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RESEARCH ARTICLE

Evaluation and differential diagnosis of eosinophilia: A tertiary allergy center experience

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ABSTRACT

Evaluation and differential diagnosis of eosinophilia: A tertiary allergy center experience

Introduction: *Eosinophilia is a hematologic finding that may indicate a wide range of underlying conditions, from common allergic diseases to rare and potentially life-threatening disorders such as hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA), and systemic mastocytosis. A structured diagnostic approach is crucial to identify the underlying etiology and guide appropriate treatment.*

Materials and Methods: *This retrospective cross-sectional study evaluated 232 adult patients with peripheral blood absolute eosinophil counts ≥1000 cells/μL, who were referred to a tertiary immunology and allergy clinic between January 2018 and December 2022. Demographic, clinical, and laboratory data were analysed. Diagnoses were grouped according to eosinophil count severity: Mild (1000-1499 cells/μL), moderate (1500-4999 cells/μL), and severe (≥5000 cells/μL). Diagnoses were based on established international guidelines, supported by laboratory, radiological, immunological, and genetic investigations.*

Results: *The most commonly observed diagnoses included atopic diseases (53.4%), with allergic bronchopulmonary aspergillosis (ABPA, 11.6%), nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (6%), and chronic eosinophilic pneumonia (3%) occurring less frequently. Rare conditions included EGPA (1.7%), HES (1.7%), parasitic infections (1.3%), systemic mastocytosis (0.4%), and Gleich syndrome (0.4%). Innate immune defect was detected in 0.4%. Molecular testing identified myeloid variant HES in four patients (FIP1L1-PDGFRA and PDGFRB mutations). The etiology remained undetermined in 19.8% of the patients. Atopic diseases were the most frequent diagnosis across all eosinophilia severity groups (38.3% vs. 14.2% vs. 0.8% p< 0.001 respectively).*

Conclusion: *Atopic diseases are the most common cause of eosinophilia in adults, but clinicians must remain vigilant for less common but clinically significant diagnoses such as ABPA, HES, EGPA, and systemic mastocytosis. Managing eosinophilia effectively depends on a multidisciplinary strategy that incorporates algorithm-based decision-making to support accurate diagnosis.*

Key words: *Atopic diseases; differential diagnosis; eosinophilia; hypereosinophilic syndrome*

ÖZ

Eozinofilinin değerlendirilmesi ve ayırıcı tanısı: Üçüncü basamak alerji merkezi deneyimi

Giriş: *Eozinofili, yaygın alerjik hastalıklardan, hipereozinofilik sendrom (HES), eozinofilik granülomatoz ile poliarterit (EGPA) ve sistemik mastositoz gibi nadir ve potansiyel olarak yaşamı tehdit edici hastalıklara kadar çok çeşitli durumlara işaret edebilen hematolojik bir bulgudur. Altta yatan etiyolojinin belirlenmesi ve uygun tedavinin yönlendirilmesi için yapılandırılmış bir tanısal yaklaşım büyük önem taşır.*

Materyal ve Metod: *Bu retrospektif kesitsel çalışmada, Ocak 2018-Aralık 2022 tarihleri arasında üçüncü basamak bir immünoloji ve alerji kliniğine başvuran ve periferik kanda mutlak eozinofil sayısı ≥1000 hücre/μL olan 232 erişkin hasta değerlendirildi. Hastaların demografik, klinik ve laboratuvar verileri analiz edildi. Tanılar, eozinofil düzeyine göre hafif (1000-1499 hücre/μL), orta (1500-4999 hücre/μL) ve şiddetli (≥5000 hücre/μL) olarak gruplandırıldı. Tanılar, laboratuvar, radyolojik, immünolojik ve genetik incelemelerle desteklenen uluslararası kılavuzlara göre konuldu.*

Bulgular: *En sık gözlenen tanılar atopik hastalıklar (%53.4) olup, bunların dışında alerjik bronkopulmoner aspergilloz (ABPA, %11.6), non-steroid antienflamatuvar ilaçlara bağlı solunum yolu hastalığı (%6) ve kronik eozinofilik pnömoni (%3) daha az sıklıkta görüldü. Nadir hastalıklar arasında EGPA (%1.7), HES (%1.7), paraziter enfeksiyonlar (%1.3), sistemik mastositoz (%0.4) ve Gleich sendromu (%0.4) yer aldı. Doğuştan bağışıklık sistemi defekti %0.4 oranında saptandı. Moleküler incelemelerde, dört hastada miyeloid varyant HES'e neden olan FIP1L1-PDGFRA ve PDGFRB mutasyonları tespit edildi. Hastaların %19.8'inde etiyoloji belirlenemedi. Atopik hastalıklar, tüm eozinofili gruplarında en sık görülen tanı oldu (%38.3'e karşı %14.2'ye karşı %0.8 p< 0.001, sırasıyla).*

Sonuç: *Atopik hastalıklar, erişkinlerde eozinofilinin en yaygın nedenidir; ancak klinisyenler, ABPA, HES, EGPA ve sistemik mastositoz gibi daha nadir fakat klinik olarak önemli tanılar konusunda dikkatli olmalıdır. Eozinofili yönetimi, doğru tanıyı destekleyen algoritmalara dayalı karar verme süreçlerini içeren multidisipliner bir strateji gerektirir.*

Anahtar kelimeler: *Atopik hastalıklar; ayırıcı tanı; eozinofili; hipereozinofilik sendrom*

INTRODUCTION

Eosinophils are a type of myeloid cell that were first identified by Paul Ehrlich in 1879 due to their bright red staining granules that react with eosin dye. These cells originate in the bone marrow and are released into the bloodstream in a mature form. They circulate throughout the body and can take up residence in various tissues, where they play important roles in immune responses and inflammation. Eosinophils may be involved in antigen presentation and stimulate innate and acquired immune response (1-3). Additionally, the granules of eosinophils serve as the primary source of their cytotoxic effects which play a significant role in combating both parasitic infections with atopic diseases. However, excessive or irregular activation of eosinophils can lead to tissue damage and inflammation (4,5).

