



Comparison of findings on thoracic computed tomography with the severity and duration of bronchial asthma in patients with eosinophilic granulomatosis with polyangiitis

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ABSTRACT

Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic necrotizing vasculitis with eosinophilia. EGPA can occur in patients with comorbid bronchial asthma (BA) and other pulmonary diseases. However, because of its rarity, there are few reports on thoracic computed tomography (CT) findings in patients with EGPA, especially in relation to comorbid BA. The aim of this study was to compare between the clinical characteristics of EGPA, the severity and duration of BA, and the findings on thoracic CT.

Methods: We retrospectively reviewed the records of patients with EGPA who were admitted to our hospital from 2001 to 2015. All patients satisfied the criteria for EGPA according to American College of Rheumatology or Lanham's criteria. Patients without asthma (n = 2) and those in whom CT was not performed (n = 3) were excluded.

Results: We identified 31 patients who had EGPA comorbid with BA. The median duration of BA was 6 years. CT revealed parenchymal opacification (ground-glass opacity and/or consolidation; n = 17), airway abnormalities (bronchial wall thickening and/or bronchiectasis; n = 15), pleural effusion (n = 4), interlobular septal thickening (n = 5), and mediastinal lymphadenopathy (n = 4). Importantly, the group with severe BA had a significantly higher incidence of airway abnormalities than the group with mild to moderate BA (81.8% vs 30.0%, $P = 0.009$). The frequency of airway abnormalities was significantly higher in patients with EGPA who had a history of asthma of 5 years or more than in their counterparts with a shorter asthma history (66.7% vs 10.0%, $P = 0.006$), particularly bronchial wall thickening (52.4% vs 10.0%, $P = 0.046$).

Conclusions: The most common finding on thoracic CT in patients who had EGPA comorbid with BA was parenchymal opacification followed by airway abnormalities. The severity and duration of BA in these patients may affect the findings on thoracic CT.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a disease characterized by systemic necrotizing vasculitis with eosinophilia [1]. EGPA is a rare disease with a reported prevalence of 10.7–17.8 per 1,000,000 adults [2,3]. EGPA was first described in detail in 1951 by Churg and Strauss [4]. Lanham et al. were the first to suggest diagnostic criteria for EGPA [5], and criteria for a diagnosis of EGPA were published by the American College of Rheumatology (ACR) in 1990 [6]. Importantly, both these sets of criteria include bronchial asthma (BA). BA is characterized by airflow obstruction associated with chronic airway inflammation

[7]. Thoracic computed tomography (CT) in patients with BA occasionally demonstrates bronchial wall thickening, bronchiectasis, and air trapping [8–10]. EGPA may involve several organs, including the lungs and skin as well as the cardiovascular, gastrointestinal, and central nervous systems [11–13]. Because of its rarity, there is limited information concerning the findings on thoracic computed tomography (CT) in patients with EGPA. Ground-glass opacity (GGO) and consolidation seemed to be characteristic findings in previous reports [14–16]. Therefore, we expected that the CT findings in patients with EGPA would be affected by comorbid BA. In this study, we investigated the relationship between the severity and duration of BA and the findings on thoracic CT in patients with EGPA.

Abbreviations: BA, bronchial asthma; CT, computed tomography; EGPA, eosinophilic granulomatosis with polyangiitis; GGO, ground-glass opacity

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2. Methods

2.1. Patients and study design

We retrospectively reviewed the medical records of patients with EGPA who were admitted to Kyorin University Hospital from 2001 to 2015. All patients fulfilled either the ACR or Lanham's criteria for a diagnosis of EGPA. Fulfilment of the ACR criteria for a diagnosis of EGPA requires the presence of four of the following: asthma, eosinophilia > 10% on a differential white blood cell count, mononeuropathy (including multiplex) or polyneuropathy, migratory or transient pulmonary opacities on radiography, paranasal sinus abnormality, and a biopsy showing accumulation of eosinophils in extravascular areas. Lanham's criteria include asthma, eosinophilia > 1500 cells/ μ L, and systemic vasculitis involving two or more extrapulmonary organs. Patients without asthma ($n = 2$) and those who did not undergo CT ($n = 3$) were excluded.

