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Exploring EGPA: Clinical perspectives on peripheral eosinophilia and lung involvement with real-life data

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Abstract. *Introduction:* The role of eosinophils in acute and chronic lung diseases becomes more evident day by day. The aim of this study is to analyze the guiding role of peripheral eosinophilia in the diagnosis of lung diseases and to present pulmonologists' perspective on EGPA with old and new diagnostic criteria through real-life data. *Patients and Methods:* In this retrospective observational cohort, the files of patients who presented to the chest diseases department with pulmonary symptoms and peripheral eosinophilia between 2017-2023 were investigated. The diagnoses of the patients and their eosinophilia severity were examined. All the cases were reviewed according to the old and new diagnostic criteria for EGPA. *Results:* Among the 1567 patients with pulmonary symptoms and peripheral eosinophilia, pulmonary infection was the most common cause, followed by asthma and COPD. Mild eosinophilia was detected in the majority of the patients (90.5%). The highest mean eosinophil counts were observed in malignancies, hematological diseases and rheumatological diseases (including EGPA), respectively. Eosinophilia severities had significant difference between the diagnostic subgroups ($p<0.001$). The data were revised for EGPA with old and current diagnostic criteria. The false positivity rate of the old criteria was found to be significantly higher than the correctly applied current criteria (92.8% and 33.3%). Proper application of the current classification criteria regarding EGPA, which is among the causes of severe eosinophilia, will prevent unnecessary tests in this regard.

Key words: eosinophilia, pulmonary disorders, EGPA, peripheral eosinophilia, differential diagnosis, eosinophilic vasculitis, real-life data, EGPA management, lung involvement in vasculitis, diagnostic challenges in egpa

Introduction

Elevated tissue and blood eosinophil levels are toxic to some body areas and structures. The lungs are among the tissues where the toxicity of eosinophils is intense (1). In other words, the lungs are attractive accommodation sites for eosinophils. A significant number of patients whose etiology of peripheral blood eosinophilia is being investigated present to Chest Diseases clinics either by referral from other clinics or directly with pulmonary symptoms. Peripheral eosinophilia, eosinophil count exceeding 500 cells per microliter on complete blood count, is a defined finding for many lung diseases. As phenotypic approaches have become increasingly popular in chronic obstructive pulmonary disease (COPD) and asthma, peripheral eosinophilia have attracted more attention (2, 3). It has been demonstrated that allergic conditions, parasitic and

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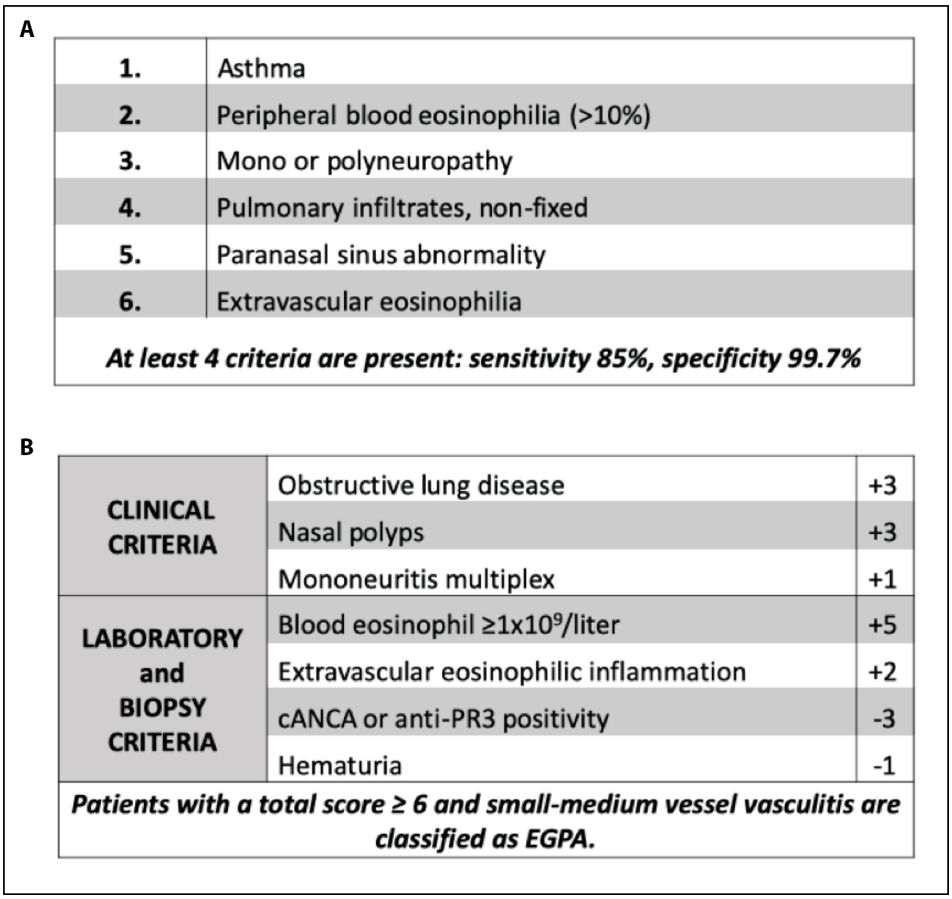

