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Should nasal biopsy inevitably be performed for classifying granulomatosis with polyangiitis in patients with rhinosinusitis? A retrospective chart review study

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Abstract

Nasal biopsy is the essential method for differentiating and diagnosing granulomatosis with polyangiitis (GPA) in patients with chronic rhinosinusitis. Nevertheless, in the real clinical settings, there are several cases unable for nasal biopsy. Hence, in this study, we investigated initial clinical manifestations and laboratory factors which could be helpful for diagnosing GPA in cases unable for nasal biopsy performance. We retrospectively reviewed the medical records of 45 patients with GPA. Twenty-five patients exhibited chronic rhinosinusitis, among which 16 patients underwent nasal biopsy. We applied the 2007 European Medicines Agency algorithm for the classification of GPA, the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis and the 2017 American College of Rheumatology/European League Against Rheumatism provisional classification criteria for GPA to them for reclassifying GPA. Among six patients without granuloma on nasal biopsy, three patients with only antineutrophil cytoplasmic antibody (ANCA) and chronic rhinosinusitis could be classified as GPA due to proteinase 3 (PR3)-ANCA (or cytoplasmic (C)-ANCA) positivity. Among nine patients without nasal biopsy, three patients with only chronic rhinosinusitis could be classified as GPA due to GPA-specific lung lesions. When we excluded an item of granuloma in ten GPA patients with granuloma on nasal biopsy, four patients without ANCAs could be classified as GPA due to GPA-specific lung lesions and cartilaginous involvement. In conclusion, PR3-ANCA (or C-ANCA) positivity, GPA-specific lung lesions and cartilaginous involvement could help physicians in charge make a final diagnosis of GPA in cases unable for nasal biopsy.

Keywords Granulomatosis with polyangiitis · Nasal biopsy · PR3-ANCA · Lung · Cartilage

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) consists of three subtypes including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. The prevalence and the annual incidence of GPA are 20–150 cases and 5–10 cases per million people, respectively [2, 3]. GPA mainly affects the upper and lower respiratory tracts, leading to histologically necrotising granulomatous inflammation. GPA-specific lung parenchymal involvement includes fixed, nodular and cavitary lesions [1, 2, 4]. In addition, ear nose throat (ENT) involvement occurs as an initial manifestation in 63–72% of GPA patients and includes conductive or sensorineural hearing loss, nasal bloody discharge, crusts, ulcerations and granuloma, sinus involvement, swollen salivary gland and subglottic

inflammation [5–8]. Among ENT symptoms, chronic rhinosinusitis is the most frequent manifestation and occasionally requires surgery [2]. However, since various conditions could cause chronic rhinosinusitis even in patients suspected of GPA [9–11], nasal biopsy is the essential method for differentiating and diagnosing GPA in patients with chronic rhinosinusitis [12, 13]. Nevertheless, in the real clinical settings, there are several cases unable for nasal biopsy such as poor general medical condition and strong refusal. Hence, in this study, we investigated initial clinical manifestations and laboratory factors which could be helpful for diagnosing GPA in cases unable for nasal biopsy performance.

Methods

Patients

We retrospectively reviewed the medical records of 47 patients with GPA based on the inclusion criteria as follows: (1) patients who were first classified as GPA at the Division of Rheumatology, the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital from October 2000 to May 2018; (2) patients who fulfilled the 2007 European Medicines Agency algorithm for the classification of GPA (the 2017 EMA algorithm) and the 2012 Chapel Hill Consensus Conferences (CHCC) Nomenclature of Vasculitis (the 2012 CHCC definitions) [1, 4]; (3) patients who were also reclassified as GPA by the 2017 American College of Rheumatology/European League Against Rheumatism provisional classification criteria for GPA (the 2017 ACR/EULAR provisional criteria) [14]; (4) patients who had well-documented medical records, with which we assessed clinical manifestations at diagnosis, particularly ENT involvement, and calculated vasculitis activity score represented by Birmingham vasculitis activity score (BVAS) for GPA and prognostic factors identified by five factor score (FFS (2009)) [8, 15]; (5) patients who had the results of cytoplasmic (C)-ANCA or proteinase 3 (PR3)-ANCA and perinuclear (P)-ANCA or myeloperoxidase (MPO)-ANCA at diagnosis [16, 17]; (6) patients who had no medical condition to mimic ENT manifestations of GPA, by the 10th revised International Classification of Diseases (ICD-10); and (7) patients who had never received immunosuppressive drugs prior to or at diagnosis of GPA, searched by the Korean Drug Utilisation Review (DUR) system. We finally included 45 GPA patients in this study. Two patients were excluded due to the administration of immunosuppressive drugs prior to diagnosis. Among 45 GPA patients, 25 patients exhibited ENT involvement, particularly chronic rhinosinusitis, among which 16 patients underwent nasal biopsy. Ten patients exhibited granuloma, whereas six patients exhibited necroinflammation without granuloma (Fig. 1). This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0673), and the patient's written informed consent was waived by the approving IRB, as this was a retrospective study.