BA was diagnosed according to the Global Initiative for Asthma (GINA) criteria [7] and classified as mild (controlled with treatment steps 1 and 2), moderate (controlled with treatment step 3), or severe (requiring treatment steps 4 and 5). The GINA guideline published in 2017 defines these treatment steps as follows: step 1, as-needed reliever inhaler medication; step 2, low-dose controller medication plus as-needed reliever medication; step 3, one or two controllers plus as-needed reliever medication; step 4, two or more controllers plus as-needed reliever medication; and step 5, higher-level care and/or add-on treatment.

Thoracic CT was performed at the time of diagnosis of EGPA. Three pulmonologists, a with more than 10 years of experience, reviewed the thoracic CT images independently and the findings were documented by consensus. Regarding the area of the lung affected by ground glass opacities, we evaluated by using the 6-level semiquantitative scoring system reported by Akira et al. [17]. Briefly, these visual scores are defined as follows: grade 0, no opacity; grade 1, 5% opacity; grade 2, 5%–24% opacity; grade 3, 25%–49% opacity; grade 4, 50%–74% opacity; and grade 5, 75% opacity. The maximum score for each level is 10 and the total score can range from 0 to 60.

Bronchial wall thickening was assessed manually and the entire bronchus was evaluated in all patients. The study was approved by the institutional review board at Kyorin University (approval number H28-149).

2.2. Statistical analysis

The data are presented as the number (percentage) or as the median (range). Differences between groups were assessed using the Mann-Whitney *U* test or Kruskal-Wallis test. Categorical variables were assessed using the chi-square test or Fisher's exact test. The statistical analyses were performed using SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). A *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Thirty-six patients with EGPA were identified to have been admitted to our hospital during the study period. Two patients who did not have BA and three who did not undergo thoracic CT were excluded, leaving 31 patients (21 women and 10 men of median age 61 [range 32–77] years) for enrolment in the study. The patient characteristics are shown in Table 1. The median time from initial onset of BA to diagnosis of EGPA was 6 years. Three patients were on treatment step 1, 5 were on step 2, 12 were on step 3, 9 were on step 4, and 2 were on step 5 according to the GINA guideline. At the time of diagnosis of EGPA, there was involvement of the lungs in 31 patients (100.0%), central

Table 1

Characteristics of patients.

Number of Patients	31
Male	10 (32.3)
Age, years	61 (32–77)
Bronchial Asthma	31 (100)
The duration (years) from initial onset of BA to the EGPA diagnosis,	6 (0–59)
GINA treatment steps	
Step 1	3 (9.7)
Step 2	5 (16.1)
Step 3	12 (38.7)
Step 4	9 (29.0)
Step 5	2 (6.5)
WBC,/ μ L	16000 (6400–36000)
Neutrophils,/ μ L	5700 (3300–13000)
Eosinophils,/ μ L	6600 (1000–23600)
CRP, mg/mL	4.5 (0.0–17.4)
IgE, IU/mL	943 (20–5023)
MPO – ANCA, positive	13 (41.9)
Respiratory involvement	31 (100.0)
Neurologic involvement	31 (100.0)
Skin involvement	22 (71.0)
Cardiovascular involvement	9 (29.0)
Gastrointestinal involvement	3 (9.7)
Renal involvement	15 (48.4)

Data are presented as number of patients (%) or median (range).

GINA; Global Initiative for Asthma, WBC; white blood cells, CRP; C-reactive protein, IgE; immunoglobulin E, MPO-ANCA; myeloperoxidase - antineutrophil cytoplasmic antibody.

nervous system in 31 (100.0%), skin in 22 (71.0%), cardiovascular system in 9 (29.0%), gastrointestinal tract in 3 (9.7%), and kidneys in 15 (48.4%). Thirteen patients (41.9%) were positive for myeloperoxidase anti-neutrophil cytoplasmic antibody.