While the normal ratio of eosinophils in bone marrow cells is 1-6%, they are found in 3-5% in peripheral blood (6,7). This ratio of eosinophils in peripheral blood corresponds to an absolute eosinophil count (AEC) of 350-500 cells/μL, and the AEC above this value is called eosinophilia (7). Eosinophilia can be seen during the course of many diseases; therefore, it is very important to notice eosinophilia in terms of early diagnosis and appropriate treatment of underlying diseases. According to the count of eosinophils in peripheral blood, eosinophilia is divided into three category as mild (500-1500 cells/μL), moderate (1500-5000 cells/μL) and severe (>5000 cells/μL) (8). Hypereosinophilia is typically characterized by an absolute eosinophil count greater than 1500 cells/μL in peripheral blood (9). Moreover, hypereosinophilic syndrome (HES) is defined by persistent eosinophilia (on two occasions at least one month) above 1500 cells/μL, organ damage caused by eosinophils, and the exclusion of other potential causes (10). However, a count of up to 1000 cells/μL eosinophils can, in some cases, be attributed to atopic causes. Some literature considers a count of 1000 cells/μL eosinophils as a cut-off value for hypereosinophilia (11-13). For instance, different cut-off values can be

seen in the diagnostic criteria for eosinophilic granulomatosis with polyangiitis (EGPA), where counts of 1000 cells/μL or 1500 cells/μL eosinophils are used to define hypereosinophilia (14,15). It has also been suggested that a definitive AEC value should not be a requirement for diagnosis, considering that significant tissue eosinophilic infiltration and subsequent organ damage developed in some patients with an AEC value of <1500 cells/μL (5).

Mild eosinophilia is often seen in atopic and allergic diseases such as allergic rhinitis (AR) and asthma (16). Mild to moderate eosinophilia may be observed in patients with chronic rhinosinusitis, especially nasal polyps seen in respiratory diseases exacerbated by nonsteroidal anti-inflammatory drugs (N-ERD) (17). Allergic bronchopulmonary aspergillosis (ABPA), which is associated with sensitivity to the fungus Aspergillus, has both high eosinophilia and serum total immunoglobulin E (IgE) levels (18).

Chronic eosinophilic pneumonia (CEP) is a rare idiopathic disease characterized by marked eosinophil inflammation in the lung parenchyma (19).

EGPA is a multisystemic disease characterized by chronic rhinosinusitis, asthma, pulmonary infiltrates and extrapulmonary vasculitis with marked blood eosinophilia (14).

The causes of eosinophilia are categorized; primary, secondary (reactive) and idiopathic. HES's, Gleich syndrome and systemic mastocytosis are among the causes of primary eosinophilia. Eosinophilia is secondary (reactive) in most cases (16). Conditions that may lead to eosinophilia in the context of respiratory diseases, as well as immunology and allergy, encompass atopic and allergic diseases [asthma, AR, atopic dermatitis (AD), food allergy (FA), urticaria, drug allergy], parasitic infections, innate immune defect (IID).

In this study, we aimed to investigate the underlying etiology, predisposing factors, clinical characteristics and final diagnosis of patients with eosinophilia who presented to the immunology and allergy unit at a tertiary care center. Our secondary objective is to share the approach algorithm that we apply to these patients in our clinic. In doing so, we hope to help the differential diagnoses of eosinophilia patients to further optimize disease management.

MATERIALS and METHODS

Our study protocol received approval from our hospital's local ethics committee, under decision number R-321, and was conducted in adherence to the standards of good clinical practice and the Declaration of Helsinki. In our retrospective cross-sectional study, we analyzed electronic or record-based medical data of 232 patients with AEC ≥1000 cells/μL among 5634 patients admitted to our Department of Allergy and Clinical Immunology between January 2018 and December 2022. In our study, the index AEC was defined as the AEC measured at the time of the patient's first presentation to our allergy clinic. In accordance with the recommendations in the literature, we included only the patients whose eosinophilia persisted after a one-month follow-up evaluation (10). Due to the nature of our patient population, individuals with secondary eosinophilia related to infectious, autoimmune, or malignant diseases are not typically referred to our department. This study excluded cases of reactive eosinophilia previously diagnosed in other clinics, including those caused by infections other than parasitic ones (such as tuberculosis), autoimmune disorders like rheumatoid arthritis, scleroderma, and systemic lupus erythematosus, as well as eosinophilia linked to malignancies such as gastrointestinal adenocarcinoma and lung cancer (16). Patients on maintenance oral corticosteroid therapy, defined as daily or alternate-day oral corticosteroid maintenance therapy, were excluded from the study (20,21). Demographic characteristics such as age, sex, smoking habit, concomitant allergic diseases, parasites infections, allergic diseases, drugs and final diagnosis were recorded (16). In patients presenting with eosinophilia, routine laboratory evaluations were performed, including complete blood counts, acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate, liver and kidney function tests, assessments of vitamin and thyroid hormone levels, as well as measurements of total Ig E, immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA). In addition to the main assessments, additional examinations such as measuring tryptase, screening for autoantibodies, and analyzing genetic mutations were performed when considered appropriate for the patient. Furthermore, patients deemed