Clinical and laboratory data

We automatically extracted clinical and laboratory data from the Clinical Data Repository (CDR) system of our institute based on the inclusion and exclusion criteria from January 2000, when the electronic medical record system has begun.

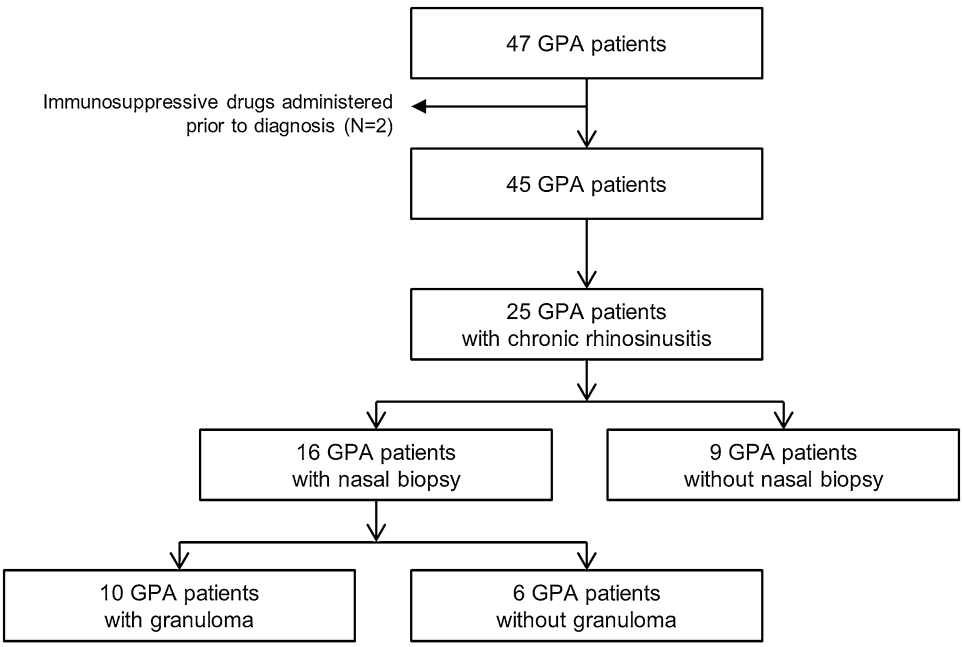

Fig. 1 Selection of the study population. *GPA* granulomatosis with polyangiitis

We collected age and gender at the time of diagnosis of GPA. In addition, we reviewed the histological results of 16 GPA patients with nasal biopsy and described "necrotising granulomatous inflammation" as a singular term of "granuloma" in the whole article. C-ANCA and P-ANCA were detected by indirect fluorescence assay. PR3-ANCA and MPO-ANCA were measured by ELISA kit for anti-PR3 and anti-MPO (Inova Diagnostics, San Diego, USA) before 2013, and by the novel anchor coated highly sensitive (hs) Phadia EliA (Thermo Fisher Scientific/Phadia, Freiburg, Germany) using human native antigens, performed on a Phadia250 analyser after 2013. We assessed clinical manifestations at diagnosis and calculated BVAS for GPA and FFS (2009).