3.2. Radiologic findings at the time of diagnosis of EGPA

All patients were evaluated by thoracic CT at the time of diagnosis of EGPA (Table 2). Sixteen (51.6%) of our 31 patients with EGPA had no lesions on chest radiography but had abnormal findings on thoracic CT. The CT findings included parenchymal opacification (GGO and/or consolidation, $n = 17$), airway abnormalities (bronchial wall thickening and/or bronchiectasis, $n = 15$), pleural effusion ($n = 4$), interlobular septal thickening ($n = 5$), mediastinal lymphadenopathy ($n = 4$), and a nodule ($n = 1$). Fig. 1 shows the representative findings on thoracic CT. Using semiquantitative scoring method, we found that the median score was 3.0 (interquartile range, 3.0–7.0), suggesting that the total area of the lung affected by GGO in patients with EGPA ($n = 15$) was relatively small. A median score of 3 is equal to 5% involvement of the total lung.

3.3. Comparison of severity of BA and thoracic CT and laboratory findings

According to the GINA criteria, 20 of the 31 patients with EGPA had

Table 2

Thoracic CT Findings of 31 patients with EGPA.

Parenchymal opacification	17 (54.8)
GGO	15 (48.4)
Consolidation	6 (19.4)
Airway abnormality	15 (48.4)
Bronchial wall thickening	12 (38.7)
Bronchiectasis	4 (12.9)
Pleural effusion	4 (12.9)
Interlobular septal thickening	5 (16.1)
Mediastinal lymphadenopathy	4 (12.9)
Nodule	1 (3.2)

Data are presented as number of patients (%). GGO; ground-glass opacity.

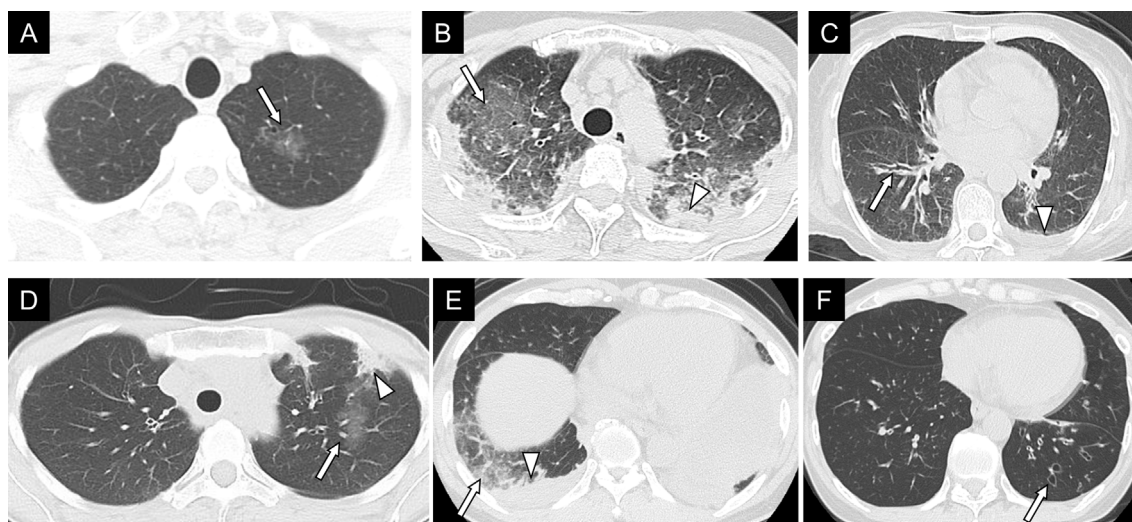


Fig. 1. Representative findings for eosinophilic granulomatosis with polyangiitis on thoracic computed tomography. (A) GGO (arrow), (B) GGO (arrow) with consolidation (arrowhead). (C) bronchial wall thickening (arrow) with pleural effusion (arrowhead), (D) GGO (arrow) with nodules (arrowhead), (E) GGO (arrow) with pleural effusion (arrowhead), and (F) bronchiectasis (arrow). GGO, ground-glass opacity.