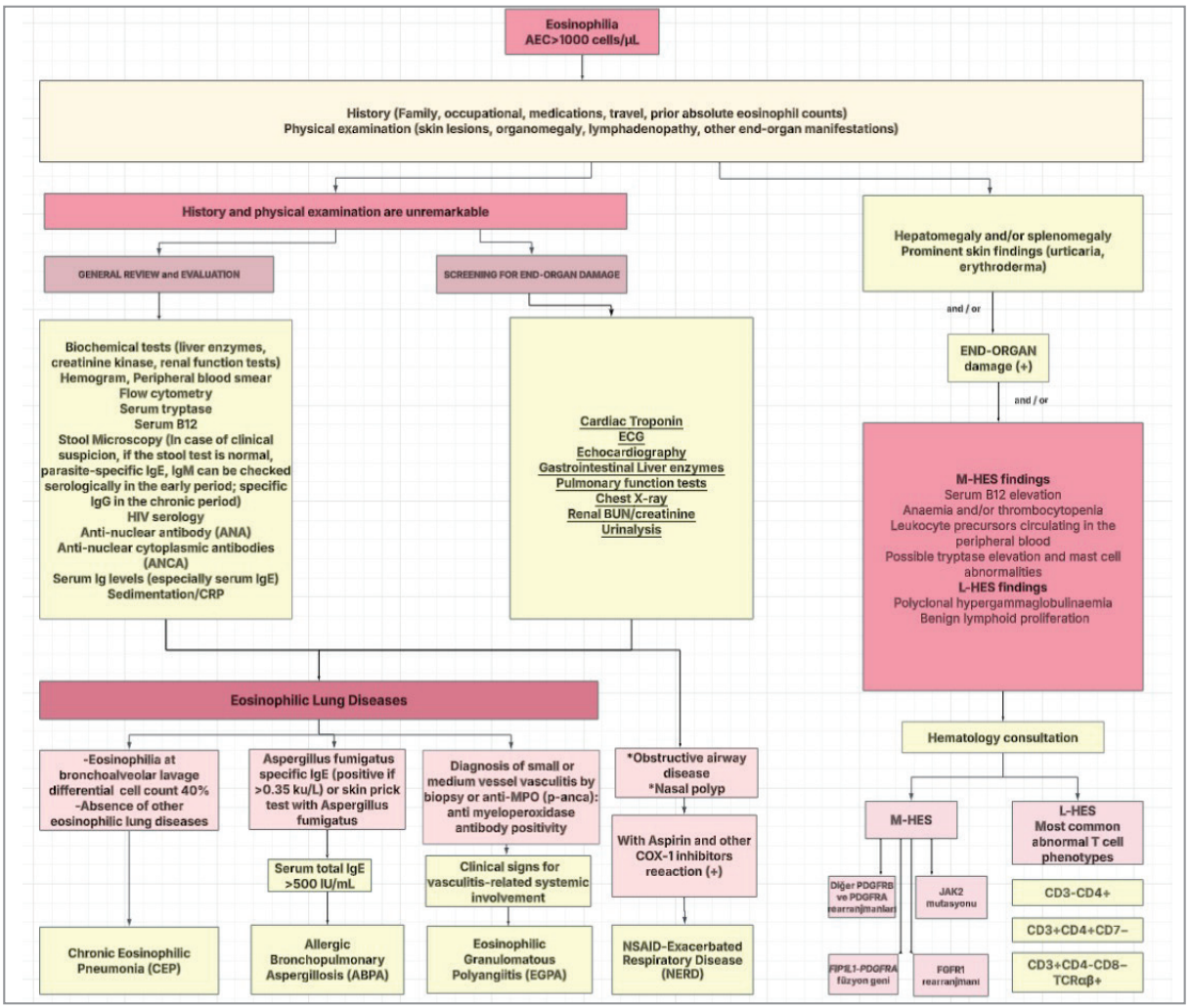

Figure 1. Algorithm for evaluation of eosinophilia.
AEC: Absolute eosinophil count, IgE: Immunoglobulin E, IgG: Immunoglobulin G, IgM: Immunoglobulin M, HIV: Human immunodeficiency virus, CRP: C-reactive protein, ECG: Electrocardiography, BUN: Blood urea nitrogen, M-HES: Myeloproliferative hypereosinophilic syndrome, L-HES: Lymphoproliferative hypereosinophilic syndrome, COX-1: Cyclooxygenase-1, FIP1L1: Factor interacting with PAPOLA and CPSF1-like 1, PDGFRA: Platelet-derived growth factor receptor alpha, PDGFRB: Platelet-derived growth factor receptor beta, FGFR1: Fibroblast growth factor receptor 1.

necessary were evaluated with imaging methods for differential diagnosis. All patients underwent skin prick tests with common inhalant allergens.

