The role of peripheral eosinophilia in diagnosing lung disorders: experience from a single pneumonological center

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Background: Eosinophilia is rare but one of the important reasons to refer patients to pneumonological centers. Determining etiology of eosinophilia has practical implications for therapeutic intervention and disease prognosis. The study aimed to determine the role of peripheral eosinophilia in the diagnosis of lung disorders.

Methods: In this retrospective study were included 46 patients diagnosed with peripheral eosinophilia with coexisting respiratory symptoms and/or radiologically detected lung lesions. All patients underwent standard diagnostic procedures, including a detailed clinical history review, physical examination, routine laboratory tests with basal cardiological examinations, and serological tests to detect parasites and allergies. Other procedures carried out depended on the symptoms of each patient. The relation between eosinophil counts in the blood and patients’ clinical manifestation was investigated to identify the degree of eosinophilia requiring immediate diagnostic procedures and treatment. Statistical analyses were performed using scientific computation libraries in the Python programming language, SciPy, v. 1.3.1. Briefly, the following tests were used: parametric Kruskal-Wallis H test, an independent t-test, ANOVA, the Shapiro-Wilk test, Fisher’s and Chi-squared tests, and the Holm-Bonferroni method.

Results: Severe eosinophilia (≥5,000 cells/μl) was associated with extrapulmonary involvement and constitutional symptoms. Skin, heart, and pleural diseases were more frequent in these patients than in patients with mild or moderate eosinophilia (p=0.010, p=0.040, and p=0.007, respectively), and only these patients showed signs of kidney disease (p=0.006). Vasculitis was significantly more frequent in the severe eosinophilia group (p=0.048) than in the other two groups. In patients with moderate eosinophilia (1,500-5,000 cells/μl), extrapulmonary symptoms were less common, although signs of cardiac involvement were confirmed in 44% of subjects. In this group, vasculitis was the most commonly observed disease (42% of cases). Mild eosinophilia (<1,500 cells/μl) was mainly associated with airway disease. In this group, vasculitis and interstitial lung diseases were identified, but most were not typically connected with eosinophilia.

Conclusions: Identification of peripheral eosinophilia may essentially determine diagnostic procedures in patients with lung disorders and may be a useful indicator of disease etiology.

Key words: Eosinophilia; diagnostics; lung disorders.

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Ethics approval and consent to participate: This was a retrospective analysis, obviating the need for approval from the local Ethics Committee, as routine procedures were used for clinical diagnosis and treatment of eosinophilia.
**Introduction**

One of the reasons for referring patients to pneumological centers is the identification of peripheral eosinophilia, which is defined as an increase in the number of eosinophils in peripheral blood exceeding 500 cells/μL [1,2]. Traditionally, eosinophilia has been classified by three stages: mild (exceeding the upper limit of normal, but fewer than 1,500 cells/μL), moderate (from 1,500 to 5,000 cells/μL), and severe (above 5,000 cells/μL) [3]. Eosinophilia can be transient, episodic, or persistent. Detection of elevated eosinophil counts in the blood on at least two occasions in an interval of time spanning more than one month is a necessary condition for diagnosing this white blood cell abnormality [1].

There are many causes of peripheral eosinophilia; the most common are allergic conditions, parasitic and fungal infections, as well as drug-related reactions. Rarer causes include vasculitis and primarily eosinophilic granulomatous with polyangiitis (EGPA), though it can also accompany granulomatosis with polyangiitis (GPA) [4]. In these clinical situations, interstitial lung disease usually occurs in connection with eosinophilic infiltration. The most common disorders typically associated with eosinophilic infiltrations limited to the lung are acute and chronic eosinophilic pneumonia (AEP and CEP, respectively). The diagnosis of eosinophilic lung diseases primarily relies on characteristic clinical-imaging features and demonstration of alveolar eosinophilia defined by differential cell counts of at least 25% eosinophil cells in bronchoalveolar lavage fluid (BALF); in these cases, lung biopsy is generally unnecessary. In other conditions, however, when there is an absence of eosinophilia in BALF, lung biopsy is typically needed. Pathomorphological evidence of lung eosinophilia requires more extensive infiltration by eosinophils exceeding the upper limits of the normal physiological range [5,6].

Determining the etiology of eosinophilic lung disorders has practical implications for therapeutic intervention and disease prognosis. Indeed, in most cases, oral corticosteroids are the key treatment, but in others, discontinuation of drug therapy or treatment of parasitic or fungal infections may be necessary. Additionally, there are many respiratory disorders that can be associated with mild eosinophilia, including asthma or organizing pneumonia (OP), but because their associations with eosinophilia is weak and usually do not affect the course of the disease, they are not considered to be eosinophilic lung diseases [7,8]. In these cases, there is usually no need for treatment of eosinophilia, although these patients, especially those with asthma, should still be monitored for the possible development of eosinophilic lung or systemic diseases. Patients with severe asthma and eosinophilia constitute a special group. In these cases biological drugs are the means of two numerical variables. Means of age were assessed using t-tests, while medians were assessed using the non-parametric Kruskal-Wallis test. For comparison of certain variables' median values, the non-parametric Kruskal-Wallis H test was used. An independent t-test was performed to compare the means of two numerical variables. Means of age were assessed.

