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ORIGINAL ARTICLE

Clinical and Serological Features of Eosinophilic and Vasculitic Phases of Eosinophilic Granulomatosis with Poliangiitis: a Case Series of 15 Patients

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Abstract

OBJECTIVES: Eosinophilic granulomatosis with poliangiitis (EGPA) which was previously called Churg-Strauss Syndrome, is classified into eosinophilic and vasculitic phases. To characterize the eosinophilic and vasculitic phases of the disease in terms of clinical findings, serology, and treatment.

MATERIALS AND METHODS: We included 15 EGPA patients in the study. The clinical, serological, and therapeutic characteristics and the treatment responses of the patients were recorded.

RESULTS: Thirteen patients were classified as being in the eosinophilic phase and two were classified as being in the vasculitic phase of EGPA. Initial symptoms were worsening asthma in all patients (n=15; 100%). All patients had rhinosinusitis, and 66.6% had hypersensitivity to nonsteroidal anti-inflammatory drugs. The two patients in the vasculitic phase did not have nasal polyposis. Pulmonary and nervous system involvement were the most common symptoms. The erythrocyte sedimentation rates (ESRs) of the two patients in the vasculitic phase were 65 mm/h and 55 mm/h, while ESR was normal in eosinophilic-phase patients. Antineutrophil cytoplasmic antibodies (ANCA) was detected in one patient (6.6%) who was in the vasculitic phase (Case 15). The disease was under control with higher doses of methylprednisolone in the vasculitic phase (Case 14: 12 mg/day, Case 15: 10 mg/day) than in the eosinophilic phase. Relapse was detected in the two patients in the vasculitic phase. Oral corticosteroid was not discontinued in any case, and no mortality was reported.

CONCLUSION: Patients with eosinophilic phase or vasculitic phase EGPA had similar clinical onset. However, higher ESR, ANCA positivity, and extrapulmonary organ involvement were only found in patients in the vasculitic phase. Corticosteroid responsiveness was very good in all patients in the eosinophilic phase, and the disease could be controlled with a very low maintenance dose of a corticosteroid.

KEYWORDS: Asthma, Churg-Strauss syndrome, eosinophilic granulomatosis with poliangiitis, eosinophilic phase, vasculitic phase

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INTRODUCTION

Eosinophilic granulomatosis with poliangiitis (EGPA), which was previously called Churg-Strauss syndrome, is a necrotizing systemic vasculitis of small to medium-sized vessels [1,2]. The criteria used for classification of vasculitis were established by the American College of Rheumatology (ACR). These criteria can only be used to define vasculitis type and cannot be used for diagnosis. The criteria consist of the following six items: asthma, eosinophilia (>10%), neuropathy, migratory pulmonary infiltrates, paranasal sinus abnormalities, and biopsy-proven extravascular eosinophils. Diagnostic yield for EGPA is reported with a sensitivity of 85% and a specificity of 99.7% when at least four of these criteria are met [3,4]. Although EGPA belongs to the spectrum of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, ANCA positivity is reported to be approximately 40-60%. The necrotizing vasculitis is missed in many pathological studies, but non-destructive eosinophilic infiltration can be detected in the vessel walls of most of the patients [5].

The manifestation of the disease varies from mild disease- including asthma, nasal polyps, and cutaneous lesions- to severe gastrointestinal (GI) or heart involvement and disabling multiplex mononeuropathies [6,7], which can be life threatening. EGPA is usually described as going through the following three phases: 1) *Prodromal phase*: Allergic rhinitis, recurrent sinusitis, and nasal polyposis, 2) *Eosinophilic phase*: eosinophilia in the peripheral blood and tissues without proven vasculitis, and 3) *Vasculitic phase:* constitutional symptoms such as fever, weight loss, fatigue, and vasculitis of small to medium-sized vessels [6,7].

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In this study, we characterized patients with EGPA. The baseline characteristics, clinical manifestations, phases at time of diagnosis, and treatment responses of the disease were analyzed. The clinical and serological features of both the eosinophilic and vasculitic phases of the disease were also evaluated.