Diseases that could cause eosinophilia within the scope of respiratory diseases and the fields of immunology and allergy have been thoroughly examined, and diagnostic tests have been conducted based on this investigation. These examinations aid in uncovering various root causes of elevated eosinophil levels, thereby supporting accurate diagnosis and effective management of patients. In the diagnostic process, a comprehensive approach has been adopted, considering laboratory tests, clinical evaluations, and medical history as described in Figure 1.

Diagnoses of asthma, AR, AD, FA, urticaria, drug allergy, and IID were made based on established international guidelines (22-27). Diagnostic criteria for inhalant or food allergies consisted of a positive skin prick test (SPT) showing a wheal at least 3 mm larger than the negative control and/or a specific IgE concentration of 0.35 kU/L or higher. Furthermore, a documented history of symptoms occurring after food or drug intake was considered supportive evidence for food or drug allergy.

ABPA was diagnosed according to ISHAM Working Group criteria (28):
In patients with predisposing conditions (asthma, cystic fibrosis, chronic obstructive lung disease, bronchiectasis) or a compatible clinic, radiological presentation:
*Essential components
- *Aspergillus fumigatus*-specific IgE ≥0.35 kUA/L,
- Serum total IgE ≥500 IU/mL.

*Other components (any two)
- Positive IgG against *Aspergillus fumigatus*,
- Peripheral blood eosinophil count ≥500 cells/μL (could be historical),
- Thin-section chest computed tomography consistent with ABPA (bronchiectasis, mucus plugging, and high-attenuation mucus) or fleeting opacities on chest radiograph consistent with ABPA.

Patients presenting with the combination of asthma, eosinophilic chronic rhinosinusitis with nasal polyps, and respiratory reactions to NSAIDs particularly aspirin and other
Cyclooxygenase-1 (COX-1) inhibitors — are diagnosed with N-ERD (17).

Parasite eggs or cysts (Tenia, Schistosomiasis, Ascaris, Strongyloidiasis, Toxocara, Trichura, Trichinella, Enterobius vermicularis, Cystoisospora belli, fasciola) were examined in faeces (7).

CEP is diagnosed according to these criteria (29):
1. Diffuse pulmonary alveolar consolidation with air bronchogram and/or ground-glass opacities at chest imaging, especially with peripheral predominance.
2. Eosinophilia at bronchoalveolar lavage differential cell count 40% (or peripheral blood eosinophils 1000 cells/μL).
3. Respiratory symptoms present for at least 2 to 4 weeks.
4. Absence of other known causes of eosinophilic lung disease (especially exposure to drug susceptible to induce pulmonary eosinophilia).

EGPA diagnosed according to ACR classification (30) and/or chest (29):
1. Asthma,
2. Peripheral blood eosinophilia greater than 1500 cells/μL and/or alveolar eosinophilia greater than 25%,
3. Extrapulmonary clinical manifestations of disease (other than rhinosinusitis), with at least one of the following:
   a. Systemic manifestation typical of the disease: mononeuritis multiplex; or cardiomyopathy confidently attributed to the eosinophilic disorder; or palpable purpura;
   b. Any extrapulmonary manifestation with histopathological evidence of vasculitis as demonstrated especially by skin, muscle, or nerve biopsy;
   c. Any extrapulmonary manifestation with evidence of antineutrophil cytoplasmic antibodies with antimyeloperoxidase or antiproteinase three specificity.

Patients were diagnosed with HES by a hematologist if they exhibited sustained eosinophil counts exceeding 1500 cells/μL on two or more separate occasions spaced at least four weeks apart, accompanied by evidence of organ dysfunction or damage related to tissue eosinophilia, and after other potential causes of organ involvement had been ruled out (10). HES subtypes are myeloproliferative (M-HES) and lymphoproliferative (L-HES) forms (9).
Myeloproliferative Variant HES
Diagnostic Criteria:
- Presence of the FIP1L1-PDGFRA fusion gene FIP1-L1: Factor Interacting with PAPOLA and CPSF1-like 1, PDGFRA: Platelet-Derived Growth Factor Receptor Alpha)
- Bone marrow findings consistent with a myeloproliferative pattern, including:
  Hypercellularity
  - Increased eosinophilic precursors
- Elevated serum vitamin B12 levels and/or elevated serum tryptase
- Splenomegaly and/or hepatomegaly
- Other clonal cytogenetic or molecular abnormalities (PDGFRB: Platelet-Derived Growth Factor Receptor Beta, FGFR1: Fibroblast Growth Factor Receptor 1)

Lymphocytic Variant HES
Diagnostic Criteria:
- Detection of an aberrant T-cell population by flow cytometry:
  - $CD3^{-}CD4^{+}$ or $CD3^{+}CD4^{+}CD7^{-}$ phenotype,
- Evidence of T-cell clonality via T-cell receptor (TCR) gene rearrangement studies
- Elevated serum IL-5 levels,
- Common clinical features include skin involvement, lymphadenopathy, and autoimmune manifestations,
- Polyclonal hypergammaglobulinemia or elevated IgE levels in serum.