A

1.	Asthma
2.	Peripheral blood eosinophilia (>10%)
3.	Mono or polyneuropathy
4.	Pulmonary infiltrates, non-fixed
5.	Paranasal sinus abnormality
6.	Extravascular eosinophilia

At least 4 criteria are present: sensitivity 85%, specificity 99.7%

B

CLINICAL CRITERIA	Obstructive lung disease	+3
	Nasal polyps	+3
	Mononeuritis multiplex	+1
LABORATORY and BIOPSY CRITERIA	Blood eosinophil ≥1x10^9/liter	+5
	Extravascular eosinophilic inflammation	+2
	cANCA or anti-PR3 positivity	-3
	Hematuria	-1

Patients with a total score ≥ 6 and small-medium vessel vasculitis are classified as EGPA.

Figure 1. Previous and current diagnostic criteria of Eosinophilic Granulomatosis Polyangiitis (EGPA), a) 1990 ACR criteria, b) 2022 ACR/EULAR Societies' Criteria.

fungal infections and drug-related reactions are at the forefront. However, differential diagnosis may not always be that easy in patients presenting with peripheral eosinophilia and pulmonary symptoms. In such complex cases, it is necessary to investigate other rarer causes such as eosinophilic interstitial lung diseases, malignancies, hematological diseases, connective tissue diseases or vasculitides (4-7). At this point, eosinophilic granulomatosis and polyangiitis (EGPA) frequently comes to our mind as a prototype of diseases in which eosinophilia and pulmonary findings coexist, as a preliminary diagnosis. As we know, until recently, criteria published by the American College of Rheumatology (ACR) in 1990 was used in diagnosis of EGPA (then known as Churg-Strauss Syndrome) (Figure 1). However, despite their widespread use, these criteria have never been validated (8). Recently, new criteria based on diagnostic classification for EGPA were defined with the scoring system revised by the ACR/European Alliance of Associations for Rheumatology (EULAR) (Figure 1) (9). The striking point when compared to the old criteria is that this new scoring is not a diagnostic criterion, but a classification criterion for the EGPA subgroup in a patient diagnosed with vasculitis. In other words, applying these criteria to a patient without proven vasculitis may lead to major errors in the diagnostic approach or, at best, unnecessary examinations. The aim of this study is to analyze the guiding role of peripheral eosinophilia in the diagnosis of lung diseases and to reveal the possibilities in differential diagnosis by presenting real-life data. We set out with the idea that with the data obtained here, more rational approaches can be put forward by avoiding unnecessary examinations for rarer conditions such as EGPA. As a subsection of the review, we planned to open a special bracket for EGPA to identfy how we should interpret the old and new diagnostic criteria in Chest Diseases practice.

Material and Method

Study design and patients

Approval was obtained from the local ethics committee for this study. The files of patients who presented to the Chest Diseases Clinic with pulmonary symptoms and peripheral eosinophilia between January 1, 2017 and January 1, 2023 were retrospectively examined. Adult patients aged 18 and over, whose demographic and clinical data could be accessed completely and reliably, whose examinations were completed and a definitive diagnosis was reached, were included in the study. Patients who did not meet these criteria were excluded from the study. Patients were first grouped according to their eosinophilia severity levels. Those with an eosinophil count between 0.5×10^9/L and 1.5×10^9/L were grouped as mild eosinophilia, those with an eosinophil count between 1.5×10^9/L and 5×10^9/L were grouped as moderate eosinophilia, those with an eosinophil count above 5×10^9/L were grouped as severe eosinophilia. The patients' demographic data, tobacco use, comorbidities, and history of lung diseases were scanned. The final diagnoses of all patients presenting with peripheral eosinophilia and their relationship with the severity of eosinophilia were determined. Patients who underwent further examination with the preliminary diagnosis of EGPA among the differential diagnoses were also examined separately. The findings and diagnoses of the patients were evaluated according to the old and current criteria for EGPA (Figure 1). For the definitive diagnosis of EGPA, the Rheumatology clinical diagnosis was taken as basis. Of course, in the past, patients were diagnosed within the 1990 criteria but only with a Rheumatology council decision. As it is known, vasculitis was not a diagnostic criterion at that time. However, the diagnosis was made with rheumatological consensus. Newer patients were diagnosed with EGPA according to the 2022 criteria.