MATERIALS AND METHODS

The Ethics Committee of Erciyes University approved the study protocol, and all subjects provided written informed consent. Fifteen patients with EGPA who were admitted to the Chest Diseases Department of Erciyes University Hospital between May 2012 and May 2014 were included in this study. The following clinical, serological, and pathological data obtained from medical records were reviewed and evaluated.

Patient characteristics: age, sex, smoking history, age at the diagnosis, atopy, nasal polyposis, allergic rhinitis and/or rhinosinusitis, asthma, non-steroid anti-inflammatory drug (NSAID) hypersensitivity, and NSAID-exacerbated respiratory disease (NERD).

Laboratory and functional tests: blood eosinophilia, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), total immunoglobulin E (IgE), ANCA, troponin, urinalysis, liver and renal function tests, and pulmonary function tests, including forced expiratory volume in first second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC.

Imaging tests: high-resolution computerized tomography of thorax (HRCT), paranasal sinus computerized tomography (PNSCT), echocardiography (ECHO), electromyography (EMG), and cranial magnetic resonance imaging (MRI).

Treatment: Systemic corticosteroids and immunosuppressants.

Prognosis data: Relapse rates and survival.

The eosinophilic phase of EGPA was diagnosed if four or more of the ACR criteria were met after excluding other causes of eosinophilic infiltration. The vasculitic phase was diagnosed when four or more of the ACR criteria were met along with biopsy-proven vasculitis.

The following systems were examined for organ involvement: The peripheral nervous system (PNS) and the central nervous system (CNS), the kidneys, the heart, the GI tract, the lungs, and the skin. EMG-confirmed mononeuropathy or polyneuropathy was considered as peripheral neurological involvement. Cardiac involvement was diagnosed by ECHO and increased troponin without other risk factors. Renal involvement was diagnosed with increased serum creatinine, proteinuria, or abnormal urinary sediment that could not be attributed to other diseases. Lung involvement was diagnosed by the presence of centrilobular nodules, bilateral ground glass opacities, and thickened bronchial wall on HRCT. Involvement of GI the tract was diagnosed by unexplained abdominal pain, nausea, vomiting, diarrhea, and hemorrhage during a vasculitic flare after excluding any other possible underlying etiology and was proven by endoscopic biopsy.

The occurrence or reappearance of EGPA features other than asthma was considered as relapse. Remission was considered when the patient was symptom-free for at least one year [8]. Asthma or sinusitis exacerbations, with or without eosinophilia, were considered as alterations in disease activity, also called grumbling disease, but not as relapse.

Statistical Analysis

Statistical analyses were performed in Statistical Package for the Social Sciences version 15.0 (SSPS Inc.; Chicago, IL, USA). A One-Sample Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables for normality, and data were presented as mean±standard deviation (SD) or median and quartiles where appropriate. Categorical variables were expressed as frequencies and percentages.

RESULTS

Out of 15 cases, 11 were female with a mean age of 44.1±9.8 years. The youngest age at diagnosis was 22 years. Dyspnea was the presenting symptom of all patients, and they all had asthma and rhinosinusitis at the time of diagnosis of EGPA (Table 1). Ten (66.6%) had comor-

Table 1. Characteristics of patients with EGPA at the time of diagnosis

Female, n (%)	11 (73.3)
Age at the time of diagnosis, mean±SD, years	42±9.8
Follow-up duration, mean±SD, (range), years	1.7±0.5 (0.5-2)
Smoking, n (%)	
Current smokers	1 (6.6)
Ex-smokers	2 (13.3)
Non-smokers	12 (80)
Housewife, n (%)	10 (66.6)
Presence of atopy, n (%)	3 (20)
Pollens, n (%)	3 (20)
House dust mites, n (%)	3 (20)
Molds, n (%)	1 (6.6)
Underlying disorders, n (%)	
Asthma	15 (100)
Rhinosinusitis	15 (100)
Nasal polyps	10 (66.6)
NSAID hypersensitivity	10 (66.6)
Asthma duration before diagnosis [median, (range)], years	10 (1-30)
Nasal polyposis duration before diagnosis [median, (range)], years	10 (3-20)
Hospitalization due to asthma in preceding years mean±SD	1.1±0.8
Admission to emergency room due to asthma in preceding years mean±SD	6±2.7