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**Methods**

The study was conducted within the statutory activity of the National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland; research task nr 7.28; *Causes of eosinophilia in patients referred to the Pneumological Department*. It was a retrospective analysis, obviating the need for approval from the local Ethics Committee, as routine procedures were used for clinical diagnosis and treatment of eosinophilia. However, all procedures performed in the study were in accordance with the ethical standards of the institutional and national research committee, and with the tenets of the 1964 Declaration of Helsinki and its later amendments.

**Patients and study design**

The study included consecutive patients diagnosed with peripheral eosinophilia (>500 cells/μL) with coexisting respiratory symptoms and/or radiological lung lesions detected at admission in the Department of Pneumonology of the National Tuberculosis and Lung Diseases Research Institute over the period from 2017 to 2019. There were 35 females (76.1%) and 11 males (23.9%), with a median age of 46.5 years (range: 19-76 years). Suspected causes of eosinophilia were ANCA (antineutrophil cytoplasmic antibody)-associated vasculitis (AAV) in 27 patients, CEP in six patients, allergic bronchopulmonary aspergillosis (ABPA) in five patients, asthma in four patients, lung tumor in two patients, hypersensitivity pneumonitis (HP) in one patient, and organizing pneumonia (OP) in one patient. Eosinophilia was considered to be mild when eosinophil count in the blood was 500-1,500 cells/μL, moderate at 1,500-5,000 cells/μL, and severe at more than 5,000 cells/μL [3].

**Diagnostic testing**

All patients underwent standard diagnostic procedures involving detailed clinical history review, physical examination, routine laboratory testing in addition to quantification of C-reactive protein (CRP) and total immunoglobulin E (IgE) concentrations, *Aspergillus* serology and ANCA testing, as well as pulmonary function tests, and serological evaluation with enzyme-linked immunosorbent assays (ELISAs) in cases where parasitic infection was suspected (e.g., *Toxocara* or *Trichinella*). Concentrations of CRP >5 mg/l and total IgE >100 IU/ml were categorized as elevated. ANCA presence (inferred from myeloperoxidase (MPO) and proteinase-3 (PR3) levels) was determined by ELISA; a positive test was confirmed if levels were ≥20 RU/ml (relative units per milliliter). *Aspergillus* serology included quantification of the concentrations of specific IgE and IgG (immunoglobulin G); elevated levels were defined as ≥0.35 kU/ml (kilo units of allergy-specific antibody per liter) and >10 AU/ml (allergy units of antibody per milliliter), respectively. In all cases, lung imaging tests were performed, including chest radiography and computed tomography (CT), and all patients were evaluated for the presence of sinusitis. All patients underwent basal cardiac examinations, including electrocardiography (EKG) and echocardiography; natriuretic peptide-B (BNP) and troponin concentrations were quantified in serum. In all cases, bacterial and fungal cultures of sputum or bronchial fluid were performed. Additional tests, such as fiberoptic bronchoscopy (FOB), BALF, cardiac magnetic resonance (CMR), and Holter monitoring, were carried out depending on the symptoms presented by patients. In the presence of demonstrable lesions, biopsy procedures were performed when feasible and indicated. In cases of high eosinophilia and severe organ symptoms, diagnostic procedures were immediately initiated, without respecting the duration of time typically required for eosinophilia recognition (≥1 month).

**Statistical analysis**

Statistical analyses were performed using scientific computation libraries in the Python programming language, SciPy, v. 1.3.1 (https://en.m.wikipedia.org/wiki/SciPy). For comparison of certain variables’ median values, the non-parametric Kruskal-Wallis H test was used. An independent t-test was performed to compare the means of two numerical variables. Means of age were assessed.
using a one-way analysis of variance (ANOVA). Normal distribution was verified by the Shapiro-Wilk test. Additionally, we used Fisher’s exact test for 2x2 nominal tests and Chi-squared tests to compare differences between expected and observed frequencies of one or more categories of nominal variables (differences in the distribution of clinical, laboratory, and radiological findings, and pulmonary function abnormalities depending on the severity and final etiology of eosinophilia). The statistical significance was set at p<0.05. For multiple tests, the Holm-Bonferroni method was used.

Results

Eosinophilia

The mean eosinophil blood count was 4,198±4,081 cells/μl (range: 750-21,000 cells/μl). Nine individuals (19.6%) had mild (500-1,500 cells/μl), 26 (56.5%) had moderate (1,500-5,000 cells/μl), and 11 (23.9%) had severe eosinophilia (≥5,000 cells/μl). The median duration of eosinophilia was eight weeks. Clinical characteristics of the study patients and a summary of the results of the diagnostic tests are described in Table 1.

