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Original Article

Computed tomography findings of paranasal sinuses in patients with eosinophilic granulomatosis with polyangiitis: Comparison with other eosinophilic sinus diseases and clinical relevance of their severity

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Abbreviations:
ABPA, allergic bronchopulmonary aspergillosis; ACR, American College of Rheumatology; ANCA, anti-neutrophil cytoplasm antibody; ATA, aspirin-tolerant asthma; CNS, central nervous system; CT, computed tomography; CRSwNP, chronic rhinosinusitis with nasal polyposis; ECRS, eosinophilic chronic rhinosinusitis; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose, and throat; EUALR, European League Against Rheumatism; FFS, Five-Factor Score; GINA, Global Initiative for Asthma; JESREC, Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis; LMS, Lund–Mackay staging; N-ERD, NSAID-exacerbated respiratory disease

ABSTRACT

Background: Although paranasal sinuses are one of the most representative organs affected by eosinophilic granulomatosis with polyangiitis (EGPA), they have not been studied sufficiently. The aim of this study was to compare computed tomography (CT) findings in paranasal sinuses of EGPA with those of other eosinophilic sinus diseases and elucidate the clinical relevance of their severity.
Methods: CT findings of paranasal sinuses in EGPA patients prior to therapeutic intervention (n = 30) were evaluated using the Lund–Mackay staging (LMS) system and compared with those of three control diseases [(NSAID-exacerbated respiratory disease (N-ERD), aspirin-tolerant asthma, and eosinophilic chronic rhinosinusitis without asthma (ECRS)]. We divided EGPA patients into three groups based on their LMS scores and examined their association with disease manifestation.
Results: Total scores of the LMS system in EGPA were significantly lower than those of N-ERD and ECRS without asthma. There was a large variation in total LMS scores in EGPA, suggesting considerable heterogeneity of their sinus lesions. Although EGPA with low LMS system scores showed only minor findings in maxillary and anterior ethmoid regions, those with high LMS system scores were characterized by high scores in the ostiomeatal complex. However, the frequencies of patients with a Five-Factor Score ≥2 and with cardiac involvement were significantly higher for EGPA with low LMS system scores.
Conclusions: Although paranasal sinus lesions in EGPA were less severe than those of other eosinophilic sinus diseases, their milder CT findings may be associated with a higher frequency of extra-respiratory organ involvement.

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is classified as anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis disease, which is often associated with asthma, eosinophilia and nasal polyps. EGPA is also characterized by multi-organ eosinophil-rich necrotic granulomatous inflammation and necrotizing vasculitis predominantly affecting small-to-medium vessels,[1,2] and paranasal sinuses are one of the most representative organs involved in EGPA. However, their characteristics, particularly their differences from other eosinophilic sinus diseases, and their association with the disease manifestation of EGPA have not been sufficiently studied to date.

Paranasal sinuses lesions are also commonly observed in patients with asthma without EGPA. Of note, more than 90% of patients with NSAID-exacerbated respiratory disease (N-ERD) have paranasal sinuses lesions, which are characterized by predominant ethmoid sinus lesions as well as nasal polyps.[3] Although the underlying pathophysiology of N-ERD and EGPA is different, they share common clinical features in that they are likely to have non-atopic adult-onset severe asthma, high peripheral blood eosinophilia, and comorbid sinusitis. However, the similarity and/or differences in computed tomography (CT) findings of paranasal sinuses lesions in EGPA and N-ERD have not been adequately studied.

Chronic rhinosinusitis is traditionally classified by the presence or absence of nasal polyps.[4] In patients with chronic rhinosinusitis with nasal polyposis (CRSwNP), there is increased eosinophilic inflammation in mucosal tissues or nasal polyps, and increased prevalence of comorbid asthma including N-ERD.[5–7] However, patients with CRSwNP from East Asia, including Japan, were reported to have different characteristics in the nasal polyp tissues compared with patients from the United States and Europe, which are characterized by more neutrophil-predominant inflammation and good response to standard therapy.[8,9] Haruna and colleagues recently denominated CRSwNP with eosinophilic inflammation as eosinophilic CRS (ECRS), in order to differentiate it from CRSwNP with good response to standard therapy.[6,7] ECRS is diagnosed using the JESREC scoring system, whereby high scores are attributed to patients with bilateral paranasal sinuses lesions, nasal polyps, lesions in the ethmoid sinus and a high percentage of eosinophils in the blood. Therefore, the CT findings of paranasal sinuses lesions in ECRS patients meeting these criteria are characterized by bilateral lesions, nasal polyps, and a predominant ethmoid sinus shadow. However, similarities and/or differences in the CT findings of paranasal sinuses lesions in EGPA and ECRS have not been adequately studied.

The clinical significance of paranasal sinus lesions on the manifestation of EGPA has been a matter of debate in the literature. Because most (41–100%) patients with EGPA have paranasal sinuses lesions, “Paranasal sinus abnormality” is one of the items in the 1990 American College of Rheumatology (ACR) classification criteria for EGPA, which was revised to “nasal polyps” in the 2022 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria.[10–15] However, the absence of paranasal abnormalities is recognized as a poor prognostic factor for EGPA. Indeed, “the absence of ear, nose, and throat (ENT) manifestations” is one of the items in the 2011 revised Five-Factor Score (FFS), a scoring system for the prediction of poor disease prognosis.[16]

The aim of this study was to clarify the features of CT findings of paranasal sinuses lesions in EGPA and compare them with those of other eosinophilic sinus diseases, as well as elucidating the association between the severity of sinus CT findings and clinical manifestations of EGPA. In study 1, we compared the CT findings of paranasal sinuses in EGPA with those of three control groups, N-ERD, aspirin-tolerant asthma (ATA), and ECRS without asthma. In study 2, EGPA patients were classified into three groups on the basis of total scores of the Lund–Mackay staging (LMS) system and the association between LMS system scores and disease manifestations was evaluated.