Statistical method

Descriptive data were analyzed. The continuous variables were expressed as mean ± standard deviation (SD), and the categorical variables were expressed as number (n) and percentage (%). The compliance of continuous variables with normal distribution was evaluated with the Kolmogrov Smirnov test. Mann Whitney U test or Student-T tests were used depending on whether the groups are normally distributed or not. The correlations of the obtained numerical parameters were also examined. A value of $p < 0.05$ was taken as statistical significance.

Results

A total of 1567 patients, 604 women (38.5%) and 963 men (61.5%), who were admitted to the Chest Diseases Clinic due to pulmonary symptoms and had peripheral eosinophilia detected in the complete blood count, were included in this study (Table 1). The mean age of the patients was 52.1 (range: 32-72.2) years. The mean eosinophil count of all patients was $0.92\pm0.69\times10^9$/L. Although the mean eosinophil count was found to be higher in

Table 1. Descriptive data on demographic, laboratory and clinical findings of patients with peripheral eosinophilia.

Parameters	**Results**	
Age, years (mean ± SD)	52.1± 20.1	
Gender n (%)	Female	604 (38.5)
	Male	963 (61.5)
#Eosinophils (10^9/L) (mean ± SD)	All patients	0.92 ± 0.69
	Female patients	0.88 ± 0.49
	Male patients	0.95 ± 0.78
Diagnosis n (%)	Asthma	574 (36.6)
	CTD	9 (0.6)
	Pulmonary infections	695 (44.4)
	COPD	124 (7.9)
	Heart failure	15 (1)
	Pleural diseases	20 (1.3)
	Pulmonary thromboembolism	38 (2.4)
	Pulmonary hypertension	4 (0.3)
	Malignancies	21 (1.3)
	Hematological diseases	8 (0.5)
	ILD	31 (2)
	Sleep apnea	3 (0.3)
	Tobacco use	25 (1.6)

Abbreviations: CTD: Connective tissue diseases, COPD: Chronic obstructive pulmonary disease, ILD: Interstitial lung diseases, SD: Standard deviation

Table 2. Distribution of eosinophil levels according to diagnostic subgroups of patients.

Disease subgroups	Total (n)	#Eosinophils (10^9/L) (mean ± SD)	Mild eosinophilia n (%)	Moderate eosinophilia n (%)	Severe eosinophilia n (%)	*p*
All patients	1567	0.92±0.69	1418 (90.5)	140 (8.9)	9 (0.6)	-
Asthma	574	0.91±0.62	521 (90.8)	52 (9.1)	1 (0.2)	<0.001
CTD	9	0.89±0.71	641 (92.2)	48 (6.9)	6 (0.9)	
Pulmonary infections	695	0.94±0.54	114 (91.9)	10 (8.1)	0	
COPD	124	1.03±0.46	13 (86.7)	2 (13.3)	0	
Heart failure	15	0.84±0.25	18 (90)	2 (10)	0	
Pleural diseases	20	1.16±0.74	30 (78.9)	8 (21.1)	0	
Pulmonary thromboembolism	38	0.73±0.18	4 (100)	0	0	
Pulmonary hypertension	4	1.96±1.66	10 (47.6)	9 (42.9)	2 (9.5)	
Malignancies	21	1.90±1.02	4 (50)	4 (50)	0	
Hematological diseases	8	0.8110.30	29 (93.5)	2 (6.5)	0	
ILD	31	1.58±0.95	6 (66.7)	3 (33.3)	0	
Sleep apnea	3	0.70±0.10	3 (100)	0	0	
Tobacco use	25	0.66±0.09	25 (100)	0	0	