Clinical symptoms

Patients were admitted to the hospital with a variety of clinical symptoms. The most common presentations were respiratory symptoms (cough and dyspnea were observed in 71.7% of patients) and symptoms associated with sinusitis/polyps (89.1% of cases). Constitutional systemic signs presenting as fever and arthralgia affected one-third of patients. Among the organ manifestations, the most common (34.8%) were cardiac symptoms (arrhythmia and breathlessness after exercise), while kidney disease was rarely observed (6.5%). Statistical analysis comparing clinical manifestations depending on eosinophil blood counts showed the significantly more frequent occurrence of fever (p=0.023) and skin (p=0.010), heart (p=0.040), and kidney signs (p=0.006) in the group of patients with severe eosinophilia compared with patients with moderate and mild eosinophilia. For the remaining clinical parameters, no statistical correlations between patients with severe eosinophilia and those with moderate and mild eosinophilia were found, although arthralgia and neurological symptoms were more common in patients with severe eosinophilia than in patients with moderate and mild eosinophilia [(63.6% versus 26.9% and 22.2% for arthralgia and 36.4% versus 11.5% and 0.0% for neurological symptoms; p=0.068 and p=0.058, respectively; Table 2, with reduced significance thresholds for 3 category tests (0.0166 0.025 0.05)].

Laboratory investigations

Comparisons of laboratory findings depending on the degree of eosinophilia are summarized in Table 2. Elevated concentrations of total IgE were significantly more common in the groups of patients with eosinophilia ≥1,500 cells/μl and ≥5,000 cells/μl compared with those with eosinophilia <1,500 cells/μl (p=0.037), while the frequency of positive troponin test results was higher in the group of patients with severe eosinophilia (p=0.003) compared with those with mild or moderate eosinophilia. Elevated *Aspergillus fumigatus*-specific serum IgE and IgG antibodies were found only in patients with moderate eosinophilia.

Imaging findings

All patients except for three (43/46; 93.5%) had abnormal chest CT scans. The coexistence of distinctly different lesions was observed in all patients. The most common lesions were thickening of the bronchial walls (18/46; 39%), pulmonary consolidations (16/46; 35%), and ground-glass opacities (16/46; 35%). We observed eight cases (17.4%) of bronchiectasis filled by bronchial mucus, five (11%) cases of pleural effusion, five (11%) cases of mediastinal lymphadenopathy, four (8.7%) cases of visible nodules, and two cases (4%) of lung tumors (one case was imitated by lobe cirrhosis, and the second case was imitated by mucoid impaction). In 41/46 patients (89%), sinusitis was confirmed by a CT scan. Abnormalities in echocardiography were found in 13/46 patients (28%), with the most common being a decrease in the left ventricular ejection fraction (below 45%) and pericardial effusion. CMR was performed in 30 patients; out of these, 16 patients (53%) exhibited features of myocarditis. Analysis of radiological findings based on eosinophil blood counts showed that pleural effusion and echocardiography abnormalities were significantly more frequent in the group of patients with severe eosinophilia compared with those with moderate and mild eosinophilia (p=0.007 and p=0.026, respectively; Table 2).

### Table 1. Characteristics of 46 study patients.

| Parameter                              | Number (%)          |
|----------------------------------------|---------------------|
| **Clinical symptoms**                  |                     |
| Cough                                  | 33 (71.7)           |
| Dyspnea                                | 33 (71.7)           |
| Sinus/polyps                           | 41 (88.1)           |
| Fever                                  | 14 (30.4)           |
| Chest pain                             | 12 (26.1)           |
| Arthralgia                             | 16 (34.8)           |
| Skin                                   | 10 (21.7)           |
| Gastrointestinal                       | 4 (8.7)             |
| Heart                                  | 16 (34.8)           |
| Nerves                                 | 7 (15.2)            |
| Kidney                                 | 3 (6.5)             |
| Hypoxemia (PaO₂<70 mmHg)               | 21 (45.6)           |
| Total IgE elevated                     | 35 (76.1)           |
| CRP elevated                           | 21 (45.6)           |
| Airway obstruction                     | 23 (51.1)           |
| Abnormal chest CT scan                 | 43 (93.5)           |
| Abnormal cardiological tests (BNP/CRP) | 18 (39.1)           |
| Bronchoscopy                           | 36 (78.3)           |
| Inflammatory lesions                   | 12 (33.3)           |
| Purulent plugs                         | 7 (19.4)            |
| Erosions                               | 1 (2.8)             |
| Tumor                                  | 1 (2.8)             |
| No lesions                             | 15 (41.7)           |
| BALF                                   | 19 (32.8)           |
| Eosinophils in BALF elevated           | 19 (100)            |
| Biopsy                                 | 17 (36.9)           |
| Positive                               | 11 (46.4)           |
| Parasites test                         | 46 (100)            |
| Positive                               | 3 (6.5)             |

PaO₂: partial pressure of oxygen; IgE, immunoglobulin E; CRP, C-reactive protein; CT, computed tomography; BNP, natriuretic peptide-B; ECG, electrocardiography; BALF, bronchoalveolar lavage fluid; ECHO-echocardiography.
Table 2. Distribution of clinical, laboratory and radiological findings depending on the severity of peripheral eosinophil blood count.