Methods

Study design

We retrospectively studied the CT findings of paranasal sinuses prior to therapeutic intervention in consecutive patients who were first diagnosed with EGPA between April 2008 and September 2020 at Sagamihara National Hospital. The LMS system was used for the evaluation of CT findings, and the LMS system scores of EGPA patients (n = 30) were compared with those of three control groups, N-ERD (n = 30), ATA (n = 21), and ECRS without comorbid asthma (n = 28) (study 1). N-ERD and ECRS without asthma were chosen as control groups because both are representative of diseases with eosinophilic sinus lesions. EGPA patients were further categorized into three groups on the basis of the scores of the LMS system, and their clinical backgrounds and disease presentation were compared between groups (study 2). The Ethics Committee of Sagamihara National Hospital (Sagamihara, Japan) approved the study protocol (No. 40–2018).

Studied EGPA cases

From April 2008 to September 2020, 144 patients were diagnosed with EGPA for the first time at their outpatient visit to the Department of Allergy and Respiratory Medicine of Sagamihara National Hospital. A diagnosis of EGPA was made when both ACR/EULAR and Lanham's criteria were met.[17,18]

Flow charts of patient selection for this study are shown in Figure 1. First, we excluded three cases of EGPA with comorbid N-ERD and one case of EGPA with comorbid allergic bronchopulmonary aspergillosis (ABPA), because N-ERD and ABPA are known to frequently develop comorbid characteristic paranasal sinuses lesions. Among them, about half of these patients (n = 72) underwent a CT scan of the paranasal sinuses. Studied patients were further limited to those who did not have a surgical history of paranasal sinuses (n = 67) and who were not treated with systemic steroids or biological therapy when the CT scan was performed (n = 31). After excluding one patient who did not have any abnormal findings on CT of paranasal sinuses, 30 patients with EGPA were finally analyzed. Therefore, all patients with EGPA who were analyzed had not started treatment with systemic steroids or biological therapy and had no history of sinus surgery.

Control groups for study 1

Consecutive patients with N-ERD, ATA, and ECRS without asthma were also selected and designated as control groups for EGPA cases. From April 2008 to September 2020, 151 patients underwent a systemic aspirin provocation test at our department. Among them, 3 patients were removed from the analysis because they had comorbid EGPA as stated previously, and the remaining 148 patients were studied (Figure 1). Among them, 79 patients with positive results and 69 patients with negative results were designated as the N-ERD and ATA groups, respectively. The aspirin provocation test was performed in our hospital as previously reported.[19,20] Briefly, a total dose of aspirin up to 930 mg was administered single-blind according to the oral loading test protocol. A positive aspirin provocation test was defined as a decrease in the FEV1 by more than 20% from baseline or greater compared with baseline or a decrease in the FEV1 by 10%–20% with the presence of nasal and/or ocular symptoms.