Abbreviations: CTD: Connective tissue diseases, COPD: Chronic obstructive pulmonary disease, ILD: Interstitial lung diseases, SD: Standard deviation

male patients than in females, the difference was not statistically significant (0.95±0.78 ×10^9/L vs. 0.88±0.49 ×10^9/L). The final diagnostic subgroups of the patients were determined (Table 1). Regardless of eosinophilia severity, pulmonary infections were the most common cause of peripheral eosinophilia in 695 patients (44.4%), followed by asthma in 574 patients (36.6%) and COPD in 124 patients (7.9%). When the patients were assessed in terms of eosinophilia severity groups, 90.5% (n=1418) of the patients were found to have mild eosinophilia, 8.9% (n=140) moderate eosinophilia, and 0.6% (n=9) severe eosinophilia.

The mean eosinophil counts and eosinophilia severity distributions were also examined according to disease subgroups. Rheumatological diseases, malignancies, hematological diseases, and EGPA, respectively, had the highest mean eosinophil counts. In most of the diagnostic subgroups, the frequency of mild eosinophilia was significantly higher than that of moderate and severe eosinophilia. Mild eosinophilia was present in more than 90% of patients in the most common diagnostic subgroups; pulmonary infections, asthma and COPD respectively. On the other hand, moderate and/or severe eosinophilia was more common in hematological diseases, malignancies and rheumatological diseases than in other groups. In general, eosinophilia severity frequencies showed a significant difference between diagnostic subgroups (p<0.001) (Table 2).

When the diagnostic subgroups were compared between the eosinophilia severity groups, the difference between the groups was also found to be significant (p <0.001) (Table 3).

In this study, diagnostic simulation was performed in patients with peripheral eosinophilia according to the old and new EGpa criteria. We wondered how often we would have made a preliminary diagnosis of EGPA if we had evaluated these patients using the old criteria, what would have happened if we had evaluated them using the new criteria ignoring the need for vasculitis. Those who met the diagnosis of EGPA according to the old criteria but were not actually diagnosed with EGPA was considered as 'false positive'. The data were evaluated specifically for EGPA, and it was observed that a total of 312 patients with peripheral blood eosinophilia above the cut-off value for EGPA (1×10^9/L and above) were admitted. Among them, 116 patients were diagnosed with asthma (37.2%), 99 with

Table 3. Distribution of patients according to eosinophilia severity groups.

	Total (n)	Asthma (n, %)	Pulmonary infections (n, %)	COPD (n, %)	Heart failure (n, %)	Pleural diseases (n, %)	Pulmonary thromboembolism (n, %)	Pulmonary hypertension (n, %)	Malignancies (n, %)	Hematological diseases (n, %)	ILD (n, %)	CTD (n, %)	Sleep apnea (n, %)	Tobacco use (n, %)	p
Mild eosinophilia	1418	521 (36.7)	641 (45.2)	114 (8)	13 (0.9)	18 (1.3)	30 (2.1)	4 (0.3)	10 (0.7)	4 (0.3)	29 (2)	6 (0.4)	3 (0.2)	25 (1.8)	<0.001
Moderate eosinophilia	140	52 (37.1)	48 (34.3)	10 (7.1)	2 (1.4)	2 (1.4)	8 (5.7)	0 (0)	9 (6.4)	4 (2.9)	2 (1.4)	3 (2.1)	0 (0)	0 (0)	
Severe eosinophilia	9	1 (11.1)	6 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (22.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

Abbreviations: CTD: Connective tissue diseases, COPD: Chronic obstructive pulmonary disease, ILD: Interstitial lung diseases

lung infections (31.7%), and 31 with COPD (9.9%). When we evaluated these patients according to the 1990 ACR criteria, we saw that 28 patients could be diagnosed as EGPA (Table 4).

All patients were also revised according to current criteria. If we used the new criteria for a direct diagnostic approach (without prioritizing the presence of vasculitis) we saw that 167 patients were compatible with EGPA (Table 5). However, if the current criteria were evaluated together with the presence of vasculitis, only three patients could have been classified as EGPA. When the files of these three patients, we saw that one patient was diagnosed with "Idiopathic Eosinophilic Vasculitis" by the Rheumatology Council, and the other two patients were indeed diagnosed with EGPA truly. The false positivity rate of the old criteria was found to be significantly higher than the correctly applied current criteria (92.8% and 33.3%) (p<0.001).