The diagnosis of **Systemic Mastocytosis** is based on the presence of one major and at least one minor criterion, or at least 3 minor criteria if the major criterion is absent (31). Major Criterion: *Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in bone marrow biopsy or in other extracutaneous organs. Minor Criteria: *>25% of mast cells in infiltrates are atypical or spindle-shaped, or presence of such morphology in bone marrow smears. *Detection of KIT D816V mutation in bone marrow, blood, or other extracutaneous organs. *Expression of CD2 and/or CD25 in addition to CD117 (KIT) on mast cells in bone marrow or other extracutaneous tissues. *Serum total tryptase level >20 ng/mL (Unless there is an associated clonal myeloid disorder that could elevate tryptase independently).
Gleich syndrome is associated with episodic angioedema, urticaria, pruritus, fever, weight gain and often high IgM levels associated with eosinophilia (32).

The diagnostic criteria for eosinophilic diseases are listed in the table below.

For the cases without underlying cause for eosinophilia, the terminology of undetermined etiology of eosinophilia (UEE) was used (33).

In this study, we divided eosinophilia patients into three groups according to peripheral blood AEC levels mild eosinophilia group 1000<AEC<1500cells/μL, moderate eosinophilia group 1500 ≤ AEC<5000 cells /μL, and severe eosinophilia group AEC ≥ 5000 cells/μL. We examined the identified etiological factors by classifying them into different categories based on their severity. This analysis allows us to gain a clearer understanding of each factor's impact and significance.

Statistical Analysis

The statistical evaluation was performed SPSS software (version 21.0 for Windows; SPSS Inc., Chicago, IL, USA). For parametric variables, means and standard deviations were reported, while non-parametric variables were described using medians and interquartile ranges. Categorical variables were presented as counts and percentages. Number of cases and percentages were used for categorical variables. Chi-square was used in the analysis of categorical variables. A p value of <0.05 was considered to show a statistically significant result.

RESULTS

A total of 232 patients were included, of whom 60% of were female, with a median age (interquartile range) of 47 (33-59) years. When smoking status was analyzed; 143 (61.6%) of the patients were non-smokers, 37 (15.9%) were current smokers and 52 (22.4%) were ex-smokers. Tryptase measurement was evaluated in 40 patients, and median tryptase level (interquartile range) was 6.36 (4.67-7.49) μg/L. B12 measurement was evaluated in 121 patients. The average B12 level was 384 ± 206 pg/mL. Sedimentation measurement was evaluated in 137 patients, and median sedimentation level was 16 (7-32) mm. The P-ANCA measurement was evaluated in 190 patients: 4/190 (2.1%) were (4/232, 1.7% overall). Out of 232 patients, 9 (3.8%) were found to have sensitivity to molds based on SPT results. Stool ova and parasite testing was performed in 66/232 patients (28.4%); 3/66 (4.5%) were positive (3/232, 1.3% overall). In 232 patients, the SPT showed that the most common sensitization was to mites (n= 70, 30.3%). Three patients tested positive for the FIP1L1-PDGFRA fusion gene, and one patient had a PDGFRB mutation, consistent with a diagnosis of myeloid variant hypereosinophilic syndrome (M-HES). Serum immunoglobulins were measured in 196 patients; ≥1 isotype was low in 19/196 (9.7%) [CVID 1/196 (0.5%), selective IgM 9/196 (4.6%), selective IgG 7/196 (3.6%), selective IgA 2/196 (1.0%)]. With the exception of CVID, cases of IID without eosinophilia-related clinical symptoms were found incidentally through lab tests. Baseline demographic, clinical and laboratory characteristics of the patients are given in Table 1.

Allergic diseases were AR (n= 65, 28%), asthma (n= 98, 42%), urticaria/angioedema (n= 22, 9%), drug allergy (n= 13, 5.6%), food allergy (n= 9, 3.8%), AD (n= 2, 0.8%). Of the patients with allergic diseases, 28% had more than one allergic disease. The most frequently co-occurring conditions were asthma and AR.

Table 1. Demographic and clinical features of the patients

	n= 232
Age, median (IQR)	47 (33-59)
Sex, female, n (%)	139 (60)
Absolute eosinophil count cells /µL, median (IQR)	1500 (1232-2115)
Total IgE IU/mL, median (IQR)	361 (104-1136)
CRP mg/dL, median (IQR)	3 (3-6)
*Sedimentation mm, median (IQR)	16 (7-32)
**Tryptase µg/L, median (IQR)	6.36 (4.67-7.49)
***B12 level pg/mL, mean ± SD	384 ± 206
Stool parasite examination, n (%)	66 (28.4)
Positive	3 (4.5)
Negative	63 (23.9)

*The sedimentation measurement was evaluated in 137 patients.
**The tryptase measurement was evaluated in 40 patients.
***B12 levelmeasurement was evaluated in 121 patients.
IQR: Interquartile ranges, IgE: Immunoglobulin E, CRP: C-reactive protein, SD: Standard deviation.