SD: standard deviation; NSAID: non-steroid anti-inflammatory drug

bid NSAID hypersensitivity. All of the patients had severe asthma and were prescribed step 4 or step 5 medications according to the GINA guideline [9]. They were followed for 1.7±0.5 years (range: 0.5-2 years). All had peripheral blood eosinophilia (21.2%±11.1%) (Table 2). ANCA was detected in one patient (6.6%) who was in the vasculitic phase (Case 15).

Upper airway pathologies, which were present in all cases, were documented on PNSCT and rhinoscopy. Ten patients (66.6%) had nasal polyposis. The two patients in the vasculitic phase (13%) had PNS damage that was documented with EMG (Table 3). Only two patients were biopsied, which included the GI tract (Table 4), and vasculitis was confirmed in the two GI tract biopsies. Two cases were considered to be in the vasculitic phase, and there were no signs of extrapulmonary involvement in the other 13 cases, which were considered as being in the eosinophilic phase. The HRCT lesions of all patients (both eosinophilic phase and vasculitic phase) were compatible with EGPA (Figure 1 and 2), and all patients met at least 4 criteria of the ACR.

Table 2. Laboratory, functional, and radiological data at the time of diagnosis of patients with EGPA

Eosinophil mean±SD, %	21.2±11.1
Total IgE, median (range), IU/mL	194 (45-2,974)
ESR, mean±SD, mm/h	18.1±18.3
CRP, mean±SD, mg/L	6.1±6
FEV_1, mean±SD, %	61.4±10.5
Thorax (HRCT), n (%)	
Ground-glass opacities	15 (100)
Centrilobular nodules	4 (26.6)
Bronchial wall thickening	3 (20)
Alveolar consolidation	2 (13.3)

EGPA: eosinophilic granulomatosis with poliangiitis; IgE: Immunoglobulin E; SD: standard deviation; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; FEV_1: forced expiratory volume in first second; HRCT: high-resolution computerized tomography of thorax

Response to initial glucocorticoid treatment was good in all patients. Only one patient was given additional immunosuppressive treatment with methotrexate (case 15). All were on oral corticosteroid treatment, 6±2.4 mg/day (range: 2-12 mg/day) methyl prednisolone. The disease was kept under control with higher methyl prednisolone doses in patients in the vasculitic phase (Case 14: 12 mg/day, Case 15: 10 mg/day) than those in the eosinophilic phase. None of the patients could discontinue oral corticosteroid treatment.

The majority of our patients (86.6%) experienced remission on treatment. Two patients (13.3%) experienced a disease relapse. Both of these patients were in the vasculitic phase, and the cause of relapse was lung involvement in both cases. Grumbling disease was experienced by all cases, and no mortality occurred on follow-up.

Table 3. Diagnostic criteria of patients with EGPA (n=15)

Patient no.	ACR Criteria number*	Asthma	Nasal polyposis	Analgesic hypersensitivity	Paranasal sinus abnormality (PNSCT)	Pulmonary infiltrates on thorax HRCT	Polyneuropathy (history and EMG), CNS involvement (Cranial MRI)	Biopsy containing a blood vessel with extravascular eosinophils
1	4	+	+	-	+	+		
2	4	+	+	+	+	+	-	
3	4	+	+	+	+	+	-	
4	4	+	+	+	+	+	-	
5	4	+	+	+	+	+	-	
6	4	+	+	+	+	+	-	
7	4	+	+	-	+	+	-	
8	4	+	-	-	+	+	-	
9	4	+	-	+	+	+	-	
10	4	+	+	+	+	+	-	
11	4	+	+	-	+	+	-	
12	4	+	+	+	+	+	-	
13	4	+	-	-	+	+	-	
14	6	+	-	+	+	+	+	+ (GI tract)
15	6	+	-	+	+	+	+	+ (GI tract)

