Eosinophilic Lung Disease: Accompanied with 12 Cases

Tülin Sevim¹, Emine Aksoy¹, Fatma Tokgöz Akyıl¹, Meltem Coşan Ağaç¹, Nilüfer Aykaç Kongar², Ferhan Özteker¹

¹Clinic of Chest Diseases, Süreyyapaşa Chest Diseases and Chest Surgery Training and Research Hospital, İstanbul, Turkey
²Department of Chest Diseases, Gayrettepe Florence Nightingale Hospital, İstanbul, Turkey

OBJECTIVES: Eosinophilic lung diseases are rare group of heterogeneous diseases characterized by the increase of the eosinophil ratio in airways and lung parenchyma. In our clinic, patients diagnosed with eosinophilic lung disease were evaluated with their clinical features and prognoses.

MATERIAL AND METHODS: In our clinic, 12 cases that were diagnosed and followed up for eosinophilic lung disease (eosinophilic granulomatosis with polyangiitis (EGPA, Churg–Strauss syndrome) (n=4), chronic eosinophilic pneumonia (CEP) (n=7), and simple pulmonary eosinophilia (Löffler's syndrome) (n=1)) were retrospectively evaluated.

RESULTS: Of the 12 cases, 8 were females, and the average age was 43 (28–72) years. All cases were undergoing bronchodilator therapy with asthma diagnosis (2 months–40 years). Additionally, 4 of the cases had sinusitis, and 1 had allergic rhinitis. The most common complaints of the patients were difficulty in breathing and coughing, and the duration of complaints was a median of 2 months. Peripheral eosinophilia and total IgE elevation were present during the admission of all cases; additionally, leucocyte elevation was recorded in 10 of them, anemia in 4 of them, and thrombocytosis in 4 of them. Moreover, 43% of the recorded DLCO values were lower than normal. Of the 10 cases that underwent bronchoalveolar lavage (BAL), the eosinophil ratio was above 25% in 7 subjects. Of the 8 cases that underwent transbronchial biopsy, eosinophil-involving infiltration was detected in 6 subjects. Additional findings in cases diagnosed with EGPA were nasal polyposis (n=1), sinusitis (n=2), polyneuropathy (n=1), cardiac involvement (n=2), and skin involvement in biopsy (n=1). Spontaneous recovery was observed in the patient diagnosed with simple pulmonary eosinophilia during the follow-up that was performed based on the history and laboratory and BAL results of the patient. Prednisolone treatment was started for all cases, except for simple pulmonary eosinophilia, and their controls were performed. Relapse was observed in eight cases (EGPA: 4, CEP: 4); during the relapse treatment of one case diagnosed with EGPA, exitus occurred. One case rejected treatment despite the presence of peripheral eosinophilia, and the other cases are being followed-up without medication.

CONCLUSION: Given that the clinical pictures in pulmonary eosinophilia syndromes are on a wide spectrum, a specific diagnosis is important. Progression may differ in each patient, and a close follow-up is necessary during and after the treatment.

KEYWORDS: Churg–Strauss syndrome, eosinophilic granulomatosis with polyangiitis, chronic eosinophilic pneumonia, Löffler’s syndrome

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INTRODUCTION

Eosinophils are leukocytes with polymorphic nuclei that play a role in host defense against helminth parasites and allergic reactions, and they are most densely found in the skin, lung, and gastrointestinal and urogenital systems. These cells, which carry specific proteins in their cytoplasmic granules, can cause cytotoxic damage in the lung and other tissues by the additional cytokine and inflammatory mediators that they secrete when they become overactive [1-3].

Eosinophilic lung diseases are a rare group of diseases characterized by tissue or peripheral eosinophilia with infiltration in the lung [4]. In this study, the clinical-radiological findings, treatments performed, treatment responses, and prognoses of patients diagnosed in our clinic with eosinophilic lung disease via bronchoalveolar lavage (BAL) or transbronchial biopsy (TBB) between 2004 and 2013 were retrospectively evaluated.

MATERIALS AND METHODS

Among the patients that underwent BAL or TBB, due to various reasons, between 2004 and 2013, the files of patients that...
were detected to have eosinophilia in their BAL fluid or ones that were detected to have eosinophilic infiltration in their TBBs were retrospectively evaluated. Informed consents were obtained from the cases for publication, and their symptoms and findings, demographic features, and smoking habits were recorded from their medical files. Routine hemogram, biochemistry, posteroanterior chest radiographies, pulmonary computed tomography (CT), respiratory function test (RFT), diffusion capacity for carbon monoxide (DLCO) measurements, and bronchoscopic findings were examined, and treatment and follow-up results were recorded.