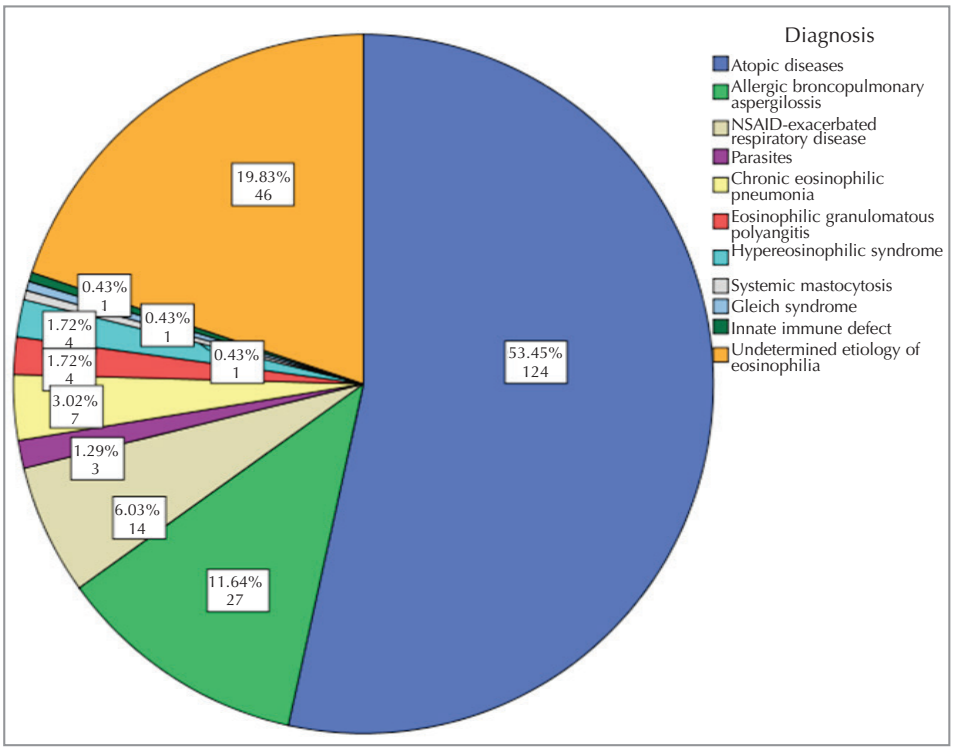

Figure 2. Diagnosis and classification of the patients with eosinophilia in the study.

Diagnoses of the patients as demonstrated in Figure 2: Atopic diseases were the most frequently identified diagnoses, observed in 124 patients (53.4%). ABPA (n= 27, 11.6%), N-ERD (n= 14, 6%), CEP (n= 7, 3%), EGPA (n= 4, 1.7%), HES (n= 4, 1.7%), Parasites (n= 3, 1.3%), systemic mastocytosis (n= 1, 0.4%), Gleich syndrome (n= 1, 0.4%), IID (n= 1, 0.4%).

When diagnoses were categorized based on eosinophilia severity, atopic diseases remained the most

Table 2. Eosinophilia severity and diagnoses of the patients in the study

	Mild 1000<AEC<1500 cells/µL n= 112 (48.2%)	Moderate 1500≤AEC<5000 cells/µL n= 112 (48.2%)	Severe 5000≤AEC cells/µL n= 8 (3.6%)	p
Atopic diseases (Allergic rhinitis, asthma, urticaria/angioedema, drug allergy, food allergy atopic dermatitis)	89 (38.3)	33 (14.2)	2 (0.8)	
Allergic broncopulmonary aspergillosis	5 (2.1)	20 (8.6)	2 (0.8)	
NSAID-exacerbated respiratory disease	9 (3.8)	5 (2.1)	-	
Parasites	-	3 (1.3)	-	
Chronic eosinophilic pneumonia	2 (0.8)	5 (2.1)	-	<0.001*
Eosinophilic granulomatosis polyangiitis	1 (0.4)	3 (1.3)	-	
Hypereosinophilic syndrome	-	3 (1.3)	1 (0.4)	
Systemic mastocytosis	-	1 (0.4)	-	
Gleich syndrome	-	-	1 (0.4)	
Innate immune defect	1 (0.4)	-	-	
Undetermined etiology of eosinophilia	5 (2.1)	39 (16.8)	2 (0.8)	

*Chi-square test.
AEC: Absolute eosinophil count.

frequently identified conditions across all severity levels (38.3% vs. 14.2% vs. 0.8% p< 0.001 respectively) (Table 2).

DISCUSSION

Increased blood eosinophil counts can often serve as an initial key indicator in laboratory findings for various diseases. The findings from our study revealed a link between blood eosinophil levels and various clinical manifestations among patients with eosinophilia. This study presented; most diagnosis of patients with eosinophilia were atopic diseases, ABPA and N-ERD respectively. Diagnoses such as parasitic infections, CEP, HES, EGPA, IID, Gleich syndrome, and mastocytosis were less frequently observed among patients with eosinophilia. Underlying etiology was identified in most of the cases (80.2%) and our study revealed three distinct patterns: Mild eosinophilia associated with especially, Atopic diseases, N-ERD and ABPA; moderate eosinophilia associated with especially UEE, atopic diseases, ABPA, CEP and EGPA; severe eosinophilia associated with especially HES and AD of atopic diseases in adult patients. Due to the few patients in the severe eosinophilia category, precise analysis was constrained.

In our study, different from the literature, we included cases with absolute eosinophil counts above 1000 cells /µL instead of those with absolute eosinophil counts above 500 cells /µL. Our aim with this method was to see the diagnoses between 1000 cells /µL and 1500 cells /µL more clearly by keeping the intervals narrower. Absolute eosinophil counts rarely exceed 1000 cells /µL patients with reactive eosinophilia (34). We think that this approach will make the results of our study more reliable and clinically meaningful. Moreover, selecting this threshold enhances the comparability of our study with existing literature and contributes to forming a more uniform patient population. Furthermore, once eosinophilia is identified, it is crucial to initially investigate possible reactive causes and determine if any eosinophil-associated organ damage is present. In some patients, tissue eosinophilia may be seen although eosinophil count is not very high, while in some patients, organ damage does not develop despite a very high absolute eosinophil count (6-7).