*the number of ACR criteria present. EGPA: eosinophilic granulomatosis with poliangiitis; ACR: American College of Rheumatology; PNSCT: paranasal sinus computerized tomography; HRCT: high-resolution computerized tomography of thorax; EMG: electromyography; CNS: central nervous system; MRI: magnetic resonance imaging; GI: gastrointestinal

Table 4. Damaged organs and laboratory and functional data in patients with EGPA

	Damaged organs								Eosinophil	ESR	ANCA
Patient No.	CNS	PNS	Heart	Lung	GI	Kidney	Skin	UA	%	mm/h	
1	-	-	-	+	-	-	-	+	18	18	-
2	-	-	-	+	-	-	-	+	14	2	-
3	-	-	-	+	-	-	-	+	12	2	-
4	-	-	-	+	-	-	-	+	22	10	-
5	-	-	-	+	-	-	-	+	23	19	-
6	-	-	-	+	-	-	-	+	58	19	-
7	-	-	-	+	-	-	-	+	16	10	-
8	-	-	-	+	-	-	-	+	18	8	-
9	-	-	-	+	-	-	-	+	29	10	-
10	-	-	-	+	-	-	-	+	14	20	-
11	-	-	-	+	-	-	-	+	20	2	-
12	-	-	-	+	-	-	-	+	23	20	-
13	-	-	-	+	-	-	-	+	14	10	-
14	-	+	-	+	+	-	-	+	20	55	-
15	-	+	-	+	+	-	-	+	18	65	+

CNS: central nervous system; PNS: peripheral nervous system; GI: gastrointestinal;
UA: upper airway; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANCA: antineutrophil cytoplasmic antibody

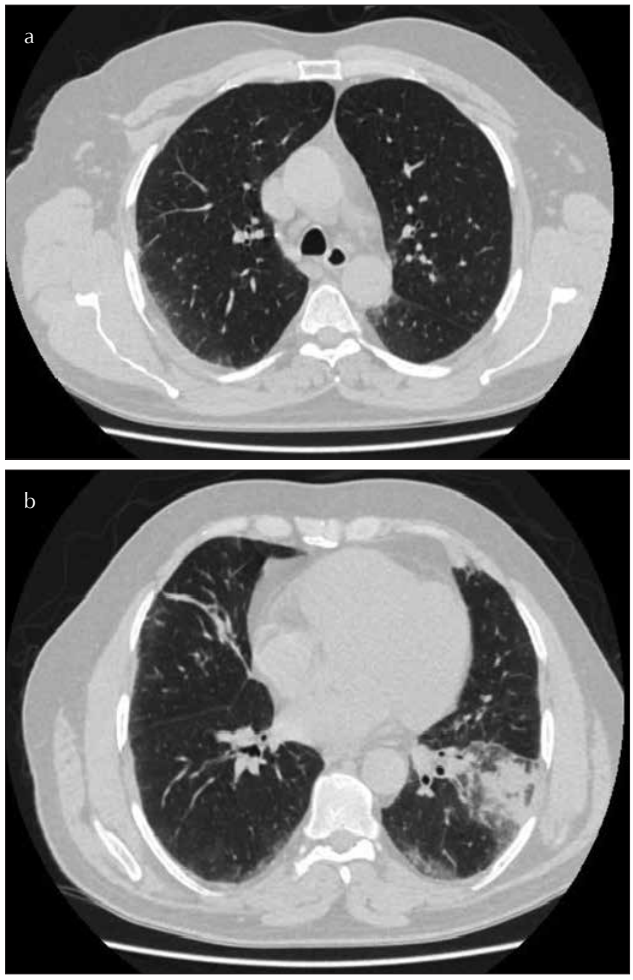

Figure 1. Centrilobular nodules mostly within the ground-glass opacity. Airspace consolidation, subpleural, and surrounded by the ground-glass opacity