| Parameter                              | Eosinophils >500<1500/1 | Percent within group | Eosinophils ≥1500<5000/1 | Percent within group | Eosinophils ≥5000/1 | Percent within group | p               | p Pair-wise comparison of the groups |
|----------------------------------------|--------------------------|----------------------|---------------------------|----------------------|----------------------|----------------------|-------------------|-------------------------------------|
| Cough                                  | 8                        | 88.9                 | 19                        | 73.1                 | 6                    | 54.5                 | 0.231            | -                                                  |
| Dyspnea                                | 6                        | 66.7                 | 18                        | 69.2                 | 9                    | 81.8                 | 0.688            | -                                                  |
| Fever                                  | 2                        | 22.2                 | 5                         | 19.2                 | 7                    | 63.6                 | 0.023            | 1.000 (I-II) 0.092 (I-III) 0.018 (I-III) |
| Arthralgia                             | 2                        | 22.2                 | 7                         | 26.9                 | 7                    | 63.6                 | 0.668            | -                                                  |
| Sinus/polyps                           | 9                        | 100.0                | 22                        | 84.6                 | 10                   | 90.9                 | 0.432            | -                                                  |
| Chest pain                             | 1                        | 11.1                 | 7                         | 26.9                 | 4                    | 36.4                 | 0.436            | -                                                  |
| Skin                                   | 1                        | 11.1                 | 3                         | 11.5                 | 6                    | 54.5                 | 0.010            | 1.000 (I-II) 0.070 (I-III) 0.011 (I-III) |
| Heart                                  | 1                        | 11.1                 | 8                         | 30.8                 | 7                    | 63.6                 | 0.040            | 0.393 (I-II) 0.025 (I-III) 0.080 (I-III) |
| Nerves                                 | 0                        | 0.0                  | 3                         | 11.5                 | 4                    | 36.4                 | 0.058            | -                                                  |
| Gastrointestinal                       | 0                        | 0.0                  | 3                         | 11.5                 | 1                    | 9.1                  | 0.570            | -                                                  |
| kidney                                 | 0                        | 0.0                  | 0                         | 0.0                  | 3                    | 27.3                 | 0.006*           | 1.000 (I-II) 0.218 (I-III) 0.021 (I-III) 0.011 (I-III) |
| Total IgE elevated                     | 4                        | 44.4                 | 21                        | 80.8                 | 10                   | 90.9                 | 0.037            | 0.001 (I-II) 0.049 (I-III) 0.646 (I-III) |
| Aspergillus specific                   | 0                        | 0.0                  | 4                         | 15.4                 | 0                    | 0.0                  | 0.185            | -                                                  |
| IgE and IgG elevated                   | 4                        | 44.4                 | 10                        | 38.5                 | 7                    | 63.6                 | 0.371            | -                                                  |
| CRP elevated                           | 0                        | 0.0                  | 9                         | 34.6                 | 5                    | 45.4                 | 0.070            | -                                                  |
| troponin elevated                      | 0                        | 0.0                  | 3                         | 11.5                 | 6                    | 54.5                 | 0.003            | 0.553 (I-II) 0.014 (I-III) 0.011 (I-III) |
| ANCA presence                          | 2                        | 22.2                 | 2                         | 7.7                  | 1                    | 9.1                  | 0.471            | -                                                  |
| Airway obstruction/severe              | 60                       | 66.7                 | 13                        | 50.0                 | 4                    | 36.5                 | 0.369            | -                                                  |
| PaO₂<70                                | 3                        | 33.3                 | 13                        | 50.0                 | 5                    | 45.4                 | 0.521            | -                                                  |
| Thickening of the bronchial walls      | 5                        | 55.6                 | 11                        | 42.3                 | 2                    | 18.2                 | 0.206            | -                                                  |
| Pulmonary consolidations               | 2                        | 22.2                 | 8                         | 30.8                 | 6                    | 54.5                 | 0.259            | -                                                  |
| Ground-glass opacities                 | 3                        | 33.3                 | 10                        | 38.5                 | 3                    | 27.3                 | 0.804            | -                                                  |
| Nodules                                | 1                        | 11.1                 | 1                         | 3.8                  | 2                    | 18.2                 | 0.253            | -                                                  |
| Bronchiectasis/mucoid impaction        | 3                        | 33.3                 | 5                         | 19.2                 | 0                    | 0.0                  | 0.137            | -                                                  |
| Pleural effusion                       | 0                        | 0.0                  | 1                         | 3.8                  | 4                    | 36.4                 | 0.007*           | 1.000 (I-II) 0.094 (I-III) 0.021 (I-III) |
| Tumor                                  | 1                        | 11.1                 | 1                         | 3.8                  | 0                    | 0.0                  | 0.471            | -                                                  |
| Lymphadenopathy                        | 0                        | 0.0                  | 2                         | 7.7                  | 3                    | 27.3                 | 0.110            | -                                                  |
| Sinusitis                              | 9                        | 100.0                | 22                        | 84.6                 | 10                   | 90.9                 | 0.432            | -                                                  |
| Abnormalities in echocardiography      | 0                        | 0.0                  | 7                         | 26.9                 | 6                    | 54.5                 | 0.026            | 0.153 (I-II) 0.014 (I-III) 0.145 (I-III) |
| Abnormalities in CMR                   | 1                        | 33.3                 | 7                         | 44.4                 | 7                    | 77.8                 | 0.200            | -                                                  |
| Parasites test positive                | 0                        | 0.0                  | 1                         | 3.8                  | 2                    | 18.2                 | 0.184            | -                                                  |

IgE, immunoglobulin E; IgG, immunoglobulin G; CRP, C reactive protein; BNP, natriuretic peptide-B; ANCA, antineutrophil cytoplasmic antibody; PaO₂, partial pressure of oxygen; CT, computed tomography; CMR, cardiac magnetic resonance; *test should be repeated for larger data; the reduced significance thresholds for 3 category tests (0.0166 0.025 0.05) have been used.
Pulmonary function tests