Patients with atopic disorders such as AR and asthma frequently present with mild eosinophilia (35). Mild to moderate eosinophilia can be observed in patients suffering from chronic rhinosinusitis and nasal polyps linked to N-ERD syndrome (17). Consistent with the literature, our study found that atopic diseases and N-ERD were common causes of mild to moderate eosinophilia (17,36).

In allergic asthma patients, ABPA linked to sensitization to Aspergillus can develop, sometimes with increased eosinophil levels (18). In this study, ABPA diagnosis was more frequent among patients with moderate eosinophilia than in those with mild eosinophilia. This finding could be explained by ABPA's tendency to trigger a stronger eosinophilic inflammatory reaction, especially during periods of active disease. Moderate eosinophilia may reflect ongoing airway inflammation and a heightened immunologic reaction to Aspergillus antigens, which are hallmarks of ABPA pathophysiology. Conversely, mild eosinophilia might represent an earlier or less active stage of the disease, potentially leading to underdiagnosis unless supported by other clinical and radiologic findings. Therefore, a moderate elevation in eosinophil count could serve as a more sensitive marker prompting further diagnostic workup for ABPA in appropriate clinical contexts.

Although parasitic infections represent a significant cause of eosinophilia, they usually lead to only mild to moderate increases in eosinophil levels (7,13,16). Only 1.3% (3/232) of eosinophilia in our study were caused by parasitic infection (including one case of Cystoisospora belli, one case of fasciolosis, one case of schistosomiasis,) and they were from the mild and moderate eosinophilia group. In another study, the frequency of parasitic infections in hypereosinophilia was 5.7% (37). Differences between these studies may be strongly related to various socioeconomic levels, hygiene conditions, climatic conditions. Given the epidemiological significance of parasitic diseases, eosinophilic patients with a history of travel to endemic zones and ongoing eosinophilia should be evaluated further through stool analysis and dermatoscopy to identify parasite eggs (38).

In patients with CEP, mild eosinophilia is present at the beginning, but moderate eosinophilia tends to develop later in the course of the disease (39). Among the seven patients diagnosed with CEP in our study, two exhibited mild eosinophilia while five presented with moderate eosinophilia. This trend indicates that as inflammation becomes more severe and pulmonary involvement increases, peripheral eosinophil counts may also gradually elevate. The predominance of moderate eosinophilia in our cohort may reflect a more advanced disease stage at the time of diagnosis or a delayed clinical presentation. These findings emphasize the importance of regularly tracking eosinophil levels and maintaining clinical vigilance in individuals with ongoing respiratory complaints, even when initial levels are only slightly elevated.

The degree of eosinophilia in EGPA cases has not been precisely determined. For example, retrospective in one analysis, mild degrees of eosinophilia were reported to be associated with certain rheumatic diseases (40). In our study, moderate eosinophilia was found in three of four patients with EGPA and mild eosinophilia was found in one patient. Eosinophilia levels may vary because diseases such as CEP and asthma might develop into EGPA over time (41). AEC ≥1000 cells /μL raises suspicion for EGPA, although a count of 5000 to 9000 cells/μL is more characteristic for EGPA (42). However, since we diagnosed EGPA at an early stage and started treatment, we did not find severe eosinophilia.

Detection of eosinophilia requires an initial examination of possible reactive factors and the assessment of end-organ damage. Organ damage cannot be diagnosed on the basis of absolute eosinophil counts (43). Tissue damage might be present in some patients without notably high eosinophil counts, while in others, high eosinophil levels do not necessarily result in organ damage (10). Absolute eosinophil count does not make a definite diagnosis, but according to its level gives an idea about differential diagnosis (1). Diagnostic evaluation of eosinophilia is challenging, in part because secondary causes of eosinophilia such as lymphocyte-variant HES (L-HES) and vasculitis are difficult to diagnose. In this study, we grouped the patients according to absolute eosinophil counts and analyzed their diagnoses. This is a comprehensive study analyzing patients with eosinophilia in our country and informing about the differential diagnosis of eosinophilia. The degree of blood eosinophilia is commonly thought to be correlated with the severity of disease, but there is no evidence to support this except anecdotal experience in patients with severe eosinophilia (44). A recent study describes a rare group of people with asymptomatic hypereosinophilia and no evidence of end-organ damage despite exhaustive and regular evaluation for it (45). HES was seen in three patients with moderate eosinophilia and in a one patient from the group with severe eosinophilia within the study cohort. This finding may suggest that the clinical manifestation of HES does not always correlate linearly with the absolute eosinophil count, highlighting the importance of comprehensive clinical evaluation rather than reli-

ance solely on eosinophil thresholds. Moderate eosinophilia levels can still result in end-organ damage. In our cohort, three HES patients were positive for the FIP1L1-PDGFRA fusion gene, while one was positive for PDGFRB. End-organ effects included cardiac involvement in four patients, thromboembolic incidents in three, pulmonary involvement mimicking asthma in two (characterized by cough and ground-glass CT findings), splenomegaly in two, gastrointestinal symptoms in one, and neurological issues such as neuropathy in one patient. The mastocytosis patient carried the KIT-D816V mutation and presented with eosinophilia-associated symptoms like maculopapular skin eruptions, splenomegaly, diarrhea, and bronchial obstruction.