Table 4. The results obtained by evaluating the cases according to the 1990 ACR diagnostic criteria.

Finding	n	At least 4 criteria positivity	True EGPA diagnosis	False positivity frequency
Asthma	116	28	2	92.8%
Peripheral blood eosinophilia (>10%)	312			
Mono or polyneuropathy	6			
Pulmonary infiltrates, non-fixed	29			
Paranasal sinus abnormality	32			
Extravascular eosinophilia	7			

Discussion

In this retrospective study, data of 1567 patients with pulmonary symptoms and peripheral eosinophilia were examined. Among the underlying diagnoses, pulmonary infections were the most common cause, followed by asthma and COPD. Mild eosinophilia was detected in the majority of the patients (90.5%). The highest mean eosinophil counts were observed in malignancies, hematological diseases and rheumatological diseases (including EGPA), respectively. When the diagnostic subgroups were compared between the eosinophilia severity, the difference between the groups was found to be significant (p<0.001). The data were evaluated from 3 different perspectives specifically for EGPA; (I) considering 1990 ACR criteria, (II) using the current criteria for diagnostic purposes directly, and (III) using the current criteria for classification purposes in patients with vasculitis (8, 9). It was determined that 28 patients could be classified as compatible with EGPA if the 1990 ACR criteria were taken as basis, 167 patients could be classified as EGPA according to the current criteria if scoring was used as a direct diagnostic approach, and 3 patients could be classified as EGPA if the current criteria were evaluated together with the vasculitis chart. In fact, during this 6-year period, only 2 of the patients we consulted to the Rheumatology clinic with a preliminary

Table 5. Results obtained by evaluating previous cases according to the EGPA criteria of 2022 ACR/EULAR Societies.

		If diagnostic evaluation is performed without signs of vasculitis			If a diagnostic evaluation is performed in a patient with vasculitis		
	n	Only Score ≥6	True EGPA diagnosis	False positivity frequency	Vasculitis + Score ≥6	True EGPA diagnosis	False positivity frequency
Obstructive lung disease	145	167	2	98.8%	3	2	33.3%
Nasal polyps	9						
Mononeuritis multiplex	6						
Blood eosinophil ≥1×10^9/L	312						
Extravascular eosinophilic inflammation	7						
cANCA or anti-PR3 positivity	0						
Hematuria	0						