Reclassification of GPA

In this study, we applied three methods to patients who had previously been classified as GPA and included only patients who were reclassified as GPA, such as the 2007 EMA algorithm, the 2012 CHCC definitions and the 2017 ACR/EULAR provisional criteria [1, 4, 14].

Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as number and the percentage. Significant difference in categorical variables between the two groups were analysed by the Chi square test and Fisher's exact test. Significant differences in continuous variables between the two groups were compared by the Mann–Whitney test. p values less than 0.05 were considered statistically significant.

Results

Baseline characteristics of GPA patients with chronic rhinosinusitis

The baseline characteristics are shown in Table 1. In terms of 45 GPA patients, the mean age at diagnosis was 58.4 years and 17 patients (37.8%) were men. Twenty patients (44.4%) had PR3-ANCA (or C-ANCA) and 17 patients (37.8%) had MPO-ANCA (or P-ANCA). The mean BVAS for GPA and FFS (2009) at diagnosis were 5.9 and 1.3. In terms of 16 GPA patients with nasal biopsy, the mean age at diagnosis was 56.5 years and 4 patients (25.0%) were men. PR3-ANCA (or C-ANCA) was detected in eight patients (50.0%), while MPO-ANCA (or P-ANCA) was found in four patients (25.0%). The mean BVAS for GPA and FFS (2009) at diagnosis were 4.2 and 0.7.

Comparison variables at diagnosis between patients with and without granuloma

In this study, to investigate whether there are meaningful baseline characteristics to predict the current presence of granuloma on nasal biopsy, we compared variables at diagnosis between patients with and without granuloma. Age at diagnosis and male gender were not significantly

Table 1 Baseline characteristics of GPA patients with paranasal sinusitis and comparison of variables between patients with and without granuloma on paranasal sinus tissues

Variables at diagnosis	All GPA patients ($N=45$)	Patients with nasal biopsy ($N=16$)	Patients with granuloma ($N=10$)	Patients without granuloma ($N=6$)	p value
Demographic data					
Age at diagnosis (years)	58.4 ± 14.3	56.5 ± 15.8	26.1 ± 14.6	56.7 ± 20.2	0.345
Male gender [N, (%)]	17 (37.8)	4 (25.0)	2 (20.0)	2 (14.3)	0.876
ANCAs					
PR3-ANCA (or C-ANCA)	20 (44.4)	8 (50.0)	4 (40.0)	4 (66.7)	0.782
MPO-ANCA (or P-ANCA)	17 (37.8)	4 (25.0)	2 (20.0)	2 (33.3)	0.876
Clinical manifestations					
ENT manifestation	25 (55.6)	16 (100)	10 (100)	6 (100)	0.251
Lung manifestation	27 (60.0)	6 (37.5)	4 (40.0)	2 (33.3)	0.608
Renal manifestation	24 (53.3)	6 (37.5)	3 (30.0)	3 (50.0)	0.315
Activity and prognosis factor					
BVAS for GPA	5.9 ± 4.8	4.2 ± 2.6	3.9 ± 2.0	4.7 ± 3.4	0.891
FFS (2009)	1.3 ± 1.0	0.7 ± 0.7	0.4 ± 0.5	1.2 ± 0.8	0.197

Variables are expressed as mean ± standard deviation or number (percentage)

GPA granulomatosis with polyangiitis, *ANCA* antineutrophil cytoplasmic antibody, *PR3* proteinase 3, *C* cytoplasmic, *MPO* myeloperoxidase, *P* perinuclear, *ENT* ear nose throat, *BVAS* Birmingham vasculitis activity score, *FFS* five factor score

different and ANCAs were evenly detected between patients with and without granuloma on nasal biopsy. The frequencies of lung and renal involvements and the mean BVAS and FFS (2009) at diagnosis were not significantly different between the two groups (Table 1).