Table 3
Patient characteristics with EGPA associated with severity of bronchial asthma.

	Mild – Moderate group (N = 20)	Severe group (N = 11)	P value
Age (years)	62 (32–77)	58 (42–73)	0.317
WBC (/μL)	13,400 (6400–36000)	17,200 (7800–26,400)	0.298
Neutrophils (/μL)	5700 (3300–13000)	5800(3300–8600)	0.823
Eosinophils (/μL)	5500 (1000–23,600)	9000 (3600–18,100)	0.183
CRP (mg/dL)	4.5 (0.0–16.0)	4.9 (0.2–17.4)	0.640
IgE (IU/mL)	899 (20–5023)	1116 (407–3609)	0.823
MPO – ANCA (+)	11 (55.0)	2 (18.2)	0.066
The duration of asthma (years)	6 (0–59)	7 (2–27)	0.555

Data are presented as number of patients (%) or median (range).

WBC; white blood cells, CRP; C-reactive protein, IgE; immunoglobulin E, MPO-ANCA; myeloperoxidase - antineutrophil cytoplasmic antibody.

Table 4
Thoracic CT Findings of 31 patients with EGPA associated with severity of bronchial asthma.

	mild – moderate group (N = 20)	Severe group (N = 11)	P value
Parenchymal opacification	9 (45.0)	8 (72.7)	0.258
GGO	8 (40.0)	7 (63.6)	0.273
Consolidation	2 (10.0)	4 (36.4)	0.151
Airway abnormality	6 (30.0)	9 (81.8)	0.009
Bronchial wall thickening	6 (30.0)	6 (54.5)	0.255
Bronchiectasis	0 (0.0)	4 (36.4)	0.010
Pleural effusion	2 (10.0)	2 (18.2)	0.601
Interlobularseptal thickening	3 (15.0)	2 (18.2)	1.000
Mediastinal lymphadenopathy	3 (15.0)	1 (9.1)	1.000
Nodule	1 (5.0)	0 (0.0)	1.000

Data are presented as number of patients (%).

GGO; ground-glass opacity.

mild to moderate BA and 11 had severe BA (Tables 3 and 4). The results of the laboratory investigations were comparable between the two groups (Table 3). However, the incidence of airway abnormalities was significantly higher in the group with severe BA than in the group with mild to moderate BA (81.8% vs 30.0%, $P = 0.009$; Table 4). Bronchiectasis was more common in the group with severe BA than in the

group with mild to moderate BA (36.4% vs 0.0%, $P = 0.010$). There were no other significant differences between the two groups.

3.4. Comparison of duration of BA and thoracic CT and laboratory findings

The median time from initial onset of BA to diagnosis of EGPA was 6 (range 0–59) years. There were no statistically significant differences in the laboratory values according to whether BA had been present for less than 5 years or for 5 years or more (Table 5). However, the frequency of airway abnormalities was significantly higher in patients with EGPA who had had BA for 5 years or more than in those with a shorter history of BA (66.7% vs 10.0%, $P = 0.006$; Table 6). Bronchial wall thickening in particular was more common in the patients who had had BA for 5 years or more than in those who had had BA for less than 5 years (52.4% vs 10.0%, $P = 0.046$). Furthermore, the frequency of parenchymal opacification was significantly higher in patients with a BA history of 5 years or more than in those with a shorter BA history (76.2% vs 10.0%, $P = 0.001$), particularly for GGO (66.7% vs 10.0%, $P = 0.006$).