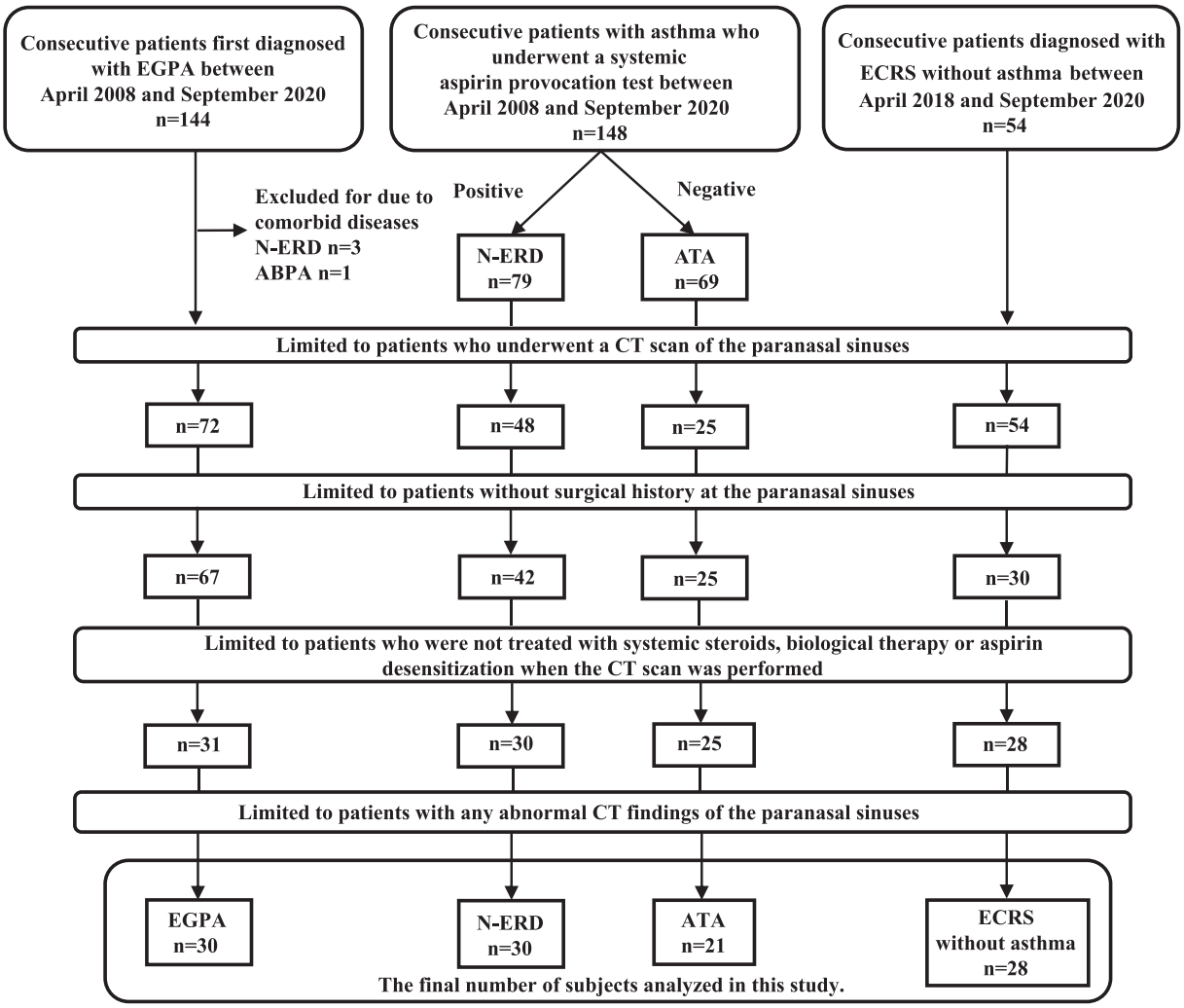

Fig. 1. Flow chart of patient enrollment. EGPA, eosinophilic granulomatosis with polyangiitis; N-ERD, NSAID-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; ECRS, eosinophilic chronic rhinosinusitis; ABPA, allergic bronchopulmonary aspergillosis.

From April 2008 to September 2020, 54 patients without asthma were diagnosed as definite ECRS after endoscopic sinus surgery at the Otorhinolaryngology Department of Sagamihara National Hospital on the basis of the JESREC scoring system, and these were designated as the ECRS without asthma group. Cases with comorbid asthma were excluded from patients with ECRS to avoid overlap of study subjects with patients in the N-ERD group, where ECRS complications are common. According to the JESREC system, comorbid asthma is a parameter used for the classification of the severity of ECRS.[7] Because of the exclusion of cases with comorbid asthma, the severity of ECRS in most cases in this group was classified as mild or moderate. In other words, numerous patients with severe ECRS and comorbid asthma were included in the N-ERD group. Definite ECRS was determined by meeting both of the following criteria: a JESREC score higher than 11 points and mucosal eosinophilia of 70 or higher eosinophils/high power field (× 400). Comorbid asthma had been definitively ruled by our allergic respiratory physician before the surgery. Additionally, we confirmed that none of them met the ACR/EULAR or Lanham's EGPA criteria.[17,18]

Similar to the EGPA cases, studied patients in the three control groups were further limited to those who did not have a surgical history of the paranasal sinuses and who were not treated with systemic steroids, biological therapy or aspirin desensitization (for N-ERD) when the CT scan was performed as shown in Figure 1. Regarding the ECRS without asthma group, CT findings prior to endoscopic surgery were analyzed. After excluding patients without abnormal findings on the CT of paranasal sinuses, 30 N-ERD, 21 ATA, and 28 ECRS without asthma patients were finally analyzed.

Paranasal sinuses CT images and LMS scoring

We reviewed the results of paranasal sinus CT imaging in cases with EGPA and in three control groups. CT images were taken before therapeutic intervention for EGPA, before the aspirin provocation test for N-ERD and ATA, and just before surgery for ECRS were used for the analysis. CT imaging was evaluated by the LMS system, which evaluates the extent of the shadow in 10 regions from 5 paranasal sinuses (maxillary, anterior ethmoids, posterior ethmoids, sphenoid, and frontal) on the right and left sides, respectively, by grading between 0 and 2, and further evaluating whether the ostiomeatal complex is obstructed or not on the right and left sides, respectively by scoring as a 0 or 2. A total of 12 sinus regions were evaluated for a score of 24 points.[21] The LMS system is a noninvasive tool for the evaluation of the severity of chronic sinusitis, which can be evaluated by a non-specialist otolaryngologist.[21,22] Two independent reviewers (one allergist and

otolaryngologist) were involved in the scores of the LMS system evaluation and any disagreements or inconsistencies were resolved by discussion, and any uncertainty or disagreement was resolved by a third reviewer.

Clinical information and laboratory data

Clinical information and laboratory data were collected by medical chart review. Regarding EGPA, clinical information including organ involvement of EGPA at the time of diagnosis, and blood/urine data just before the therapeutic intervention for EGPA were used for the analysis. Regarding the N-ERD and ATA groups, clinical information and laboratory data before the aspirin provocation test were used. Regarding ECRS, data just before paranasal sinus surgery were used.

Patients who showed one or more positive results in serum IgE Abs testing to respiratory allergens were considered atopic. Patients with asthma were evaluated for asthma treatment steps by the Global Initiative for Asthma (GINA).[23] Urinary leukotriene E4 levels were measured as described previously. Briefly, after purification by chromatography, urinary leukotriene E4 was quantitatively determined by enzyme immunoassay.[24]

The Five-Factor Score

The disease activity of each EGPA case was evaluated using 1996 The Five-Factor Score (FFS) and 2011 revised FFS on the basis of clinical information at disease onset.[16,25] The FFS is a tool designed to assess disease prognosis at the diagnosis of EGPA, which was first devised by Guillevin *et al.*, in 1996 and revised by Guillevin *et al.* in 2011. Although the FFS has been used to guide the treatment of EGPA, the ACR/Vasculitis Foundation recommendation revised in 2021 does not use FFS for this purpose.[26] The 1996 FFS included the following 5 items with the presence of each accorded 1 point for a maximum score of 5: proteinuria >1 g/day, renal insufficiency (stabilized peak creatinine 140 μmol/L), cardiomyopathy, severe gastrointestinal manifestations, and central nervous system (CNS) involvement.[16] The 2011 revised FFS included the following 5 items: age >65 years, cardiac manifestations, gastrointestinal tract involvement, and renal insufficiency (stabilized peak creatinine ≥150 μmol/L), with no ear, nose, and throat (ENT) manifestations.[25] For the 1996 FFS and 2011 revised FFS, a score of ≥2 correlates with poor disease prognosis.[16,25] In the current study, all EGPA patients studied did not meet the criterion item of "no ear, nose, and throat (ENT) manifestations" in the 2011 revised FFS, because they all had a manifestation in their paranasal sinuses as evidenced by CT.