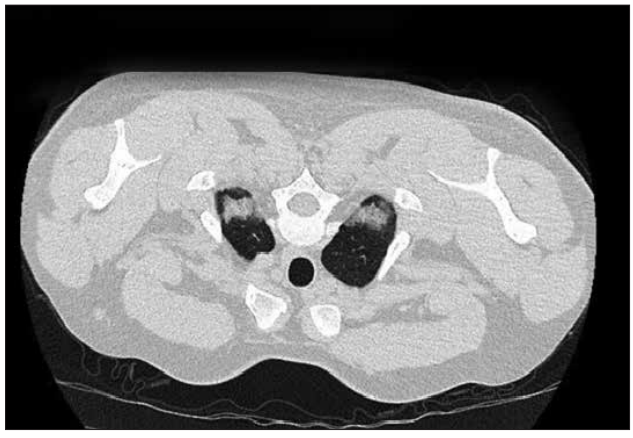

Figure 2. Bilateral ground-glass opacity in the upper lobes

DISCUSSION

Our case series had some important characteristics of EGPA phases. Although age, gender distribution, and prodromic EGPA phase were similar to previous studies, the organ/system involvements were different. The majority of patients were in the EGPA eosinophilic phase, and increased ESR, ANCA positivity, and extrapulmonary organ involvement were only found in the patients in the vasculitic phase. Corticosteroid responsiveness was very good in all patients in the eosinophilic phase, and the disease could be controlled with a very low maintenance dose of a corticosteroid.

Nasal polyposis and recurrent sinusitis characterize the prodromic EGPA phase [10]. Nasal polyps affect approximately half of the patients and can recur after surgery in patients not receiving immunosuppressive therapy [11]. In our study, the upper airways were affected in all patients, and two thirds of the patients had nasal polyposis. However, the two patients in the vasculitic phase did not have nasal polyposis.

These rates were similar to those of other studies [10-12]. The rate of NSAID hypersensitivity was similar (66%) to our previous study [12]. NSAID hypersensitivity is characterized by exacerbation of bronchoconstriction and other symptoms of asthma and/or upper airway symptoms (nasal congestion, rhinorrhea, and itching) after use of acetylsalicylic acid and/or other NSAIDs. In particular, hypersensitivity to cyclooxygenase-1 enzyme inhibitors is frequent among the EGPA cases with severe asthma [13]. This condition is also called aspirin-exacerbated respiratory disease or NSAID-exacerbated respiratory disease. Recurrent nasal polyps and increased peripheral eosinophilia are among the common characteristics of EGPA [14].

Commonly involved organs are the upper airway tract, lung, skin, heart, GI tract, and nervous system. The kidney is not a commonly affected organ in EGPA, but it might be involved in some patients, especially those with ANCA positivity [15]. The involved organs in our study had partial similarity with what has been seen in previous larger studies [6,8,16-18]. The lung was the most commonly involved organ in our series, and all of the patients in the eosinophilic phase only had pulmonary involvement. The clinical manifestations of patients referred to our department, which included asthma, eosinophilia, and pulmonary infiltrates, were most likely caused by lung involvement. Although PNS involvement was the second most commonly involved system in our series, its frequency was lower than in previous studies [6,8,16-18]. PNS involvement was only detected in patients in the vasculitic phase. GI system involvement was also only detected in patients in the vasculitic phase. GI tract involvement was also lower in our study with a frequency of 13.3% [6,8,16-18]. None of the patients had skin, heart, CNS, or renal system involvement.