Fulfilment of the 2007 EMA algorithm and the 2012 CHCC definitions in six patients with chronic rhinosinusitis and without granuloma on nasal biopsy

We applied the 2007 EMA algorithm and the 2012 CHCC definitions to six patients with chronic rhinosinusitis and without granuloma on nasal biopsy. All six patients had ANCAs and GPA surrogate markers: six patients had chronic rhinosinusitis and patient #1 had refractory otitis media; patient #2 showed saddle nose; and patient #6 exhibited subglottic stenosis. Meanwhile, there is a dilemma in classifying patients #3, #4 and #5 as GPA according to the 2007 algorithm and the 2012 CHCC definitions. Patients #3, #4 and #5 could be classified as GPA on the basis of ANCA positivity and a GPA surrogate marker of chronic rhinosinusitis. Whereas, they could also be classified as MPA based on ANCA positivity and necroinflammation without granuloma on nasal biopsy with incidental chronic rhinosinusitis (Table 2).

Fulfilment of the 2017 ACR/EULAR provisional criteria in three patients with chronic rhinosinusitis and without granuloma on nasal biopsy

In addition, we applied the 2017 ACR/EULAR provisional criteria to three patients with chronic rhinosinusitis and without granuloma on nasal biopsy. All three patients exhibited sino-nasal congestion due to rhinosinusitis (3 points) and had PR3-ANCA (or C-ANCA) (5 points), leading to the total score of 8. Since the sum of scores is more than 5, they could be classified as GPA (Table 3).

Fulfilment of the 2007 EMA algorithm and the 2017 ACR/EULAR provisional criteria in nine patients with chronic rhinosinusitis and without nasal biopsy

On the other hands, we investigated how nine patients with chronic rhinosinusitis and without nasal biopsy could be classified as GPA. In terms of the fulfilment of the 2007 EMA algorithm, all nine patients had ANCA positivity and GPA surrogate markers including chronic rhinosinusitis and/or septal perforation, nasal crust, refractory otitis media and subglottic stenosis. Therefore, they all could be classified as GPA based on the 2007 EMA algorithm, despite no performance of nasal biopsy (Table 4). In terms of the fulfilment of the 2017 ACR/EULAR provisional criteria, all nine patients showed the sum of scores of 5 or greater. Therefore, they all could be classified as GPA based on the 2017 ACR/EULAR provisional criteria, despite the absence of histology on paranasal sinus tissues (Table 4).

Table 2 Fulfilment of the 2007 EMA algorithm and the 2012 CHCC definitions in six patients with chronic rhinosinusitis and without granuloma on nasal biopsy

Patient number	PR3-ANCA or C-ANCA	MPO-ANCA or P-ANCA	Histology	GPA surrogate marker (the 2007 EMA algorithm)
1	No	Yes	Necroinflammation	Chronic rhinosinusitis, otitis media
2	Yes	No	Necroinflammation	Chronic rhinosinusitis, saddle nose
3	Yes	No	Necroinflammation	Chronic rhinosinusitis
4	Yes	No	Necroinflammation	Chronic rhinosinusitis
5	Yes	No	Necroinflammation	Chronic rhinosinusitis
6	No	Yes	Necroinflammation	Chronic rhinosinusitis, subglottic stenosis

EMA European medicine agency, *GPA* granulomatosis with polyangiitis, *CHCC* Chapel Hill Consensus Conference, *ANCA* antineutrophil cytoplasmic antibody, *PR3* proteinase 3, *C* cytoplasmic, *MPO* myeloperoxidase, *P* perinuclear

Table 3 Fulfilment of the 2017 ACR/EULAR provisional criteria in three patients with chronic rhinosinusitis and without granuloma on nasal biopsy

Patient number	Positive items (scores) (the 2017 ACR/EULAR provisional criteria)	Total score
3	Sino-nasal congestion (3), PR3-ANCA (or C-ANCA) (5)	8
4	Sino-nasal congestion (3), PR3-ANCA (or C-ANCA) (5)	8
5	Sino-nasal congestion (3), PR3-ANCA (or C-ANCA) (5)	8

ACR American College of Rheumatology, *EULAR* European League Against Rheumatism, *GPA* granulomatosis with polyangiitis, *ANCA* antineutrophil cytoplasmic antibody, *PR3* proteinase 3, *C* cytoplasmic

Table 4 Fulfilment of the 2007 EMA algorithm and the 2017 ACR/EULAR provisional criteria in nine patients with chronic rhinosinusitis and without nasal biopsy