Statistical analysis

Significance testing was performed using Fisher's exact test or Chi-squared test for categorical variables and the Mann–Whitney *U*-test or Kruskal–Wallis test for continuous variables. Total scores of the LMS system were divided into tertiles: 1–4 (1st tertile, low LMS score group), 5–10 (2nd tertile, middle LMS score group), and 11–24 (3rd tertile, high LMS score group). To test for trends by scores of the LMS system tertile, the Cochran–Armitage test was used for binary variables, and the Jonckheel-Terpstra trend test was used for continuous variables. A Receiver Operating Characteristic curve was constructed with scores of the LMS system as independent variables and the 2011 revised FFS ≥2 as a dichotomous variable. A p-value of 0.05 was considered statistically significant. The collected data were analyzed using SPSS V.25.0 software (SPSS, Chicago, IL, USA).

Results

Background of patients with EGPA and three controls in study 1

Table 1 shows the characteristics of the studied EGPA cases (n = 30) and three control groups [N-ERD (n = 30), ATA (n = 21), and ECRS (n = 28)]. There were no significant differences in sex, age, onset age of asthma, and asthma treatment steps between groups. The frequency of patients who used LTRA among the EGPA cases was significantly lower than that of the N-ERD group, and marginally higher than that of the ECRS group. The number of patients who used nasal steroids among EGPA cases was significantly lower than that in the N-ERD and ECRS groups. Eosinophil counts and total IgE levels were significantly higher in the EGPA group than in the other three groups. Pathological diagnosis by

Table 1
Characteristics of the studied EGPA cases and three control groups (N-ERD, ATA, ECRS).

Characteristics	Cases	Controls					
		EGPA vs N-ERD		EGPA vs ATA		EGPA vs ECRS	
	EGPA (n = 30)	N-ERD (n = 30)	p-value	ATA (n = 21)	p-value	ECRS (n = 28)	p-value
Women, n (%)	18 (60)	19 (63)	0.791	17 (81)	0.112	10 (36)	0.064
Age (y), median (IQR)	49 (38–68)	55 (34–63)	0.469	46 (42–64)	0.435	60 (56–66)	0.183
Asthma onset age ≥20 yrs, n (%)	27 (90)	27 (90)	1.000	18 (86)	0.640	–	–
Smoking status, n (%)							
Current smoker	1 (3)	1 (3)	0.566	2 (10)	0.643	4 (14)	0.234
Past smoker	10 (33)	14 (47)		7 (33)		11 (39)	
Never smoker	19 (63)	15 (50)		12 (57)		13 (46)	
Drug usage, n (%)							
LTRA	11 (37)	26 (87)	<0.001	9 (43)	0.656	4 (14)	0.052
Nasal steroids	3 (10)	16 (53)	<0.001	5 (24)	0.182	15 (54)	<0.001
Asthma treatment step, n (%)							
Steps 1-3	12 (40)	11 (37)	0.791	9 (43)	0.838	–	–
Steps 4 and 5	18 (60)	19 (63)		12 (57)		–	–
Blood sampling							
Blood eosinophil count (10*3/μL), median (IQR)	5.42 (2.90–9.10)	0.43 (0.24–0.78)	<0.001	0.40 (0.26–0.53)	<0.001	0.41 (0.23–0.52)	<0.001
Blood eosinophil rate (%), median (IQR)	44 (37–54)	7 (3–12)	<0.001	6 (4–9)	<0.001	7 (5–11)	<0.001
Atopy, n (%)	14 (47)	16 (53)	0.344	15 (71)	0.367	8 (3)	0.172
Total IgE level (IU/mL), median (IQR)	870 (378–2300)	192 (77–279)	<0.001	464 (74–2300)	<0.001	188 (110–450)	<0.001

Date are presented as n (%) or median (interquartile range). Values in bold are statistically significant (p < 0.05).
EGPA, eosinophilic granulomatosis with polyangiitis; N-ERD, NSAIDs-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; ECRS, eosinophilic sinusitis; LTRA, leukotriene receptor antagonist; IQR, interquartile range.

histological biopsy was attempted in 28 of the 30 cases of EGPA, and was proven in 5 of them.

Paranasal sinus CT scores in study 1

Figure 2 shows the scores of the LMS system at each region of paranasal sinuses among cases and three control groups. The scores