Airway obstruction determined by spirometry was observed in 23 (50%) cases; in eight of these cases, the airway was mildly obstructed (35%). This abnormality was observed with nearly the same frequency in patients with moderate eosinophilia (13/26; 50%) as in patients with mild eosinophilia (6/9; 66.7%), which was considerably more frequent than in patients with severe eosinophilia (4/11; 36.4%). These differences between the groups were not statistically significant. Hypoxemia (defined in this study as \( PaO_2 \leq 70 \) mmHg) was detected in half of the patients, mainly in those with moderate and severe eosinophilia (13/26; 50% and 5/11; 45%, respectively; Table 2).

FOB, BALF, and biopsy

The procedures were performed using a Pentax fiberoptic bronchoscope EB 1970AK (Pentax Medical Co; Tokyo, Japan; distributor Varimed Co) and biopsy forceps (model HM-101-A; 18/1200S). FOB was performed in 36/46 patients (78%); in 15 among them (42%) no lesions were found. In 12 cases (33%), inflammatory features of the bronchial tree were detected, which are described in detail in Table 1. There were no significant differences in these features between groups based on the degree of eosinophilia. Out of these 36 patients, BALF was performed in 19 (53%): two of these patients belonged to the mild eosinophilia group (2/9 total), eleven of these patients belonged to the moderate eosinophilia group (11/26 total), and six of these patients belonged to the severe eosinophilia group (6/11 total). Eosinophil counts quantified from BALF ranged from 25%-85% of all cells. Biopsy was performed in 17/46 patients (37%); in most cases (14/17; 82%), these were bronchial mucosa (8 patients) or transbronchial lung biopsies (3 patients), but open lung biopsy was performed on two patients (12%), and nasal biopsy was performed on one patient (6%). Positive pathologies were confirmed in 11 of the 17 total biopsies performed (65%), three of which were taken from patients with mild eosinophilia, whereas seven of which were taken from moderate eosinophilia patients, and one from a severe eosinophilia patient. As to the histopathological examination, in 4/8 cases of bronchial mucosa biopsy eosinophilic infiltrates predominated, which corresponded to CEP and/or EGPA diagnosis, and in 1/8 cases there was lung adenocarcinoma, while in the material from the transbronchial lung biopsies there were eosinophilic infiltrates consistent with a diagnosis of CEP (1 case), features of eosinophilic vasculitis (1 case), and features of OP (1 case). Other biopsy cases (open lung and nasal biopsy) showed pattern typical for GPA. No significant differences in the frequency of positive biopsy results were observed among the groups based on the degree of peripheral eosinophilia (\( p=0.104 \)).

Table 3. The relation between the value of peripheral eosinophilia and final diagnoses in study patients.

| Final diagnosis | Eosinophils ≥500/1500/l | Percent within group | Eosinophils ≥1500–5000/l | Percent within group | Eosinophils ≥5000/l | Percent within group | p | p Pair-wise comparison of the groups |
|-----------------|-------------------------|----------------------|---------------------------|----------------------|---------------------|----------------------|---|-----------------------------------|
| AAV             | 3                       | 33.33                | 11                        | 42.31                | 9                   | 81.82                | 0.048 | 0.712 (I-II) 0.065 (I-III) 0.006 (II-III) |
| ILD             | 3                       | 33.33                | 5                         | 19.23                | 0                   | 0.00                | 0.137 | -                                |
| Asthma          | 3                       | 33.33                | 5                         | 19.23                | 0                   | 0.00                | 0.137 | -                                |
| ADEF            | 0                       | 0.00                 | 5                         | 19.23                | 2                   | 18.18               | 0.395 | -                                |

AAV, antineutrophil cytoplasmic antibody associated vasculitis; ILD, interstitial lung disease; ADEF, allergic diseases caused by external factors; the reduced significance thresholds for 3 category tests (0.0166 0.025 0.05) have been used.

Microbial cultures

Positive bacterial cultures were found in 8/46 (17%) cases (one case with mild eosinophilia, six cases with moderate eosinophilia, and one case with severe eosinophilia), while positive fungal cultures were detected only in 4/46 (9%) patients, all of whom had moderate eosinophilia. There was no significant difference between the groups based on the degree of peripheral eosinophilia (\( p=0.185 \)).

Parasitology

Positive parasitic serologic tests (assessed by ELISAs) for toxocariasis were observed in 3/46 cases (6.5%): one case in a patient with moderate eosinophilia, and two cases in patients with severe eosinophilia. There was no significant difference in the rate of infection among the groups based on the degree of eosinophilia (\( p=0.184 \)).

