without PR3-ANCA, $p = 0.010$ by Mann–Whitney test). The initial serum creatinine levels were lower in PR3-ANCA-positive patients (0.89 [0.48–13.5] mg/dl) than that in PR3-ANCA-negative patients (2.47 [0.51–16.50] mg/dl, $p = 0.048$ by Mann–Whitney test). The initial glomerular filtration rate were higher in PR3-ANCA-positive patients (81.0 [3.4–180.0] ml/min) that in PR3-ANCA-negative patients (22 [2.3-125.2] ml/min, $p = 0.025$ by Mann–Whitney test) whereas the presence of fever, hematuria, or proteinuria did not differ between the two groups. Upper airway involvement was present in a higher proportion in the PR3-ANCA-positive patients ($n = 13$, 72.2%) than in the PR3-ANCA-negative patients ($n = 24$, 35.8%, $p = 0.008$). Other clinical manifestations including skin, lung, neurologic, and eye involvement did not differ between PR3 ANCA-positive and -negative groups. The number of deaths at 12 weeks (with PR3-ANCA, $n = 1$, 5.6% vs. without PR3-ANCA, $n = 4$, 6.0%) and at 1 year (with PR3-ANCA, $n = 2$, 11.1% vs. without PR3-ANCA, $n = 8$, 11.9%) were similar between patients with and without PR3-ANCA.

Discussion

Patients with dual-ANCA-positive (MPO+ PR3+) AAV had proportions of kidney involvement similar to patients with MPO+ PR3− AAV, which was much higher than patients with MPO− PR3+ AAV. They also showed more upper airway involvement than those with MPO+ PR3− AAV, whose upper airway involvement seemed to be similar to that of patients with MPO− PR3+ AAV. Therefore, the clinical manifestations of AAV might be linked to the specific ANCA type. In this study, dual-ANCA-positive AAV appeared to have combined features of MPO+ PR3− AAV and MPO− PR3+ AAV.

Although dual-ANCA-positive AAV is not common, several studies have reported that some proportion of patients with AAV have both PR3- and MPO-ANCA. Hagen et al. reported that 10 of 459 patients with AAV were positive for both MPO- and PR3-ANCAs [9]. Franssen et al. found that 4 patients had dual-ANCA positivity among 110 vasculitis or nephritis patients [11]. In the report from the Diagnostic and Classification Criteria in Vasculitis (DCVAS) study, 9 patients had dual-PR3- and MPO-ANCA positivity among 1217 AAV patients. However, there was no clinical description of them [12]. Regarding the conditions associated with ANCA positivity, one retrospective study identified 15 dual-ANCA-positive persons. Among them, three had vasculitis whereas the others had autoimmune diseases, infections, or malignancies [13]. Several case reports of dual-ANCA positivity have been published on patients with AAV or other diseases including lupus nephritis [15], mixed connective tissue disease [16], drug-induced interstitial nephritis [17], Henoch–Schönlein purpura [18], and subacute bacterial endocarditis [19]. Considering all these reports, it appears that MPO-ANCA and PR3-ANCA positivity are not to be mutually exclusive and that dual-ANCA positivity can occur in a variety of diagnoses. However, our study selected only patients with biopsy-proven vasculitis. Thus, ANCA positivity might be attributed to vasculitis in the patients included in this study.

Comparison of ANCA positivity and clinical manifestations revealed that age at diagnosis and proportion of kidney involvement were significantly higher in patients with MPO-ANCA than that in patients without MPO-ANCA. Upper airway involvement in patients with PR3-ANCA was also higher than that in patients without PR3-ANCA. These results are compatible with those of previous studies showing that ANCA type was associated with clinical manifestations. MPO-ANCA was related to renal involvement [20, 21], lung fibrosis [22, 23], and peripheral neuropathy [24]. In this study, no difference in lung involvement or peripheral neuropathy was detected between the MPO-ANCA-positive and MPO-ANCA-negative groups. A previous study reported that lung involvement might not differ according to ANCA type [25]. Since peripheral nervous system involvement was rare, the negative finding might be due to a small number of patients with the involvement and the retrospective nature of this study. Thus, taking into account the potential role of ANCA types in clinical presentation, consideration of the ANCA type along with the clinical diagnosis is crucial to patients' care.

The reason why the ANCA type is linked to specific manifestations was not clearly identified. However, ANCAs play an important role in the pathogenesis of AAV. They can activate human neutrophils in vitro [26]. The transfer of anti-MPO antibody to murine models was shown to provoke microscopic polyangiitis-like pathology [27]. MPO-ANCA and PR3-ANCA have different biologic characteristics. Immune response to Staphylococcal antigen can explain the upper airway predilection in GPA or PR3-ANCA AAV [28]. The expression of PR3 antigen in lung or renal tissue may be associated with the involvement of these organs [29, 30]. Anti-MPO response to renal tissue can explain renal predilection [31]. Since ANCAs per se are closely connected to organ involvement in AAV pathogenesis, their effects should be reflected in clinical syndromes.

Clinical syndromes are in discordance with ANCA specificity and GPA can have either MPO-ANCA or PR3-ANCA [9]. Although whether MPO-ANCA-positive GPA has different characteristics from those of PR3-ANCA-positive GPA is controversial [32], several articles on the differences between MPO-ANCA-positive GPA and PR3-ANCA-positive GPA have been published [33–35]. Thus, whether GPA and MPA represent distinct diseases or a spectrum remains a matter of debate. Although epidemiological data suggest that considering GPA and MPA as a single entity for clinical studies and trials is questionable [36], the spectrum concept has justified the enrollment of patients with GPA and MPA in the same clinical trials [37, 38]. In addition, the current classification systems are not interchangeable and should be used cautiously because the same patient can be classified differently by different systems [36, 39]. Adding ANCA specificity to the classification of AAV can modify the diagnostic performance [40]. The presence of dual-ANCA-positive AAV patients in this study emphasizes the importance of ANCA and supports the spectrum concept of clinical diagnosis rather than a distinct disease entity. Moreover, tailored therapy according to ANCA specificity was suggested [41] because the response to rituximab treatment is related to PR3-ANCA positivity rather than to GPA diagnosis [24, 42]. In light of the evidence for the relationship between ANCA and many aspects of AAV, ANCA should be a critical component in the management of AAV.

This study had certain limitations. It was a retrospective study. Thus, retrospective data retrieval could influence the results. In addition, long-term follow-up data could not be obtained to determine the long-term prognosis of the patients. Moreover, the clinical diagnoses were made by several doctors based on different schemes, although we reviewed the clinical diagnoses.

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Author contributions SMK designed the study, analyzed data and wrote the initial draft of the manuscript. SYC contributed to data analysis and data interpretation of data, and preparation of the manuscript. SYK contributed to data collection and data interpretation, and critical review of the manuscript. JK designed the study, analyzed data, and wrote the initial draft of the manuscript. All the authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interests.

Ethical approval This study was approved by Chungnam National University Hospital Institutional Review Board (2017-1-31/2017-01-023) and Chungbuk National University Hospital Institutional Review Board (2019-4-25/CBNUH 2017-04-001) and informed consent was waived by each ethics committees. This study was conducted in accordance with the Declaration of Helsinki.

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