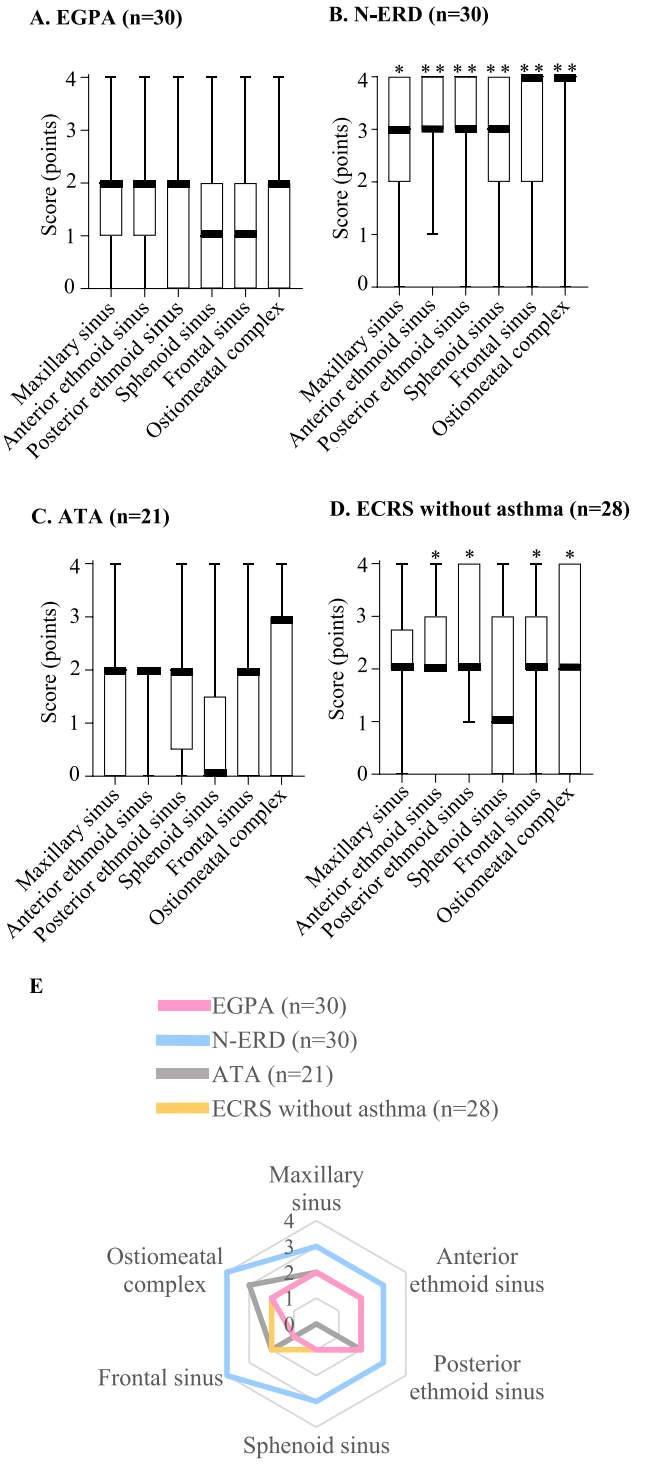

Fig. 2. Comparisons of scores of the Lund–Mackay staging system for paranasal sinus CT findings between EGPA and control groups. Box-and-hide diagram for the sum of the left and right scores of each sinus region in EGPA (**A**), N-ERD (**B**), ATA (**C**), and ECRS (**D**). Radar chart showing the median scores of each sinus region by patient group (**E**). *p < 0.05 and **p < 0.001 compared with scores of the same region of EGPA cases.

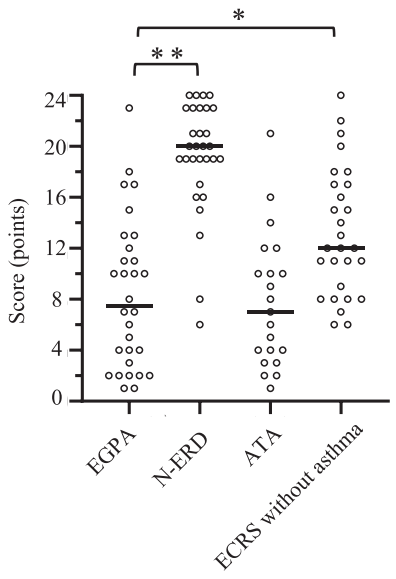

Fig. 3. Total scores of the Lund–Mackay staging system for EGPA cases and three control groups. *p < 0.05 and **p < 0.001 compared with EGPA cases.

of each sinus in the EGPA group were significantly lower than those in the N-ERD group for all regions. There were no significant differences in paranasal sinus scores between the EGPA and ATA groups. Compared to the ECRS group, the EGPA group had significantly lower scores for all regions except the maxillary sinus and sphenoid sinus. In the N-ERD and ECRS groups, scores in the ethmoid sinus were significantly higher than scores in the maxillary sinus, which were compatible with previous studies.[27,28]

Figure 3 shows the total score for the 12 sinus regions in each group. The EGPA group had significantly lower total scores than the N-ERD ($p < 0.001$) and ECRS groups ($p = 0.042$), although there was no significant difference between the EGPA and ATA groups.

Association between scores of the LMS system and the manifestation of EGPA (study 2)

Considering the great variation in scores of the LMS system in EGPA group (Fig. 2), we assumed that there are several subtypes of EGPA with different disease presentations in association with variations in LMS scores. Thus, we attempted to classify EGPA cases based on scores of the LMS system. Thirty EGPA cases were divided into three groups on the basis of the tertiles of scores of the LMS system: total scores of the LMS system of 1–4, 5–10, and 11–25 were designated as low ($n = 11$), middle ($n = 10$), and high ($n = 9$) score groups, respectively. Figure 4 shows the scores of the LMS system for each lesion in these patient groups. CT findings of the low and middle LMS score groups were characterized by a low score in the ostiomeatal complex. However, CT findings in the high LMS score group were characterized by a high score in the ostiomeatal complex, which was similar to the CT findings in N-ERD or ECRS shown in Figure 2B and D.