Diagnoses

In most patients (23/46; 50%), AAV was identified (21/23 with EGPA, 2/23 with GPA). In 8/46 (17.4%) patients, different interstitial lung diseases (ILDs) were identified, six of which were determined to be CEP and two of which were determined to be OP. In 8/46 patients (17.4%), asthma was found to be the sole cause of peripheral eosinophilia. In 7/46 cases (15.2%), allergic diseases caused by external factors (ADEF) were recognized: ABPA in four patients, and parasitic infection in three patients. Patients with AAV were significantly younger (\( p=0.025 \)) compared with those with other diagnoses (ILDs, asthma, ADEF), but no statistical difference was observed between males and females (\( p=0.615 \)). The median eosinophilic blood count did not differ significantly in individual disease groups (AAV, ILDs, asthma, ADEF), but no statistical difference was found in median total IgE concentration based on individual diagnoses (\( p=0.190 \)). AAV was frequently identified in the group of patients with severe eosinophilia (\( p=0.048 \)) compared with those with moderate or mild eosinophilia (Table 3, reduced significance thresholds for 3 category tests: 0.0166 0.025 0.05).

The results of the comparative analysis of the patient groups based on the final etiology are presented in Table 4. In 27/46 patients (58.7%), final causes of eosinophilia matched those suspected initially at the time of referral, while in 19/46 cases (41.3%), the etiological causes determined from the final diagnoses were inconsistent with the initially suspected causes of eosinophilia (Table 5). Interestingly, the final diagnosis of AAV was the most consistent cause among the patients’ initial suspected diagnoses, compared to other diseases (\( p=0.001 \); Table 4, significant thresholds for 6 comparisons with values: 0.0083 0.01 0.0125 0.0166 0.025 0.05).
Discussion

Our study demonstrates that the severity of peripheral eosinophilia may be an essential predictor of diagnostic procedures in patients with lung disorders. Lung diseases associated with marked peripheral blood or tissue eosinophilia are unusual and are nearly always clinically significant, providing important information to guide diagnosis. Our study indicates that eosinophilia ≥5,000 cells/μL requires rapid diagnostics to allow for urgent treatment due to the possibility of organ involvement and the dangers of irreversible organ injury. The diagnostics should be primarily directed to identify the possibility of AAV (with cardiological and nephrological tests), but tests for parasites should also be conducted to exclude the possibility of parasitic infection, which would require different treatment. Eosinophilia with counts of 1,500-5,000 cells/μL can reflect various conditions; therefore, in these cases, extensive diagnostic testing should be performed to search for various causes of eosinophilia, with a particular focus on identifying vasculitides, but also other eosinophilic lung diseases, as well as allergic and airway diseases and parasitic infections. Eosinophilia with counts <1,500 cells/μL is usually mild and mainly connected with symptoms of airway disease, but the need for more extensive diagnostics should not be ignored, particularly when lung and/or other organ lesions are present.

Severe eosinophilia with counts ≥5,000 cells/μL was exhibited by 11 patients (24%) in our study, was associated with extrapulmonary involvement and constitutional symptoms. Patients mainly reported pulmonary symptoms (71.7%), but simple diagnostic tests to quantify CRP, troponin, or BNP, and echocardiography revealed a variety of abnormalities. Skin and heart diseases were significantly more frequent (p=0.010 and p=0.040, respectively), and only this group – compared to those with mild or moderate eosinophilia - displayed signs of kidney disease (p=0.006), mainly manifesting as proteinuria. Similarly, neurological symptoms were more frequent in this group (36.4% versus 11.5% and 0.0% of patients with moderate and mild eosinophilia, respectively). A common feature of these patients was inflammatory syndrome manifesting as fever (p=0.023), as well as CRP elevation (63.6% versus 44.4% and 38.5% of patients with moderate and mild eosinophilia, respectively). In this group, abnormalities in echocardiography and increased troponin concentrations occurred significantly more frequently (p=0.026 and p=0.003, respectively), and positive results of CMR were the most common (78%) compared to the groups with mild and moderate eosinophilia. In radiological studies, we predominantly observed parenchymal infiltrations, but pleural effusion was significantly more often detected in this group (p=0.007) compared to moderate and mild eosinophilia groups. Patients with severe eosinophilia reported shortness of breath more often than cough, but airflow obstruction was less common, and reversibility was observed significantly more frequently in this group only (p=0.013) compared to moderate and mild eosinophilia groups. Patients in the severe eosinophilia group, compared to those with mild or moderate eosinophilia, were predominantly diagnosed with AAV (9/11; p=0.048), although in two out of 11 cases, parasitic infections (toxocariasis) were found. This result was surprising because toxocariasis infection usually does not cause eosinophilia ≥5,000 cells/μL [10,11].

Patients with moderate eosinophilia comprised the largest group in our study (26/46 patients; 56.5%). They reported dyspnea

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Table 4. Comparative characteristics of the study patients depending on the final etiologies