diagnosis of EGPA were diagnosed with EGPA. There is limited data about the effects of peripheral blood eosinophil counts and organs (10, 11). In Okada et al.'s retrospective study, severe eosinophilia was frequently associated with EGPA (12). They found that the relationship between milder eosinophilia (>2,000 cells/μl) and asthma was weak. In the study of Fijolek et al., asthma was identified as the only underlying cause in 20% of patients with moderate eosinophilia (13). According to our results, mild eosinophilia comes to the fore in most cases of peripheral eosinophilia and pulmonary disease. The most common pulmonary pathologies in those with mild and moderate eosinophilia were found to be infections, asthma and COPD. On the other hand, 37.1% of patients with moderate eosinophilia were associated with asthma, which means that asthma was detected as the etiological cause in one of every three patients with peripheral eosinophil counts between 1.5-5×10^9/L. A point emphasized by some studies in this field is that there is no significant correlation between peripheral blood eosinophil count, organ involvement and pulmonary findings (14). It is stated that the activity of eosinophils rather than their number is the main determinant of this issue. On the other hand, there are also studies reporting the opposite (15-17). A similar interpretation can be made with our results. Of the 9 patients with severe eosinophilia, 1 (11.1%) was associated with asthma, 2 (22.2%) with malignancy, and 6 (66.6%) with acute pulmonary infections. In other words, acute inflammatory conditions found to be more common than a permanent or chronic disease. When talking about peripheral eosinophilia and lungs, EGPA has been one of the diseases that comes to mind most in the differential diagnosis, although it is very rare (8, 18, 19). Until recently, diagnostic criteria published in 1990 were used to diagnose EGPA (8). Chest Diseases physicians were able to perform unnecessary tests for EGPA in many patients with eosinophilia and asthma, triggered by these criteria. The control group of the old diagnostic criteria, which was obtained from only 20 patients, included 787 patients with large vessel vasculitis such as giant cell arteritis, which is very easy to distinguish from EGPA. While the very high specificity (99.7%) of the old criteria was attributed to this methodology, its sensitivity (85%) is considered quite low. The 3 of the 6 criteria in the old definition were closely related to pulmonary conditions, and asthma, peripheral eosinophilia and transient lung infiltrates all of who are not uncommon in clinical practice. Despite all these methodological weaknesses, the 1990 ACR criteria have survived unchanged for approximately 22 years. This confusion has been largely clarified with the new guideline published in 2022 (9). When the old criteria were applied to the new 2022 criteria, sensitivity decreased further (44%), although it maintained excellent specificity (99%) (95% CI 0.68–0.75). In other words, with the old criteria, the test had a high probability of overdiagnosis. Considering that these criteria included findings such as migratory lung infiltrates, unnecessary tests were also required (8). According to the new criteria, a patient with a diagnosis of small or medium vessel vasculitis can be classified as EGPA if the cumulative score is ≥6 points. In the guideline, the sensitivity of these criteria is stated as 85% and the specificity as 99% (CI 95%). In light of these results, the guideline has been approved for this new diagnostic scoring for EGPA (9). So, what should we pay attention to in the new EGPA criteria from a Chest Diseases perspective? It can be said that the critical point is that the new criteria put the vasculitis condition at the top. In other words, looking for these criteria to diagnose a patient with small/medium vessel vasculitis seems to reduce this possibility. In cases with other organ vasculitis, the diagnostic journey for EGPA has the opportunity to continue if we detect conditions such as asthma, peripheral eosinophilia, bronchoalveolar lavage (BAL) eosinophilia (9). In other words, if this patient group is referred to us with a diagnosis of vasculitis, our job becomes much easier. On the other hand, vasculitis may be limited to the pulmonary area only. In this case, the need to demonstrate eosinophilic vasculitis in samples taken from our lung tissue becomes evident. This requirement reduces the contribution of samples such as BAL or transbronchial biopsy, where we are unlikely to show vasculitis (20-23). At this point, cryobiopsy, transthoracic tru-cut biopsies and surgical biopsies, which are larger and not subject to crush artifacts, may be more useful (24, 25). Cryobiopsies, with their minimally invasive nature, may be very advantageous in this regard in experienced hands. It is likely that cryobiopsy, in which both tissue eosinophilia and vasculitis can be demonstrated together, will stand out as an important diagnostic step in this patient group. With more experience, it is possible that cryobiopsy, which has taken its place in the diagnostic approach of idiopathic pulmonary

fibrosis (IPF), will be included in the diagnostic algorithms in vasculitic lung diseases such as EGPA (26). When we examined our own data according to the old criteria, it was seen that only 2 of 28 patients who underwent further examination with a preliminary diagnosis of EGPA had EGPA. If these cases had been evaluated according to the new criteria, it seems that only 3 patients would have undergone further examination in this regard. Our results also showed that the false positive rate of the old criteria was significantly higher than the new criteria (92.8% and 33.3%) ($p<0.001$). Of course, when examining these new EGPA criteria in patients, it should not be forgotten that the essential point is vasculitis. It is obvious that neglecting the vasculitis condition will lead to unnecessary examinations and invasive interventions with false positivity rates higher than the old criteria. This real-life data proves that the severity of peripheral eosinophilia with pulmonary symptoms and lung involvement can give clues about the true diagnosis and assist in diagnostic procedures. Particularly in patients with severe eosinophilia; malignancy, hematological diseases and connective tissue diseases should be considered. We can conclude that a multidisciplinary approach in patients with peripheral eosinophilia is necessary for a definite diagnosis and to avoid superfluous medical tests. As the role of eosinophils in acute and chronic lung diseases becomes more evident day by day, the need for clinicians to pay more attention to this issue and approach it individually has emerged. The mild and moderate eosinophilia can be primarily associated with infectious diseases and asthma, but other relatively rarer causes such as pulmonary thromboembolism, interstitial lung diseases, and pleural diseases should not be forgotten. Although most cases of severe eosinophilia are secondary to infectious diseases, the malignancies and hematological diseases should also be considered. This study demonstrates the importance of distinguishing between old diagnostic criteria and new classification criteria for EGPA. We believe that this information will prevent unnecessary advanced examinations and invasive procedures. It is now clear that the finding of vasculitis is essential and that we should not make a classification for EGPA only when other findings accompany it. Proper application of the current classification criteria regarding EGPA, which is among the causes of severe eosinophilia, will prevent unnecessary tests in this regard. Multidisciplinary approach should be prioritized in this patient group.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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