Table 2 shows the differences in characteristics and disease presentation among these three groups. There were no significant differences in sex, onset age of asthma, BMI, smoking history, other organ involvement, medications used, asthma severity, eosinophil counts, MPO-ANCA positivity and total IgE levels between groups. However, cardiac involvement was significantly more frequent in the low LMS score group (p for trend = 0.006). In contrast, pulmonary involvement was more common among those with high LMS scores although this association did not reach statistical significance (p for trend = 0.066). The number of affected extra

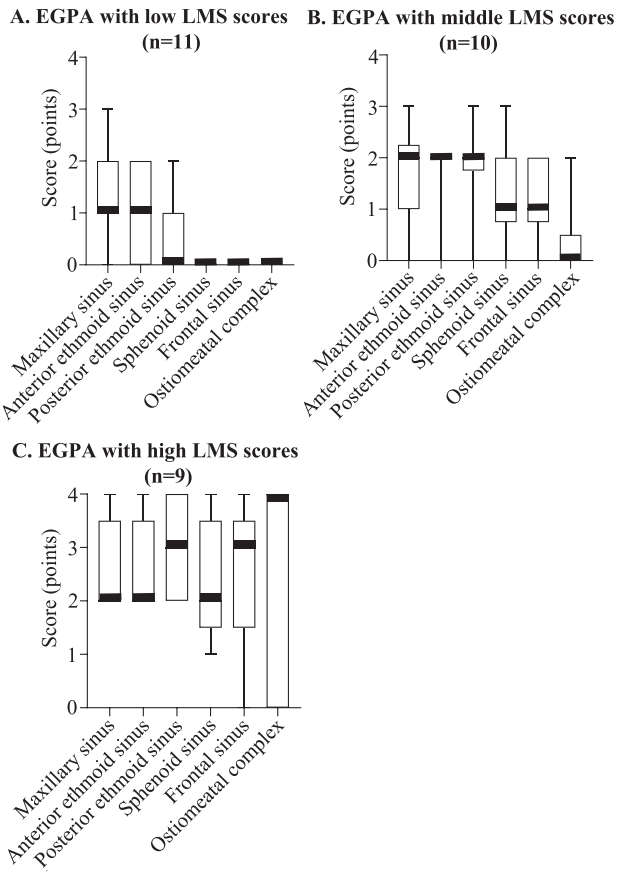

Fig. 4. Sum of left and right scores of each sinus region in EGPA patients with low (n = 11) **(A)**, middle (n = 10) **(B)**, and high (n = 9) **(C)** scores of the Lund–Mackay staging system.

pulmonary organs was higher in those with low scores of the LMS system, although this association did not reach statistical significance (p for trend = 0.092). The frequency of cases with a 2011 revised FFS ≥2, a known high risk factor for poor disease prognosis, was higher among those with a low LMS score (p for trend = 0.019).

Cutoff value for scores of the LMS system as a predictor for an FFS ≥2

Receiver Operating Characteristic curves were created with scores of the LMS system as independent variables and a 2011 revised FFS ≥2 as a dichotomous variable (Fig. 5). The area under the curve for an FFS ≥2 by scores of the LMS system was 0.775, indicating that low scores of the LMS system were a good predictor for an FFS ≥2. Table 3 shows the sensitivity and specificity of scores of the LMS system to predict an FFS ≥2 at different cutoff points. Applying a cutoff point of ≤4.0, the sensitivity and specificity of scores of the LMS system to predict an FFS ≥2 were 50.0% and 83.4%, respectively. We selected this cutoff point because its specificity exceeded 80%.

Discussion

To the best of our knowledge, this study is the first to provide a detailed review of the CT findings of the paranasal sinuses in EGPA prior to therapeutic intervention and to show their relationship with the disease manifestations of EGPA. Overall, paranasal sinus findings in EGPA were less severe than in other eosinophilic sinus diseases (N-ERD and ECRS). Additionally, there was a large variation in the scores of the LMS system in EGPA, indicating a large variation in the severity of paranasal sinus lesions. Although EGPA with low LMS scores showed only minor findings in maxillary and anterior ethmoid regions, those with high LMS scores were characterized by high scores in the ethmoid sinus region and ostiomeatal complex, which were similar to the CT findings of N-ERD and ECRS. However, low scores of the LMS system were associated with a higher frequency of patients with an FFS ≥2 and cardiac involvement, implying a poor disease prognosis. These findings suggest that the intensity of paranasal sinus lesions and their distribution are associated with the clinical subtype of EGPA with different disease manifestations.

Previous studies on the CT findings of paranasal sinus lesions in EGPA have been controversial. Of note, whether CT findings of paranasal sinus lesions in EGPA resemble those of ECRS has been a matter of debate. In a retrospective multicenter study of EGPA cases performed in France, 66% of EGPA patients who had a clinical manifestation of chronic rhinosinusitis had maxillal rhinosinusitis on CT, whereas about half of the EGPA patients also had a history of nasal polyps.[13] In a study of EGPA patients in Japan, higher CT scores for ethmoid sinus lesions than maxillary sinus lesions were observed in more than 70% of the studied EGPA patients, indicating that most of the EGPA patients had ethmoid sinus lesions in a predominant pattern resembling the CT findings of ECRS.[29] However, a more recent study by the same Japanese research group reported that, although the sinus findings of EGPA resembled those of ECRS, ethmoid-dominant inflammation in EGPA was weaker than that in ECRS, and some EGPA cases “lacked” the typical nasal findings of ECRS.[30]

Paranasal sinuses are considered one of the most representative organs involved in EGPA. In the 2022 ACR/EULAR criteria for the classification of EGPA, nasal polyps are considered an important disease classifier.[15] However, the findings of our study revealed that patients with EGPA with severe paranasal sinus findings are not the majority of those with EGPA. The most important finding of our study was the considerable heterogeneity in CT findings of paranasal sinus lesions in EGPA. This heterogeneity may explain the controversy in the findings of paranasal sinus lesions in EGPA in the literature discussed above. In our study, the high and low LMS score groups differed by the pattern of sinus lesion distribution and by the frequency of organ involvement of EGPA. These findings suggest that the pathological background of EGPA has partial heterogeneity and that paranasal sinus findings may be associated with this heterogeneity.

