ISTANBUL UNIVERSITY PRESS

RESEARCH / ARAŞTIRMA
DOI: 10.26650/IUITFD.1068715
İst Tıp Fak Derg 2022 / J Ist Faculty Med 2022

CHARACTERIZATION OF CONSULTATIONS REQUESTED FOR PATIENTS WITH ELEVATED BLOOD EOSINOPHILS: A TERTIARY IMMUNOLOGY AND ALLERGY CLINIC EXPERIENCE

YÜKSEK KAN EOZİNOFİL SAYISI NEDENİYLE TALEP EDİLEN KONSULTASYONLARIN KARAKTERİZASYONU: ÜÇÜNCÜ BASAMAK BİR İMMUNOLOJİ VE ALERJİ KLİNİĞİ DENEYİMİ

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Cite this article as: Beyaz S, Celebi Sozener Z, Soyyigit S. Characterization of consultations requested for patients with elevated blood eosinophils: A tertiary immunology and allergy clinic experience. J Ist Faculty Med 2022;85(3):370-7. doi: 10.26650/IUITFD.1068715

ABSTRACT

Objective: Blood eosinophilia has become a common laboratory abnormality and its characterization poses a dilemma for physicians. As a result, physicians often consult specialists in immunology and allergy in order to evaluate patients with high eosinophils, with the general assumption of an underlying allergic or immunologic cause. However, there is little data in the literature regarding consultations requested from immunology and allergy clinics because of eosinophilia. This study aimed to evaluate the clinical and demographic characteristics of patients who were consulted to the allergy clinic because of eosinophilia and detail the etiologies of eosinophilia.

Methods: The medical records of 1366 patients consulted to the allergy clinic were evaluated retrospectively, and the data of 143 patients who were consulted for eosinophilia were investigated.

Results: The median (range) eosinophil count was 2456 cells/mm^3 (520-42920). Eighty six (60.1%) patients were classified as mild (500 to 1500 cells/mm^3), 44 (30.8%) patients as moderate (1500 to 5000 cells/mm^3), and 13 (9.1%) patients as severe (≥5000 cells/mm^3) eosinophilia. The most frequently consulted departments were chest diseases (37.1%), internal medicine (34.2%), and dermatology (14.7%), respectively. While the most common clinical symptoms at presentation were cough, dyspnea, pruritus, rhinitis, and gastrointestinal symptoms, 49 (34.3%) patients were asymptomatic. The mean±SD vitamin B12 and tryptase levels were 424.2±240.5 pg/mL, and 4.48±1.76 ng/mL, respectively. The median total IgE level was 150 IU/mL (1.5-9464). Atopy was

ÖZET

Amaç: Tam kan sayımı ölçümlerinin yaygın olarak kullanılmaya başlanmasıyla eozinofil yüksekliği sık görülen bir laboratuvar anormalliği haline gelmiştir. Tanısal değerlendirmesi hekimler için zorluk teşkil eden eozinofili, genellikle altta yatan bir alerjik veya immünolojik hastalık varlığı genel varsayımı ile immünoloji ve alerji uzmanlarına sık konsülte edilmektedir. Ancak eozinofili nedeniyle immünoloji ve alerji kliniklerinden istenen konsültasyonların değerlendirmelerine ilişkin literatürde çok az bilgi vardır. Bu çalışmada eozinofili nedeniyle alerji kliniğine yönlendirilen hastaların klinik ve demografik özelliklerinin değerlendirilmesi ve eozinofili etiyolojilerinin detaylandırılması amaçlanmıştır.

Yöntem: Bir yıllık süre içinde immünoloji ve alerji kliniğimize konsülte edilen 1366 hastanın tıbbi kayıtları geriye dönük olarak tarandı.

Sonuçlar: Hastaların medyan (aralık) eozinofil sayısı 2456 hücre/mm^3 (520-42920) idi. Eozinofil yüksekliklerine göre sınıflandırıldıklarında; 86 (%60,1) hasta hafif (500 ila 1500 hücre/mm^3), 44 (%30,8) hasta orta (1500 ila 5000 hücre/mm^3) ve 13 (%9,1) hasta şiddetli (≥5000 hücre/mm^3) eozinofili olarak sınıflandırıldı. En sık konsültasyon isteyen bölümler sırasıyla göğüs hastalıkları (%37,1), iç hastalıkları (%34,2) ve dermatoloji (%14,7) idi. Başvuru anında en sık görülen klinik semptomlar öksürük, nefes darlığı, kaşıntı, rinit ve gastrointestinal semptomlar iken, 49 (%34,3) hasta asemptomatikti. Ortalama±SD vitamin B12 ve triptaz seviyeleri sırasıyla 424.2±240,5 pg/mL ve 4.48±1.76 ng/mL idi. Medyan total IgE seviyesi 150 IU/mL (1.5-9464) idi. Hastaların %26,6'sında

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Submitted/Başvuru: 07.02.2022 • **Revision Requested/Revizyon Talebi:** 13.03.2022 •
Last Revision Received/Son Revizyon: 13.03.2022 • **Accepted/Kabul:** 21.03.2022 • **Published Online/Online Yayın:** 10.05.2022

identified in 26.6% (n=38) of the patients. Among 143 eosinophilia patients, there were no patients diagnosed with myeloproliferative or lymphocytic variants of hypereosinophilic syndrome (HES), eight patients were diagnosed with idiopathic HES. While the most common underlying causes were asthma (n=38) and allergic rhinitis (n=20), 30 patients had non-allergic causes.