Detection of eosinophilia in BAL fluid with infiltration in the lung or detection of eosinophilic infiltration from the pulmonary parenchymal tissue in TBB was defined as eosinophilic lung disease. Exclusion of the causes of other eosinophilic lung diseases, in accompaniment with consistent clinical, radiological, and laboratory findings, was accepted as the diagnostic criteria for chronic eosinophilic pneumonia [5]. The 1990 American College of Rheumatology diagnostic criteria were used for eosinophilic granulomatosis with polyangiitis (EGPA) diagnosis [6,7].

**Statistical Analysis**

Patient data were recorded using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) 16.0 program. Values were given as average±standard deviation (SD).

**RESULTS**

Eosinophilic lung disease was detected in 12 of the cases who underwent BAL and/or TBB between 2004 and 2013 in our clinic. Of these cases, 8 (67%) were women, and the average age was 43 years. The most common complaints were difficulty in breathing and coughing, with a median of 2 months (15 days–1.5 years). Four (33%) cases had a history of smoking cigarettes.

Upon admittance to our clinic, all cases were undergoing treatment for asthma, with a median of 2 years (2 months–40 years). There were histories of sinusitis in four cases, and histories of allergic rhinitis, hypertension, nasal polyposis, immunotherapy, and anti-IgE in one case each.

Apart from peripheral eosinophilia and total IgE elevation, leukocytosis (n=10), anemia (n=4), and thrombocytosis (n=4) were recorded. ANCA was negative in seven cases. In the spirometric examinations, a mixed breathing pattern was observed in half of the cases (n=5), and a normal breathing pattern was observed in two of the cases. DLCO values were low in 3 of the 7 cases.

In pulmonary CT imaging analysis, 10 (84%) cases had bilateral involvement, and the most common radiological pictures were ground-glass opacity (66%), nodular lesions (42%), and consolidation (33%).

Bronchoalveolar lavage was performed in 10 patients, and eosinophils comprised more than 25% of the total cell count in 6 of them (60%). Eosinophil-involving infiltration in the parenchymal tissue was reported via TBB in 6 of the 8 cases (75%).

Based on these findings, 7 cases were diagnosed with CEP, 4 cases with EGPA, and 1 with simple pulmonary eosinophilia (SPE). When we look at the clinical feature of patients, we observed the following:

Five (71%) of the chronic eosinophilic pneumonia cases were women; 2 have a history of smoking cigarettes. Sinusitis (n=2), allergic rhinitis (n=1), and hypertension (n=1) were additionally detected in cases diagnosed with asthma, for an average, 1 year.

Two (50%) of the cases diagnosed with EGPA were women. Two have a history of smoking cigarettes; the duration of asthma was, on an average, 2 years. Additionally, sinusitis (n=3) and nasal polyposis (n=1) were other comorbidities. Skin lesions were detected in 3 of our cases, cardiac involvement in 2 (acute coronary syndrome in 1 case, pericarditis in 1 case), and mononeuritis multiplex in 1. In one of our cases, anti-IgE treatment was started because of uncontrollable asthma, and diagnosis was made based on the parenchymal lesions that developed under this treatment.

The SPE case did not smoke and had an asthma diagnosis for 2 years. In the anamnesis, the case stated finding parasites in the stool.

The laboratory and functional features of the patients are shown in Table 1.

In lung imaging analysis, bilateral involvement was observed in 85% of CEP cases and in 75% of EGPA cases, while dominant involvement was observed in the upper areas in approximately half of the cases. Consolidation was recorded as more common in CEP cases (CEP: 43%, EGPA: 25%), and nodular lesions were recorded as more common in EGPA (EGPA: 75%, CEP: 29%). Radiological patterns are shown in Table 2.

The eosinophil percentages in BAL was 60% in the SPE case, and, on an average, 48% and 30% in CEP and EGPA cases, respectively (Table 3). Eosinophil-involving infiltration was reported in the 2 EGPA cases that underwent TBB, and it was

| Table 1. Laboratory and functional parameters of the cases* |
|-------------------------|-------------------------|-------------------------|
|                          | EGPA (n=4)              | CEP (n=7)               | SPE (n=1)               |
| Eosinophil (%)           | 29.2 (17–52)*           | 36.1 (30–70)*           | 22.2                    |
| WBC (10⁹/L)              | 14.6                    | 13.6                    | 18.8                    |
| Hb (g/dL)                | 12.5                    | 13.4                    | 14.2                    |
| IgE                     | 604 (269–23,000)*       | 775 (206–835)*          | 1710                    |
| FEV₁ (%)                | 58                      | 66                      | 93                      |
| FVC (%)                 | 74                      | 70                      | 94                      |
| FEV₁/FVC                | 105                     | 84                      | 104                     |
| DLCO (%)                | 62                      | 102                     | 84                      |

*The median values are given for all parameters.