In the literature, ANCA status has been considered one of the most important factors for characterizing the subtypes of EGPA.[31] A recent genome-wide association study of EGPA also revealed genomic loci specific for ANCA status.[32–34] MPO-ANCA was reported to be positive in about 30% of EGPA patients,[35–40] and was associated with differences in pathological findings.[41] Sural nerve biopsy specimens in MPO-ANCA-positive cases showed findings suggestive of vasculitis (i.e. destruction of vascular structures) in epineural vessels, whereas those in ANCA-negative cases had a higher number of eosinophils in the lumen of the epineurial vessels and the endoneurium as well as eosinophilic vascular occlusion.[41] ANCA status has been also associated with specific organ involvement. ANCA-positive cases were associated with renal and neurological involvement, whereas negative cases were likely to have cardiac involvement.[31,35,42,43] However, in our study, there was no statistically significant association between ANCA positivity and the frequency of organ involvement (data not shown), although a low score of LMS was associated with a higher prevalence of those with cardiac involvement and those with an FFS ≥2. These findings

Table 2
Characteristics of EGPA cases at disease onset by Lund–Mackay score.

	Total (n = 30)	Low LMS score group (n = 11)	Middle LMS score group (n = 10)	High LMS score group (n = 9)	p-value	p-trend
Score of the LMS system, median (range)	7.5 (1.0–23.0)	2.0 (1.0–4.0)	9.0 (5.0–10.0)	15.0 (11.0–23.0)	0.000	0.000
Female, n (%)	18 (60)	8 (73)	5 (50)	5 (56)	0.551	0.418
Age (y), median (IQR)	49 (38–68)	45 (38–72)	59 (42–67)	46 (37–70)	0.963	0.849
Current smoker, n (%)	1 (3)	0 (0)	0 (0)	1 (11)	0.322	0.067
Past smoker, n (%)	10 (33)	2 (18)	4 (40)	4 (44)		
Never smoker, n (%)	19 (63)	9 (82)	6 (60)	4 (44)		
LTRA usage, n (%)	11 (37)	2 (18)	6 (60)	3 (33)	0.144	0.428
Nasal steroids usage, n (%)	3 (10)	1 (9)	1 (10)	1 (11)	0.989	0.883
Duration of asthma (months)[†], median (IQR)	66 (11.25–132)	9 (3–108)	66 (30–162)	120 (32.5–378)	0.010	0.002
Asthma severity, n (%)						
Steps 1-3	12 (40)	5 (46)	6 (60)	1 (11)	0.085	0.164
Steps 4, 5	18 (60)	6 (54)	4 (40)	8 (89)		
Blood and urine sampling						
Blood eosinophil count (10*3/μL), median (IQR)	5.42 (2.90–9.10)	3.78 (2.66–6.80)	7.14 (4.94–10.76)	1.47 (0.79–7.04)	0.112	0.833
Total IgE level (IU/mL), median (IQR)	870 (380–2300)	380 (310–2050)	124 (580–2970)	930 (380–5020)	0.514	0.295
IgG4 (mg/dL), median (IQR)	439 (377–603)	439 (400–475)	673 (626–911)	200 (38–396)	0.026	0.175
Urinary leukotriene E4 (pg/mL), median (IQR)	346 (209–1192)	307	4588.4	297 (200–789)	0.343	0.499
MPO-ANCA positive, n (%)	8 (27)	2 (18)	4 (40)	2 (22)	0.507	0.808
Manifestation of EGPA, n (%) Respiratory						
Otologic involvement	3 (10)	1 (9)	0 (0)	2 (22)	0.283	0.378
Asthma	28 (93)	10 (91)	9 (90)	9 (100)	0.639	0.443
Lung involvement Extra respiratory	17 (57)	5 (46)	4 (40)	8 (89)	0.070	0.066
Cutaneous involvement	18 (60)	7 (64)	5 (50)	6 (67)	0.733	0.928
Cardiac involvement	13 (43)	8 (73)	4 (40)	1 (11)	0.024	0.006
Renal involvement	5 (17)	1 (9)	3 (30)	1 (11)	0.393	0.844
Gastro-intestinal involvement	14 (47)	7 (64)	4 (40)	3 (33)	0.363	0.175
Neurologic involvement	27 (90)	10 (91)	9 (90)	8 (89)	0.989	0.883
Cerebrovascular disorders	5 (17)	2 (18)	3 (30)	0 (0)	0.212	0.324
Number of involved extra respiratory organs, median (IQR)	2.0 (2.0–4.0)	4.0 (2.0–4.0)	2.0 (2.0–4.3)	2.0 (1.0–3.0)	0.229	0.092
Five-Factor Score ≥2, n (%)	10 (33)	6 (55)	3 (30)	1 (11)	0.127	0.042
Five-Factor Score revised ≥2, n (%)	12 (40)	7 (64)	4 (40)	1 (11)	0.064	0.019

Date are presented as n (%) or median (interquartile range).
Values in bold are statistically significant ($p < 0.05$). OMC, ostiomeatal complex; y, years; m, months; IQR, interquartile range.
[†] Duration (months) from onset of asthma to when CT for paranasal sinus lesions was performed.

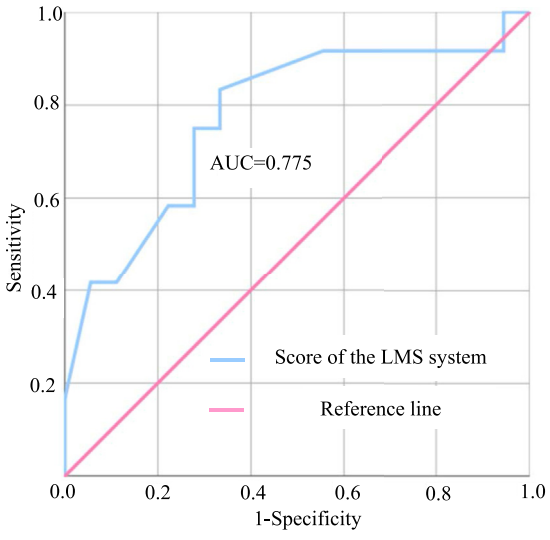

Fig. 5. Receiver-operating characteristic curve for scores of Lund–Mackay staging system in EGPA patients and a 2011 revised FFS ≥2. AUC, area under the curve; FFS, Five-Factor Score.

suggest that CT findings in the paranasal sinus are a more important factor for characterizing the subtypes of EGPA than ANCA status.