4. Discussion

In this study, the most common findings on thoracic CT in patients with EGPA were parenchymal opacification (GGO) followed by airway abnormalities (particularly bronchial wall thickening), which is consistent with previous reports [15,16]. For example, Worthy et al.

Table 5
Patient characteristics with EGPA associated with prior duration of bronchial asthma.

	< 5years group (N = 10)	≥ 5years group (N = 21)	P value
Age, years	63 (32–77)	61 (42–74)	1.000
WBC (/μL)	13,100 (6400–26,400)	16300 (6500–36,000)	0.633
Neutrophils (/μL)	5500 (3300–13,000)	5800(3300–12,600)	0.787
Eosinophils (/μL)	5200 (1000–210000)	8900 (1100–23600)	0.217
CRP (mg/dL)	7.4 (0.0–16.0)	3.5 (0.2–17.4)	0.268
IgE, (IU/mL)	1482 (100–5023)	865 (20–3769)	0.546
MPO – ANCA (+)	3 (30.0)	10 (47.6)	0.452

Data are presented as number of patients (%) or median (range).

WBC; white blood cells, CRP; C-reactive protein, IgE; immunoglobulin E, MPO-ANCA; myeloperoxidase - antineutrophil cytoplasmic antibody.

Table 6

Thoracic CT Findings of 31 patients with EGPA associated with prior duration of bronchial asthma.

	Total (N = 31)	< 5years group (N = 10)	≥ 5years group (N = 21)	P value
Parenchymal opacification	17 (54.8)	1 (10.0)	16 (76.2)	0.001
GGO	15 (48.4)	1 (10.0)	14 (66.7)	0.006
Consolidation	6 (19.4)	1 (10.0)	5 (23.8)	0.634
Airway abnormality	15 (48.4)	1 (10.0)	14 (66.7)	0.006
Bronchial wall thickening	12 (38.7)	1 (10.0)	11 (52.4)	0.046
Bronchiectasis	4 (12.9)	0 (0.0)	4 (19.0)	0.277
Pleural effusion	4 (12.9)	1 (10.0)	3 (14.3)	1.000
Interlobular septal thickening	5 (16.1)	1 (10.0)	4 (19.0)	1.000
Mediastinal lymphadenopathy	4 (12.9)	0 (0.0)	4 (19.0)	0.277
Nodule	1 (3.2)	1 (10.0)	0 (0.0)	0.323

Data are presented as number of patients (%).

GGO; ground-glass opacity.

reported the most common CT findings in patients with EGPA to be parenchymal opacification, i.e., consolidation and ground-glass attenuation [15]. We also found a significantly higher incidence of bronchiectasis in the group with severe BA than in the group with mild to moderate BA. Furthermore, we detected significantly higher rates of GGO and bronchial wall thickening in patients with EGPA who had a BA history of 5 years or more than in those with a shorter BA history. In general, patients with BA alone rarely have GGO on thoracic CT. The high frequency of GGO in the group with a BA history of 5 years or more suggests that GGO with a relatively small involved area to total lung on semiquantitative scoring method is a characteristic radiologic feature of EGPA.

Thus, thoracic CT findings can be influenced by the severity of BA regardless of whether or not the patient has EGPA. In our study, GGO and bronchial wall thickening on thoracic CT were more common in patients who had had BA for 5 years or more than in those who had had BA for less than 5 years. Surprisingly, 16 (51.6%) of our 31 patients with EGPA had no lesions on chest radiography but had abnormal thoracic CT findings, including consolidation, GGO, bronchial wall thickening, and mediastinal lymphadenopathy, suggesting that thoracic CT is better than chest radiography for evaluation of EGPA. To our knowledge, the present study is the first to provide evidence of a relationship between the duration and severity of BA and the findings on thoracic CT in patients with EGPA.