SPE: simple pulmonary eosinophilia; CRP: C-reactive protein; DLCO: diffusing capacity of the lungs for carbon monoxide; EGPA: eosinophilic granulomatosis with polyangiitis; FEV₁; %: forced expiratory volume in 1 s, predicted %; FVC%; forced vital capacity, predicted %; Hb: hemoglobin; CEP: chronic eosinophilic pneumonia; PLT: platelet; WBC: white blood cell.
reported in 4 of the 6 CEP cases. In one patient, extravascular eosinophilia was detected in the sampling conducted to the skin lesion in the dorsum of hand.

Apart from the SPE case, corticosteroid treatment (1 mg/kg prednisolone) was started, and a 6-month/1-year treatment was planned by lowering the dose according to the clinical response. The corticosteroid dose was increased or restarted in case of relapse.

In one EGPA case, in the second year of the diagnosis, exitus occurred while under treatment (Figure 1). In the 1–9-year follow-ups of three cases, relapse was observed. One of the relapse cases is under initial relapse treatment, 1 of them is being followed up with low-dose steroid treatment, and the final case is being followed up without medication (Figures 2, 3).

One of our seven CEP patients refused treatment. Relapse was observed in 4 cases (2 cases once and 2 cases twice), and 2 cases are stable without relapse (Figures 4, 5, 6).

The SPE case was informed about the possibility of SPE due to observing parasites in the stool and BAL eosinophilia, and showed spontaneous radiological and clinical recovery without treatment 1 month later (Figure 7). The case is still stable in the fourth year of diagnosis.

**DISCUSSION**

Eosinophilia is defined as the eosinophil count being more than 5% in peripheral smears [8]. Eosinophilic lung disease is defined as the eosinophil infiltration of pulmonary parenchyma (with or without peripheral eosinophilia) that is proved by BAL or biopsy [2].

Basically, eosinophilic lung diseases are classified as those whose causes are known and those whose causes are...
unknown. Those whose causes are unknown include SPE, acute eosinophilic pneumonia, CEP, EGPA, idiopathic hypersensitivity syndrome, whereas allergic bronchopulmonary aspergillosis, bronchocentric granulomatosis, parasite infections, and drug reactions are interpreted among those whose causes are known [9]. In our study, the features of 4 EGPA cases, 7 CEP cases, and 1 SPE case were discussed.

Chronic eosinophilic pneumonia was first defined in 1969 by Carrington et al. [10]. It is a chronic disease that may be progressive; that is observed more commonly during the middle-ages and in women; that can be accompanied by total IgE elevation, anemia, and thrombocytosis along with pulmonary infiltrations and peripheral eosinophilia; and that relapses can be observed. Obstruction and restriction can be present in spirometric evaluation [10-16]. The eosinophilia percentage can be very high in the BAL fluid [2, 17]. Symptoms that lasted for longer than 2 weeks, eosinophilia increase in airways and/
or blood, presence of more intense pulmonary infiltrations in the periphery, and exclusion of other eosinophilic lung diseases are accepted as sufficient for diagnosis [5]. Although some drugs, blood transfusions, and parasitic infections are in its etiology, it is generally idiopathic [4]. In our study, 5 of our 7 CEP cases were women, and the average age was 47 years, with a median complaint period of 1.5 months. Anemia was detected in 2 cases, thrombocytosis in 1, and mixed function disorder in 3. The BAL eosinophil percentage was below 25% in 2 cases, while the average of those with high percentages was 65%. TBB was performed in four of the CEP patients, and eosinophilic inflammation was demonstrated in the pulmonary parenchymas of those four patients.

Photographic negative shadow of pulmonary edema, which is reported to be typical in CEP, is observed in approximately 25% of patients in the lung radiology analysis [5]. In CT, consolidations involve a more dominant air bronchogram.
mostly in the periphery, but ground-glass areas and nodular and reticular images can also be observed [11,18,19]. In our cases, photographic negative shadow of the classic pulmonary edema was not detected. Three cases had a dominant involvement in the upper areas, whereas ground-glass was recorded in 4 cases and reticular marks in 2 cases. Ground-glass opacities were patchy in 3 of the 4 cases.

A 10% spontaneous recovery without treatment is reported for chronic eosinophilic pneumonia [20]. With treatment, recovery begins within days after treatment with corticosteroids, and a complete resolution is observed after a treatment of 6–12 months. Relapse is common and is most commonly reported when the steroid dose is being lowered [21,22]. In the 1–5-year follow-up of our 6 cases whose treatments were completed, a total of 6 relapses were observed in 4 cases. Three of the relapses occurred during the initial treatment when the steroid dose was being lowered. In case of a relapse, the steroid dose was increased or restarted with the dose that established remission.