In asthma patients without EGPA complication, it has been shown that the severity of sinusitis (assessed by LMS) correlates with higher asthma severity.[44] Particularly in N-ERD, nasal tissue is the source of cysteinyl leukotrienes, and its higher urinary levels have been correlated with higher asthma severity and lower lung function.[45] These findings suggested a strong correlation between the severity of upper and lower respiratory manifestations. However, regarding EGPA, a negative association between ENT manifestation and disease activity has been documented. “The absence of ear, nose, and throat (ENT) manifestations” is one of the items in the 2011 revised FFS, and is considered a predictor of poor disease prognosis.[25] In our study, a low LMS was associated with a high frequency of an FFS ≥2, and we suggested a cutoff point of 4.0 or below for scores of the LMS system as a predictor for an FFS ≥2. This suggests that even if a CT scan of the paranasal sinus of an EGPA patient shows any abnormal findings, an LMS score of 4 or less may need to be considered as a risk factor for a poor disease prognosis. However, it was not possible to investigate the actual prognosis of EGPA in the present study due to the small sample size. Because patients with EGPA without paranasal sinus involvement were

Table 3
Sensitivity and specificity of the scores of the LMS system as a predictor of 2011 revised FFS ≥2 at different cut-off points in EGPA patients (n = 30).

Cut off values of the score of the LMS system (points)	Sensitivity	Specificity
0.00	0.000	1.000
≤2.00	0.292	0.972
≤4.00	0.500	0.834
≤6.00	0.667	0.722
≤8.00	0.778	0.667
≤10.00	0.889	0.518
≤12.00	0.917	0.361
≤14.00	0.917	0.222
≤16.00	0.917	0.167
≤18.00	0.931	0.056
≤20.00	0.986	0.056
≤22.00	1.000	0.032
≤24.00	1.000	0.000

Low score of the LMS system indicates a higher frequency of an FFS ≥2.
FFS, Five-Factor Score.

excluded from our study, we could not examine the association between FFS and patients without paranasal sinus involvement.

The reason for the higher frequencies of patients with an FFS ≥2 and with cardiac involvement among EGPA patients with a low LMS score is unknown. One possible explanation for this may be related to the potential difference in pathophysiological background between EGPA patients with high and low LMS scores. Another explanation may be related to the significantly lower asthma duration in patients with lower LMS scores (Table 2). Lower asthma duration in this group may suggest that their disease is more rapidly progressive than patients with a high LMS score, and the development of serious paranasal sinus lesions might take longer after the onset of EGPA. This may also be related to the fact that biopsies of airway tissues are often characterized by intense eosinophilic inflammation rather than severe vasculitis.[35,46,47]

One of the strengths of our study is that the CT findings of paranasal sinuses were evaluated prior to therapeutic intervention for all the EGPA patients and controls. Another strength is that we reliably excluded N-ERD patients from the 30 EGPA patients studied, even performing an aspirin provocation test when necessary. EGPA and N-ERD share common clinical features including eosinophilia and comorbid sinusitis, and a recent study reported that N-ERD cases can have cardiac manifestations,[48,49] which sometimes makes it difficult to differentiate N-ERD from EGPA.

One important limitation of our study was related to potential selection bias. We excluded patients who had a surgical history of paranasal sinuses or those treated with systemic corticosteroids when the CT scan was performed, which might have resulted in the exclusion of more severe EGPA patients, leading to potential selection bias. Five EGPA cases were excluded from the analysis owing to a surgical history of paranasal sinus. Pathological evaluation of nasal tissues obtained from four of those cases showed extensive eosinophilic infiltration, thereby pathologically meeting the diagnostic criteria for ECRS (≥70 eosinophils/high-power field). Another limitation may be related to the lack of a pathological evaluation of the paranasal sinus tissue or endoscopic evaluation for nasal polyps in patients with EGPA. It was difficult to evaluate the pathology of sinus tissues or nasal polyps in many cases before therapeutic intervention. This is because paranasal sinus is not life-threatening organ and is not useful for the pathological evaluation of vasculitis.[35,50] Thus, their pathological evaluation is not prioritized at the onset of disease or initial diagnosis.

In conclusion, the characteristics of the CT findings of paranasal sinus lesions of EGPA and their association with disease manifestations were investigated in this study. Although paranasal sinus lesions in EGPA were less severe than those of other eosinophilic sinus diseases, these milder sinus CT findings were associated with a higher frequency of patients with an FFS ≥2 and cardiac involvement, implying a poor disease prognosis. The findings of our study indicate that, when assessing paranasal sinus lesions in patients with EGPA, clinicians should evaluate not only the presence or absence of the lesion, but also its severity. More research including studies of patients with other ethnic backgrounds is needed to verify the findings of this study.

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Conflict of interest

YH received lecture fee from Novartis Pharma and Astra Zeneca. YK received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, Glaxo Smith Kline, and Astra Zeneca. KS received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novartis Pharma, Kyorin Pharmaceutical, Sanofi, Taiho Pharmaceutical, Glaxo Smith Kline, and Astra Zeneca. MT received research grant from Glaxo Smith Kline and lecture fees from Glaxo Smith Kline, Sanofi, Novartis Pharma and Astra Zeneca. The rest of the authors have no conflict of interest.

Authors' contributions

MI and KS developed the concept; MI, YH, YN, KW, YK, TI and KS were responsible for collecting the data; MI, YF, and YH were responsible for statistical analyses. All the authors were responsible for the interpretation of results; MI and YF wrote the manuscript; and MT contributed to the critical revision of the manuscript.

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