| Parameter (n) | AAV (N=23) | ILD (N=8) | Asthma (N=8) | ADEF (N=7) | p |
|---------------|------------|-----------|--------------|------------|---|
| Age (yrs, mean) | 41.39±14.0 | 50.75±15.8 | 53.88±17.7 | 61.14±13.6 | **0.025** |
| Mean blood eosinophil count (range) | 5816±5781 (1400-4600) | 2254±1451 (920-3980) | 1984±877 (1083-7600) | 3632±2436 (1889-2436) | **0.002** |
| IGE elevated | 19 (82.6) | 6 (75.0) | 4 (50.0) | 6 (85.7) | 0.273 |
| Mean | 912±1768 | 425±400 | 366±506 | 1889±1481 | 0.184 |
| CRP elevated | 13 (56.5) | 5 (62.5) | 2 (25.0) | 1 (14.3) | 0.104 |
| Mean | 47.7±64.6 | 19.7±28.4 | 7.7±14.2 | 6.8±8.2 | 0.113 |
| BNP elevated | 11 (47.8) | 6 (75.0) | 2 (25.0) | 1 (14.3) | 0.051 |
| Mean | 8 (34.8) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 0.063 |
| ANCA presence | 5 (21.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.132 |
| Positive cultures (bacterial and/or fungal) | 5 (21.7) | 6 (75.0) | 2 (25.0) | 3 (42.9) | 0.250 |
| Positive biopsy | 11 (47.8) | 4 (50.0) | 1 (12.5) | 1 (14.3) | 0.148 |
| According with the initial diagnosis | 20 (86.9) | 8 (100.0) | 5 (62.5) | 7 (100.0) | **<0.001** |

\[\text{PaO}_2, \text{partial pressure of oxygen}; \text{CT}, \text{computed tomography}; \text{IGE}, \text{immunoglobulin E}; \text{CRP}, \text{C-reactive protein}; \text{BNP}, \text{natriuretic peptide B}; \text{ANCA}, \text{antineutrophil cytoplasmic antibody associated vasculitis}; \text{ILD}, \text{interstitial lung disease}; \text{ADEF}, \text{allergic diseases caused by external factors}; \text{the significant thresholds for 6 comparisons with values}: 0.0003 \text{ 0.01 0.0025 0.0166 0.025 0.05 have been used.} \]
Table 5. Comparison of differences in the identifiable causes of eosinophilia dictating initial working and final diagnoses in study patients.

| Initial working diagnosis (n) | Final diagnosis in accordance with the initial diagnosis (n) | Final diagnosis inconsistent with the initial diagnosis (n) |
|-----------------------------|----------------------------------------------------------|----------------------------------------------------------|
| AAV                         | 27                                                       | 20                                                       |
| CEP                         | 6                                                        | 1                                                        |
| ABPA                        | 5                                                        | 3                                                        |
| Asthma                      | 4                                                        | 2                                                        |
| Lung tumor                  | 2                                                        | 0                                                        |
| HP                          | 1                                                        | 0                                                        |
| Total n                     | 46 (100%)                                                | 27 (58.7%)                                               | 19 (41.3%)                                               |

AAV, antineutrophil cytoplasmic antibody associated vasculitis; CEP, chronic eosinophilic pneumonia; EGPA, eosinophilic granulomatosis with polyangiitis; ABPA, allergic bronchopulmonary aspergillosis; HP, hypersensitivity pneumonitis; OP, organizing pneumonia.
to 33.3% of patients with mild eosinophilia were diagnosed with AAV, as were 33.3% of those with ILD, but the majority of these diseases were not typically connected with pulmonary eosinophilia (2/3 cases of GPA and 2/3 cases of OP).

Another aspect of this study concerned the analysis of causes of eosinophilia in our patient groups and comparisons between initial suspected and final diagnoses. In this group of 46 patients, the most frequent cause of eosinophilia was AAV (diagnosed in half of the cases), which was highly representative of the group with eosinophilia ≥5,000 cells/μl, followed by ILD, which was found in eight cases (17.5%); asthma was the sole cause of eosinophilia in eight cases as well (17.5%), and allergic pulmonary diseases (including ABPA or parasitic infections) were identified in seven patients (15%). These results differ from other studies. The probable reason for these differences was discrepancies between the pneumonological profiles of our patients and our hospital characteristics. For example, in the study by Lombardi et al. [16], in 1,862 cases diagnosed due to eosinophilia, allergic disorders were largely predominant (80% of cases), while AAV and CEP were much rarer and were found only in 0.16% and 0.05% of cases, respectively. Similarly, in a report by Sade et al. [13], which analyzed 100 hospitalized patients, allergic or atopic diseases were the most frequent cause of eosinophilia. EGPA, in their study, was identified in only 4% of cases (compared with 21/46, or 45.6%, in our study), while the frequency of parasitic infections they reported (5%) was similar to our own results (3/46; 6.5%).

Comparative analysis of initial and final diagnoses in our patients revealed that in 27/46 patients (58.7%), there was no discrepancy between the final etiologies of eosinophilia determined after testing and the initial working diagnoses, while in 19 cases (41.3%), the final diagnoses were inconsistent with the initial suspected causes of eosinophilia, and other disorders were ultimately identified. These findings highlight the difficulties in diagnosing eosinophilic lung diseases, which can overlap with various other pulmonary and/or respiratory disorders. For example, before the onset of manifestations of vasculitis, it may be difficult to distinguish EGPA from eosinophilic asthma, whereas CEP, which may be confused with EGPA, has no vasculitic and extrapulmonary signs, and thus remains an exclusionary diagnosis. In our study, among the six patients referred due to CEP suspicion, a diagnostic confirmation was achieved in only one patient, while in the next five cases, other diseases were recognized (EGPA in two cases, one case of parasitic infection, one case of OP, and one case where asthma was the sole cause of eosinophilia). In all our patients who were ultimately diagnosed with a parasitic infection, the initial admission was for suspected asthma or CEP, not parasitosis. Interestingly, although overlap between the initial suspected and final confirmed cause of eosinophilia was observed in roughly 60% of cases, AAV was most accurately recognized from the onset compared to other diseases (p=0.001).