Patient number	PR3-ANCA or C-ANCA	MPO-ANCA or P-ANCA	GPA surrogate marker (the 2007 EMA algorithm)	Positive items (scores) (the 2017 ACR/EULAR provisional criteria)	Total score
1	Yes	No	Chronic sinusitis, septal perforation	Sino-nasal congestion (3) cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5), nodule on chest imaging (2)	12
2	Yes	No	Chronic sinusitis, nasal crust	Sino-nasal congestion and nasal crusting (3), PR3-ANCA (or C-ANCA) (5)	8
3	No	Yes	Chronic sinusitis, septal perforation	Sino-nasal congestion (3), cartilaginous involvement (2), nodule on chest imaging (2)	7
4	Yes	No	Chronic sinusitis, subglottic stenosis	Sino-nasal congestion (3), cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5), nodule on chest imaging (2)	12
5	Yes	No	Chronic sinusitis, otitis media	Sino-nasal congestion (3), hearing reduction (1), PR3-ANCA (or C-ANCA) (5)	9
6	No	Yes	Chronic sinusitis	Sino-nasal congestion (3), nodule on chest imaging (2)	5
7	No	Yes	Chronic sinusitis	Sino-nasal congestion (3), nodule on chest imaging (2)	5
8	Yes	No	Chronic sinusitis	Sino-nasal congestion (3), PR3-ANCA (or C-ANCA) (5), nodule on chest imaging (2)	10
9	Yes	No	Chronic sinusitis, subglottic stenosis	Sino-nasal congestion (3), cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5)	10

ACR American College of Rheumatology, *EULAR* European League Against Rheumatism, *GPA* granulomatosis with polyangiitis, *ANCA* antineutrophil cytoplasmic antibody, *PR3* proteinase 3, *C* cytoplasmic, *MPO* myeloperoxidase, *P* perinuclear

Reassessment of the fulfilment of the 2007 EMA algorithm and the 2017 ACR/EULAR provisional criteria in ten patients with chronic rhinosinusitis and granuloma on nasal biopsy, by excluding granuloma on nasal biopsy

We excluded the item of granuloma on nasal biopsy in ten GPA patients with granuloma on nasal biopsy and reassessed the fulfilment of the 2007 EMA algorithm and the 2017 ACR/EULAR provisional criteria in them. In terms of the fulfilment of the 2007 EMA algorithm, four of ten patients had no ANCAs and only exhibited GPA surrogate markers. Therefore, four patients (patients #2, 5, 7, 8) were not reclassified as GPA based on the 2007 EMA algorithm, unless granuloma on nasal biopsy is counted (Table 5). Meanwhile, in terms of the fulfilment of the 2017 ACR/EULAR provisional criteria, all ten patients had the sum of scores of 5 or greater, despite the exclusion of granuloma on nasal biopsy (Table 5).

Discussion

We investigated initial clinical manifestations and laboratory factors which could be helpful for diagnosing GPA in cases unable for nasal biopsy performance. First, among six patients without granuloma on nasal biopsy, three patients with ANCAs and only chronic rhinosinusitis could be classified as either GPA or MPA with ENT manifestation, based on the 2007 EMA algorithm. However, they all were classified as GPA by the 2017 ACR/EULAR provisional criteria. Second, nine patients without nasal biopsy had ANCAs and chronic sinusitis and/or other GPA surrogate markers and met both the 2007 EMA algorithm and the 2017 ACR/EULAR provisional criteria. Third, when an item granuloma was not counted, among ten patients with granuloma on nasal biopsy, four patients did not fulfil the 2007 EMA algorithm, but they were classified as GPA by the 2017 ACR/EULAR provisional criteria. Thus, as far as a need for the differential diagnosis between GPA and other aetiologies is not apparent, patients with chronic rhinosinusitis could be classified as GPA though ANCA positivity and GPA surrogate markers without nasal biopsy.