EGPA is a rare disease in Japan with an estimated prevalence of 17.8/1,000,000 [3], so little is known about its clinical features. However, diagnostic clues for the disease include eosinophilia, BA, and some degree of organ involvement [1,18]. Although various sets of criteria for the diagnosis of EGPA have been proposed, we only enrolled patients in this study if they satisfied Lanham's criteria or the American College of Rheumatology criteria. Previous studies in patients with EGPA did not report any sex predominance [19,20]; however, our data indicated a female to male ratio of approximately 2 to 1. Furthermore, we found that 41.9% of our patients with EGPA were positive for serum myeloperoxidase anti-neutrophil cytoplasmic antibody, which again is consistent with previous reports [3,11].

Because of the low incidence of EGPA, there have been no investigations of whether or not the duration and severity of BA can influence the radiologic features of this disease. Several studies have investigated the thoracic CT findings in patients with BA alone and demonstrated bronchial wall thickening, bronchiectasis, hyperlucency, and mucoid impaction to be characteristic features of BA [8,21,22]. Interestingly, bronchial wall thickening on thoracic CT has been associated with airflow restriction and the severity [22] and duration [9] of BA. Indeed, in the present study, we found a significantly higher incidence of bronchiectasis on thoracic CT in patients with EGPA and severe BA than in their counterparts with mild to moderate BA,

indicating that the presence of BA could affect the CT findings in patients with EGPA. Furthermore, Inoue et al. [23] reported that the ratio of the area of the airway wall to that of the outer area of the bronchus is higher in patients with eosinophilic asthma than in those with non-eosinophilic asthma. However, eosinophil counts in the sputum, which might be one of the reasons for the airway abnormalities found in patients with EGPA, were not measured in this study.

Although several articles have focused on the relationship between EGPA and control of asthma and/or airway hyperresponsiveness [24,25], none have addressed the relationship between duration of BA and CT findings in patients with EGPA. In our study, bronchial wall thickening and GGO were significantly more common in patients with EGPA who had had BA for 5 years or more than in those who had had BA for a shorter duration. Therefore, our study demonstrates that both the severity and duration of BA can affect the thoracic CT findings in patients with EGPA, which include bronchiectasis, bronchial wall thickening, and GGO.

This study has several limitations in that it had a retrospective design and included a relatively small number of patients, which reflects the rarity of EGPA. Furthermore, we excluded patients who had not undergone thoracic CT, which could have introduced a degree of selection bias. However, our study provides the first evidence of a relationship between the severity and duration of BA and the findings on thoracic CT in patients with EGPA.

5. Conclusion

The most common findings on thoracic CT in patients with EGPA comorbid with BA are GGO and bronchial wall thickening, which can be influenced by the severity and duration of BA.

Declarations of interest

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None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2018.05.003>.

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Supplemental Table 1. Comparison of thoracic CT findings in 31 patients with EGPA according to whether they were MPO-ANCA-positive or MPO-ANCA-negative

	Total (n = 31)	MPO-ANCA negative group (n = 18)	MPO-ANCA positive group (n = 13)	P-value
Parenchymal opacification	17 (54.8)	9 (50.0)	8 (61.5)	0.717
GGO	15 (48.4)	8 (44.4)	7 (53.8)	0.722
Consolidation	6 (19.4)	4 (22.2)	2 (15.4)	1.000
Airway abnormality	15 (48.4)	10 (55.6)	5 (38.5)	0.473
Bronchial wall thickening	12 (38.7)	7 (38.9)	5 (38.5)	1.000
Bronchiectasis	4 (12.9)	4 (22.2)	0 (0.0)	0.120
Pleural effusion	4 (12.9)	2 (11.1)	2 (15.4)	1.000
Interlobular septal thickening	5 (16.1)	4 (22.2)	1 (7.7)	0.368
Mediastinal lymphadenopathy	4 (12.9)	4 (22.2)	0 (0.0)	0.120
Nodule	1 (3.2)	0 (0.0)	1 (7.7)	0.419

The data are presented as the number (percentage). GGO, ground-glass opacity; MPO-ANCA; myeloperoxidase-antineutrophil cytoplasmic antibody