Eosinophilic granulomatosis with polyangiitis was defined as asthma, hypereosinophilia, and vasculitis by Churg and Strauss in 1951, as the Churg–Strauss syndrome (CSS) [7]. Initially named CSS, changing the name to “eosinophilic granulomatosis with polyangiitis” was recommended in the 2012 Chapel Hill Consensus Conference to attract attention to the histopathology of the disease. It is characterized by the eosinophil-rich necrotizing granulomatous inflammation in respiratory tracts and by necrotizing vasculitis, most commonly in small or mid-sized veins, which accompany asthma and eosinophilia [23]. The incidence of EGPA is reported as 2.4 in one million [24]. The disease affects both sexes equally, and it can occur in all ages, the average being the 50s. Its etiology is unknown. Autoimmunity is considered to be influential regarding genetic and environmental factors. In EGPA, asthma is 90% found prior, and it is generally accompanied with allergic rhinitis, nasal polyposis, and sinusitis. The first of the three stages defined for the disease is the prodromal stage. Atopic asthma and rhinitis that can be difficult to control is dominant, and it can last for many years. This stage is followed by the eosinophilic stage that involves the eosinophilia infiltration of the lung and various organs, after which the vasculitic stage ensues, observed with severe systemic vasculitis [25-28].

Eosinophilic granulomatosis with polyangiitis cases that develop after leukotriene antagonist use are controversial for years. In particular, the fact that the use of steroids in mild-advanced asthma patients can mask underlying EGPA symptoms makes one think that findings occur because of decreasing the dose of steroid with the use of leukotriene antagonist in these patients [29-30]. In the recent years, it is known that EGPA develops in patients that use anti-IgE as well [31]. Anti-IgE use prior to EGPA diagnosis was present in one of our cases as well. In Turkey, an EGPA case whose symptoms were triggered with clarithromycin use was also reported [32].

In the disease, 75% skin-muscle involvement (vasculitic purpura, livedo reticularis, subcutaneous nodules), 75% neurological involvement (most commonly peripheral neuropathy and mononeuritis multiplex), and 27%-47% cardiac involvement (ECG changes, eosinophilic myocarditis, coronary vasculitis, and pericardial effusion) are observed. Cardiac involvement can be an indicator of a poor prognosis, and it is more commonly reported in ANCA-negative patients. Renal involvement (most commonly focal and segmental necrotizing glomerulonephritis) and gastrointestinal system involvement (stomach ache caused by eosinophilic gastroenteritis and vasculitis) are also reported. Pancreatitis, gastrointestinal perforation, and hemorrhage indicate underlying vasculitis and are accepted as the indicator of a poor diagnosis [25,26,33-35]. In our study, paranasal sinus involvement was present in 3 patients, nasal polyposis in 1 case, skin involvement in 3 cases, cardiac involvement in 2 cases, and neurological involvement in 1 case.

In the 5-year follow-up study of 353 EGPA cases, Comarmond et al. [36] reported relapse in 97 of them (25%) and death in 45 of them (12%). Deaths occurred with a median of 21 months, and the causes could not be determined in 13 cases.
Cardiac involvement (n=14), malignancy (n=5), infection (n=5), active vasculitis (n=4), and respiratory failure (n=4) are indicated as causes of death. In one of our cases, exitus occurred because of respiratory failure after clinical-radiological progression at the second year of the diagnosis. Relapse occurred twice in one case and once in one case, and the 4 mg methylprednisolone treatment of both patients is still stable. In our fourth case, relapse did not occur after the initial treatment. In the recent years, it was reported that cyclophosphamide, intravenous immunoglobulin, rituximab, and mepolizumab, which is an anti-IL-5 antibody, can also be used in EGPA patients where corticosteroid is not sufficient [37-39].

Simple pulmonary eosinophilia is a benign disease with unknown causes or that can develop secondarily because of reasons such as drugs and parasites and that is observed with mobile pulmonary opacities, eosinophil increase in peripheral blood, minimal respiratory symptoms, and spontaneous resolution. Pulmonary infiltrations are generally peripheral- and pleural-based [40, 41]. In our CPE case, bronchodilator treatment was started 2 years ago with asthma diagnosis, and the case consulted our clinic with a complaint of ongoing coughing. Peripheral eosinophilia and infiltrations were present in the case, and 60% eosinophils were detected in the case’s BAL fluid. Spontaneous remission was observed in the follow-up.

In conclusion, specific diagnosis is important for prognosis in eosinophilic lung diseases. The clinical course is quite variable in these cases, and a close follow-up is necessary during and after the treatment.

Ethics Committee Approval: Ethical committee approval was not taken due to retrospective case series design of the study.

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

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