MPA with ENT involvement could mimic GPA without granuloma on histology, and in this study, three GPA patients with chronic rhinosinusitis might have been classified as MPA with ENT involvement. However, they all were classified as GPA according to the 2017 ACR/EULAR provisional criteria (Tables 2, 3). In the 2017 ACR/EULAR provisional criteria, the score of 5 is allocated to the presence of PR3-ANCA (or C-ANCA). In other words, he/she, who has PR3-ANCA (or C-ANCA) without nasal polyps

Table 5 Reassessment of the fulfilment of the 2007 EMA algorithm and the 2017 ACR/EULAR provisional criteria in ten patients with chronic rhinosinusitis and granuloma on nasal biopsy, by excluding granuloma on nasal biopsy

Patient number	PR3-ANCA or C-ANCA	MPO-ANCA or P-ANCA	GPA surrogate marker (the 2007 EMA algorithm)	Positive items (score) (the 2017 ACR/EULAR provisional criteria)	Total score
1	No	Yes	Chronic sinusitis, otitis media	Sino-nasal congestion (3), hearing reduction (1), nodule on chest imaging (2)	6
2	No	No	Chronic sinusitis, nasal crusting, otitis media	Sino-nasal congestion (3), hearing reduction (1), nodule on chest imaging (2)	6
3	Yes	No	Chronic sinusitis, otitis media	Sino-nasal congestion (3), hearing reduction (1), cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5), nodule on chest imaging (2)	13
4	Yes	No	Chronic sinusitis, hoarseness	Sino-nasal congestion (3), cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5)	10
5	No	No	Chronic sinusitis, septal perforation, saddle nose	Sino-nasal congestion (3), cartilaginous involvement (2)	5
6	Yes	No	Chronic sinusitis, otitis media	Sino-nasal congestion (3), hearing reduction (1), PR3-ANCA (or C-ANCA) (5), nodule on chest imaging (2)	11
7	No	No	Chronic sinusitis, septal perforation	Sino-nasal congestion (3), cartilaginous involvement (2)	5
8	No	No	Chronic sinusitis	Sino-nasal congestion (3), nodule on chest imaging (2)	5
9	Yes	No	Chronic sinusitis, nasal crusting, otitis media	Sino-nasal congestion (3), hearing reduction (1), PR3-ANCA (or C-ANCA) (5), nodule on chest imaging (2)	11
10	No	Yes	Chronic sinusitis, nasal crusting	Sino-nasal congestion (3), nodule on chest imaging (2)	5

EMA European medicine agency, *ACR* American College of Rheumatology, *EULAR* European League Against Rheumatism, *GPA* granulomatosis with polyangiitis, *ANCA* antineutrophil cytoplasmic antibody, *PR3* proteinase 3, *C* cytoplasmic, *MPO* myeloperoxidase, *P* perinuclear

or eosinophilia, could be classified as GPA based on the 2017 provisional criteria, although he/she has no clinical manifestations related to GPA [14]. Chronic rhinosinusitis is not confined to AAV patients, and its overall prevalence was reported as 7–8% of the general population [18, 19]. Is it possible to assume that he or she has chronic sinusitis with the transient false positivity of PR3-ANCA (or C-ANCA)? However, the false positivity of PR3-ANCA (or C-ANCA) is uncommon. A previous study reported that 56 of 74 PR3-ANCA (or C-ANCA) individuals (75.7%) eventually classified represented clinical evidence supporting the classification of AAV [20]. Therefore, we concluded that PR3-ANCA (or C-ANCA) may be a strong factor suggesting GPA and it could replace nasal biopsy in GPA-suspected patients with chronic rhinosinusitis.

It was also difficult to choose a final AAV variant, MPA or limited GPA, in three patients with only one GPA surrogate marker of chronic rhinosinusitis and without nasal biopsy (Table 4). Particularly, two of them had MPO-ANCA (or P-ANCA), but they exhibited nodule on chest imaging, which was supporting for the classification of GPA. Another patient had PR3-ANCA (or C-ANCA). Therefore, we concluded that lung lesions on chest imaging specific for GPA may be a strong factor suggesting GPA and it could replace nasal biopsy in GPA-suspected patients with chronic rhinosinusitis.

Among ten GPA patients with granuloma on nasal biopsy, four patients had no ANCAs.