In summary, our study indicates that evaluation of eosinophilia in patients with lung disorders should be based on its severity, the symptoms related to the results of diagnostic tests, ECG and echocardiographic abnormalities, and the results of diagnostic tests. ECG and echocardiographic abnormalities are important and should be performed in all patients diagnosed with eosinophilia, but mainly in those cases where eosinophilia ≥1,500 cells/μl should be mandatory in those cases where eosinophilia ≥5,000 cells/μl. CMR seems to be more sensitive than the techniques used in the above-mentioned investigations and in agreement with current recommendations [17]; therefore, it should be performed even in asymptomatic patients diagnosed with eosinophilia. This method, through its great versatility, gives valuable information not only about specific cardiac inflammation, but also provides information about cardiac function, type of fibrosis, vascular integrity, and thrombosis that may significantly aid treatment decisions and improve prognosis [18-20]. In our study, myocarditis in CMR was generally detectable in up to 53% of patients, but the highest percentage of positive CMR results was observed in cases with eosinophilia ≥5,000 cells/μl (78%), followed by cases with eosinophil counts between 1,500-5,000 cells/μl (≤45%). In our study, chest CT scans revealed abnormalities in 93% of cases, and the type of lesions varied depending on the severity of eosinophilia. In patients with eosinophilia ≥5,000 cells/μl, parenchymal infiltrations were predominant, while in cases of eosinophilia <1,500 cells/μl, bronchial lesions were the most common findings. Airway obstruction detected by spirometry was found in half of our patients and was most frequently observed in the group with eosinophil counts <1,500 cells/μl (66.7%). In all cases of eosinophilia, serologic tests for parasites should be performed to exclude the possibility of parasitic infection requiring other treatments [16,21,22].

Our study is the first clinical study to analyze the role of peripheral eosinophilia in diagnosing lung disorders, but it does have some limitations. First, the study was retrospective and included only hospitalized patients who probably had more severe symptoms and a greater degree of eosinophilia compared with what one would typically expect to see in outpatient diagnosis, which could have affected the results. Therefore, it would be advisable to include patients who are managed in primary care also, in the cohort of future research, to obtain more generalizable results. Second, some patients received short-term oral glucocorticoids, which could have contributed to a reduction in the degree or severity of eosinophilia. A potential confounding effect of steroids should be a matter of interest in future studies. Finally, the small sample size provides preliminary results requiring further investigation and confirmation through larger prospective studies. An increase in the number of patients could provide more accurate and reliable statistical results.

Conclusions

Peripheral eosinophilia is one of the important reasons to refer patients to pneumonological centers. Eosinophilia ≥5,000 cells/μl is significantly associated with extrapulmonary organ involvement and requires immediate diagnostic procedures, primarily to identify the possibility of vasculitis, with a particular emphasis on basic cardiological tests, which should also be performed in patients with a lesser, but marked, degree of eosinophilia. Eosinophilia with counts of 1,500-5,000 cells/μl is associated with a wide variety of conditions; therefore, in these cases, extensive diagnostic testing should be performed to identify the cause of eosinophilia, with particular emphasis on identifying the possibility of vasculitis, but also other eosinophilic lung diseases, as well as allergy and airway diseases. While mild eosinophilia with counts <1,500 cells/μl is mainly associated with symptoms of airway disease, one must not rule out the need for more extensive diagnostics, particularly when lung and/or organ lesions are present. Patients with mild eosinophilia without signs of organ damage should be monitored for development of eosinophilic lung or systemic diseases, especially when they suffer from asthma, as asthmatic patients experience EGPA even 34 times more frequently than those in the general population [23,24]. In any case, parasitic infections should be ruled out to avoid over-prescribing glucocorticoids, which is the key therapy used to treat most eosinophilic lung diseases. While vasculitis, especially EGPA, is classified as a rheumatological disease, it was the most common cause of eosinophilia in our study. Although the overlap of first and final etiology of eosinophilia affected only about 60% of cases, AAV was most accurately recognized. The degree of peripheral eosinophilia may essentially deter-
mine the diagnostic procedures in patients with lung disorders and may be a strong indicator of disease etiology.

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Abbreviations

AAV, ANCA-associated vasculitis; ABPA, allergic bronchopulmonary aspergillosis; ADEF, allergic diseases caused by external factors; AEP, acute eosinophilic pneumonia; ANCA, antineutrophil cytoplasmic antibody; BALF, bronchoalveolar lavage fluid; BNP, natriuretic peptide-B; CEP, chronic eosinophilic pneumonia; CRP, C-reactive protein; CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiography; EGPA, eosinophilic granulomatosis with polyangiitis; FOB, fiberoptic bronchoscopy; GPA, granulomatosis with polyangiitis; HES, hypereosinophilia; HP, hypersensitivity pneumonitis; IgE, immunoglobulin E; IgG, immunoglobulin G; HP, hypersensitivity pneumonitis; NEAE, non-episodic angioedema with eosinophilia; OP, organizing pneumonia; PaO₂, partial pressure of oxygen; PR3, proteinase-3.

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