HES's, Gleich syndrome and systemic mastocytosis are the causes of primary eosinophilia, while other etiologies are the causes of secondary eosinophilia (16). Our research identified Gleich syndrome as the underlying condition in a single patient presenting with severe eosinophilia. Gleich syndrome, also known as episodic angioedema with eosinophilia, is an extremely rare disorder characterized by recurrent episodes of angioedema, weight gain, fever, and marked peripheral eosinophilia (32). The exact pathogenesis is unclear, but it is thought to involve an imbalance in cytokine production, with interleukin-5 driving eosinophil expansion and activation (46). Due to its rarity and overlapping features with other eosinophilic disorders, Gleich syndrome is often under-recognized and may be misdiagnosed as HES or EGPA in the absence of a detailed clinical history. Recurrent episodes of angioedema and laboratory evidence of isolated eosinophilia, in the absence of systemic or organ involvement, supported the diagnosis. This case highlights the importance of considering rare eosinophilic syndromes in the differential diagnosis of severe eosinophilia and underscores the role of clinical vigilance in identifying atypical presentations.

The research by Çetinkaya et al. showed that allergic diseases mainly caused eosinophilia in pediatric patients with mild and moderate severity, with IID being most frequent in the severe group (33). Similarly, our findings in the adult group indicated that allergic conditions were the predominant causes of mild to moderate eosinophilia. However, unlike the pediatric cohort, IID was only identified in the mild eosinophilia group. The observed difference might be due to distinct clinical features and diagnostic processes of IID in adult populations compared to children. In adulthood, IID often manifest with atypical or milder eosinophilic responses, which may delay recognition or result in underdiagnosis, particularly in severe eosinophilia cases where other secondary causes are prioritized. A possible reason for the higher frequency of IID in severe eosinophilia among pediatric cases is their prompt evaluation by immunology experts. The data suggest that even in cases of mild eosinophilia, clinicians should remain alert to the potential for IID in adults, particularly if immune dysfunction or repeated infections are present.

While most cases had an identified underlying diagnosis, existing literature shows inconsistent findings and variable prevalence of unexplained eosinophilia etiologies. For example, Çetinkaya et al. reported that 11.5% of hypereosinophilic patients lacked a clear diagnosis, Beyaz et al. observed a 9% rate of undetermined causes, and another study found that nearly 30% of patients did not have a definitive etiology (33,36,47). More recently, a report documented the frequency of UEE as 23.3% (48). The etiology of eosinophilia remained unexplained in 19.8% of patients in this research. The variability between study findings may arise from limitations in retrospective data, insufficient patient history information, and the unavailability of comprehensive diagnostic techniques and collaborative specialist evaluations.

This study had several limitations, primarily due to its retrospective nature, which restricted access to complete clinical data for all patients. In addition, not every patient underwent stool parasite examination, bone marrow biopsy, or peripheral blood smear analysis. The findings are based on data from a single tertiary care center, which may limit generalizability. We developed a systematic algorithm to categorize patients referred to the Chest Diseases, Immunology, and Allergy Clinic with eosinophilia and to guide their clinical management. In this study, the comprehensive evaluation of patients with eosinophilia revealed that atopic diseases remain the most common underlying conditions, regardless of the severity of eosinophilia. However, the detection of rarer but clinically significant diagnoses such as ABPA, HES, and EGPA highlights the importance of a thorough differential diagnosis. These results offer important guidance to pulmonologists and allergy/immunology specialists, acting as a useful resource for the diagnostic evaluation of eosinophilia in everyday clinical settings. Nonetheless, by including a relatively large

patient cohort and being conducted in a specialized tertiary setting, the study offers valuable insights into the clinical characteristics of eosinophilia.

CONCLUSION

This study contributes to a better understanding of the relationship between atopic diseases and peripheral blood eosinophilia, highlighting the diagnostic value of blood eosinophil levels as they often correlate with distinct clinical conditions. The level of eosinophilia may guide clinicians toward different diagnostic pathways; however, it should not be interpreted in isolation. Accurate differential diagnosis still relies on a comprehensive clinical history, careful physical examination, and focused diagnostic tests. Although this study is limited by its retrospective design, it underscores the value of a comprehensive, multidisciplinary assessment in the evaluation of eosinophilia and supports the integration of more advanced diagnostic approaches into routine clinical practice. Further prospective research with broader patient populations is essential to enhance comprehension of the diagnostic relevance of eosinophilia.

Ethical Committee Approval: This study was approved by the S.B.Ü. Süreyya Paşa Chest Diseases and Thoracic Surgery Non-Interventional Clinical Research Ethics Committee (Decision no: 116.2017.R-321, Date: 21.09.2023).

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CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: ÖA, AC, FMT

Analysis/Interpretation: ŞÖ, BA, ÖA

Data acquisition: AC, FMT, BA

Writing: ÖA, FMT, AC, ŞÖ

Clinical Revision: BA, FMT, ŞÖ

Final Approval: AC, ÖA, FMT

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