Assuming the absence of evidence of granuloma, they could not be classified as GPA according to the 2007 EMA algorithm. By contrast, on the basis of the 2017 ACR/EULAR provisional criteria, two patients could be classified as GPA due to nodule on chest imaging and two patients could be diagnosed with GPA due to cartilaginous involvement (Table 5). Therefore, we also concluded that GPA-specific cartilaginous involvement may be a strong factor suggesting GPA as much as lung lesions on chest imaging supporting for GPA, and it could replace nasal biopsy in GPA-suspected patients with chronic rhinosinusitis.

However, if lung lesions are not specific for GPA or it is not a proper situation when lung biopsy is recommended or there is no cartilaginous involvement, nasal biopsy should be considered for a differential diagnosis between MPA and localised GPA, for three reasons. First, although ENT involvement is not frequently observed in MPA patients, MPA can be histologically discriminated from GPA by

nasal biopsy [21]. Second, nasal biopsy is useful for the classification of early GPA, and particularly localised GPA and ANCA-negative GPA [13, 22]. Third, the induction therapeutic regimens are different: immunosuppressive drug plus corticosteroid for MPA vs. Co-trimoxazole for localised GPA [23]. Therefore, we suggest nasal biopsy, when it is not easy to differentiate between MPA and localised GPA, until the 2017 ACR/EULAR provisional criteria are not fully established. In addition, we suggest nasal biopsy, when the severity of chronic rhinosinusitis is high enough to require endoscopic sinus surgery under the general anaesthesia [24], and when a differential diagnosis from lymphomas, [25], immunoglobulin G4-related disease [26] and infections [27].

To make a definite diagnosis in GPA-suspected patients with chronic rhinosinusitis, nasal biopsy should be performed for disclosing granuloma. Nonetheless, necrotising granulomatous inflammation is usually found in only a half of GPA patients, and furthermore, this histological feature may be confirmed by nasal biopsy in only 30% of GPA patients [12]. Moreover, the concern over procedure-related complications of pain, bleeding and infection discourage patients to refuse nasal biopsy performance. In these cases, our study suggests that PR3-ANCA (or C-ANCA) positivity, GPA-specific lung lesions and cartilaginous involvement could be helpful for diagnosing GPA. However, these markers are complementary to the histological confirmation, so they should be carefully applied to only GPA-suspected patients, who cannot undergo nasal biopsy.

With these results together, we suggest that nasal biopsy could be replaced with PR3-ANCA (or C-ANCA) positivity, GPA-specific lung lesions and cartilaginous involvement in GPA-suspected patients with chronic rhinosinusitis.

Our study has two advantages. First, this study provided a valuable information that PR3-ANCA (or C-ANCA) positivity, GPA-specific lung lesions and cartilaginous involvement could be helpful for the classification of GPA in cases unable for nasal biopsy performance. Second, we included immunosuppressive drug-naïve patients in a single centre, which can avoid both the influence of immunosuppressive drugs on ANCAs positivity and histology, and minimise the inter-centric variation. However, our study also has several issues. First, our study was designed as a retrospective study, which could not completely control the confounding factors. Second, the number of patients was too small to apply our results to other Korean patients with GPA. For this reason, we could not elucidate the multi-directional correlations and associations among clinical and laboratory data. However, as a pilot study, we believe that this study provided a new concept of the performance of nasal biopsy in patients suspected of GPA. Future prospective studies with a larger number of GPA patients will more clearly provide information on the clinically proper time to perform nasal biopsy in GPA-suspected patients with chronic rhinosinusitis. In conclusion, the histological confirmation of GPA is undoubtedly the best method to diagnose and classify GPA [28, 29]. However, for diverse reasons unable to undergo nasal biopsy, PR3-ANCA (or C-ANCA) positivity, GPA-specific lung lesions and cartilaginous involvement could help physicians in charge make a final diagnosis of GPA in GPA-suspected patients with chronic rhinosinusitis.

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Author contributions JY, SSA and SWL collected the data and analysed the results and wrote the manuscript, under the guidance of SMJ and JJS; YBP contributed to writing and critically reviewed the manuscript; JY and SWL designed, analysed the results, critically reviewed the manuscript and wrote the final version. All the authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0673), and the patient's written informed consent was waived by the approving IRB, as this was a retrospective study.

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