The majority of the patients in our study were considered as being in the EGPA eosinophilic phase. EGPA and other small and medium-sized vessel vasculitides have been defined as clinicopathological entities to underline the fact that they require a combination of clinical and histopathological findings in order to be diagnosed with confidence [1-4,19]. The diagnosis of the eosinophilic phase of EGPA is rapid and convenient because pathological evidence is not mandatory in the ACR criteria. Thus, delayed diagnosis and the irreversible morbidity rate can decrease. However, using the criteria for diagnostic purposes might lead to the risk of overdiagnosis of the eosinophilic phase of EGPA in patients with milder eosinophilic diseases and might lead to overtreatment. In differential diagnosis of the EGPA eosinophilic phase, parasitic infections, chronic eosinophilic pneumonias, hypereosinophilic syndrome, NERD, allergic bronchopulmonary aspergillosis, microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's), lymphoreticular malignancies, and collagen vascular diseases should be considered. We considered all possibilities in the differential diagnosis of EGPA eosinophilic phases. Coincidental bacterial or viral pneumonia can occur in conjunction with asthma and eosinophilia, and therefore pneumonia must be excluded for the differential diagnosis of the EGPA eosinophilic phase. In our patients, pneumonia was ruled out by means of the patients' clinical and laboratory findings and corticosteroid response without antibiotics.

Thirteen patients in the eosinophilic phase met 4 criteria, and all of them had the prodromic phase of EGPA. In the present study, eosinophilic and vasculitic phase differentiation was not shown with transbronchial biopsy in patients who were considered to be in the eosinophilic phase of EGPA. Bronchoscopy could not be performed in these patients because they had severe asthma attacks at the time of diagnosis. Because of small-vessel vasculitis, the patients did not exhibit typical characteristics of vasculitis, which is considered by the combination of constitutional symptoms and paradoxical improvement of asthma. ESR is expected to be higher, especially during the phase of active vasculitis. Our patients who were considered to be in the eosinophilic phase had none of the above. ESR was normal in patients in the eosinophilic phase of the disease, while ESR was greater than 50 mm/h in patients in the vasculitic phase.

Anti-neutrophil cytoplasmic antibody positivity is an important laboratory finding of EGPA, and ANCA positivity, renal disease, peripheral neuropathy, and pulmonary hemorrhage are frequent among EGPA patients. Endomyocardial involvement and lung infiltrates are more common in the ANCA-negative subset [20]. ANCA, with an immunofluorescence pattern usually consisting of P-ANCA and anti-MPO specificity, is present in up to 40% of EGPA patients, but only a minority of patients have cytoplasmic ANCA with antibodies to proteinase 3 [21-23]. In our study, only one of the 15 patients (6.6%) was positive for ANCA, and this patient was in the vasculitic phase. The low ANCA profile in our study might be associated with low renal disease rate, as well as GI, neural system, and pulmonary involvement without hemorrhage.

Glucocorticoids and immunosuppressive treatments form the cornerstone of therapy for improved prognosis and survival rates of EGPA patients if they are given early [22,23]. The Five-Factor Score (FFS) is usually used to determine prognosis in EGPA, and patients with FFS ≥1 have a worse prognosis and higher mortality [17,24]. FFS consist of the following items: age >65 years, heart involvement, renal insufficiency, GI involvement, and ENT manifestations, which are associated with better outcomes, and ENT involvement absence is associated with a good prognosis [25]. In our study, only the two patients in the vasculitic phases had poor prognostic factors. In the patients in the vasculitic phase, it was possible to control the disease with higher doses of corticosteroids compared to patients in the eosinophilic phase of EGPA. Although we could not discontinue corticosteroid treatment, the disease activity was under control with low doses in the eosinophilic phase of EGPA.

In conclusion, patients in the eosinophilic phase or vasculitic phase of EGPA had similar clinical onsets. However, higher ESR, ANCA positivity, and extrapulmonary organ involvement were only found in patients in the vasculitic phase. Corticosteroid responsiveness was very good in all patients in the eosinophilic phase, and the disease could be controlled with a very low maintenance dose of a corticosteroid.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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