Conclusion: Although parasitic infections and allergic diseases are the first etiologies that come to mind when eosinophilia is detected in a patient, a specific anamnesis and advanced diagnostic tests for differential should be performed in order to detect other underlying or accompanying conditions apart from these diseases.

Keywords: Allergy consultation, Eosinophilia, Eosinophil-related disorders, Hypereosinophilia, Hypereosinophilic syndrome

(n=38) atopi tespit edildi. 143 eozinofili hastası arasında hipereozinofilik sendrom (HES)'in miyeloproliferatif veya lenfositik varyantları tanısı konan hiçbir hasta yoktu, sekiz hastaya idiyopatik HES tanısı kondu. En sık altta yatan eozinofili nedenleri astım (n=38) ve alerjik rinit (n=20) iken, 30 hastada altta yatan nedenler alerjik değildi.

Tartışma: Bir hastada eozinofili saptandığında akla ilk gelen etiyolojiler paraziter enfeksiyonlar ve alerjik hastalıklar olsa da, bu hastalıklar dışında altta yatan veya eşlik eden diğer durumların saptanması için detaylı bir anamnez ve ayırıcı tanı için ileri tanı testleri yapılmalıdır.

Anahtar Kelimeler: Alerji konsültasyonu, Eozinofili, Eozinofil-ilişkili hastalıklar, Hipereozinofili, Hipereozinofilik sendrom

INTRODUCTION

Eosinophils are cells that develop from myeloid cells in the bone marrow and differentiate terminally before being released into the blood (1). Eosinophil development is dependent on many cytokines, including IL-5, IL-3, and GM-CSF (1-3). Although eosinophils are found in the circulation, they are mainly tissue-dwelling leukocytes, where they are found a hundred times more (3). Eosinophils can contribute to tissue damage, repair, remodeling, and disease persistence by producing granule proteins and chemical mediators in various diseases such as asthma, chronic rhinosinusitis with nasal polyps, eosinophilic gastrointestinal disorders (EGID), eosinophilic granulomatosis with polyangiitis (EGPA), drug hypersensitivity reactions (DHRs), or hypereosinophilic syndrome (HES) (1-4). In addition to their well-known role in body defense against parasitic infections, eosinophils are also recognized to contribute to body homeostasis (2, 3).

Absolute eosinophil count (AEC) is used for defining an increase in eosinophils (5). The normal eosinophil count is 350 to 500 cells/mm^3 (5). In the case of greater than 500 eosinophils/mm^3, eosinophilia is mentioned (5). The severity of eosinophilia is classified as mild (500 to 1500 cells/mm^3), moderate (1500 to 5000 cells/mm^3), and severe (≥5000 cells/mm^3) (5). The persistent eosinophilia ≥1500 cells/mm^3 is defined as hypereosinophilia (HE) (5). HES refers to a group of disorders in which the evidence of end-organ damage is found as a result of hypereosinophlia (HE) (5). With the widespread use of complete blood count measurement, eosinophilia has begun to be detected frequently in general clinical practice, and thus it has become a more common problem that causes more frequent referrals to specialists. Eosinophilia can be caused by clonal disorders (primary) or by reactive (secondary) conditions that account for the vast majority of cases (5). Although eosinophilia is often associated with parasitic infections, pulmonary disorders, non-parasitic infections, skin diseases, inflammatory and autoimmune diseases, and malignancies, allergic diseases are one of the common causes of reactive eosinophilia. Thus, eosinophilia, which requires a multidisciplinary approach, leads to more consultations from various fields of expertise especially immunology and allergic diseases specialists. In addition, there is little data in the literature regarding consultations requested from immunology and allergy clinics because of eosinophilia. Herein, this study aimed to evaluate the clinical and demographic characteristics of patients who were consulted to the allergy clinic because of eosinophilia and detail the etiologies of eosinophilia.

METHODS

Study group

This retrospective chart review study was performed in the adult allergy clinic at a tertiary center in Ankara, Turkiye. Data were collected between August 2020 and September 2021. The study population consisted of patients consulted to our adult allergy clinic for the evaluation of peripheral eosinophilia (≥500 cells/mm^3). Patients aged 18 years and older, who were measured at least four weeks apart and who had eosinophilia at least twice, were included in the study. This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was obtained from the Ankara City Hospital Ethics Committee (Date: 01.09.2021, No: E2-21-790), and written informed consent was obtained from all study subjects.

Clinical and demographic assessment

In a one year period, 143 patients, who were referred for eosinophilia from 1366 consultations requested from our allergy clinic and whose full evaluation was performed, were included in the study. Baseline data on patient detailed demographic and clinical characteristics including the presence of symptoms, the types of symptoms, the duration of eosinophilia, treatment details, the presence of comorbidities, and/or concomitant drug use were recorded. In addition, data on the standard diagnostic

evaluation of patients involving laboratory testing [CBC, liver and kidney function tests, peripheral smear, vitamin B12, troponin, serum tryptase, total immunoglobulin (Ig) E, IgA, IgM, IgG, skin prick test or allergen-specific IgE, aspergillus specific IgE and IgG, antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibodies (ANCAs) (myeloperoxidase and proteinase-3), rheumatoid factor (RF), anti-citrullinated protein antibody (anti-CCP), stool/serology for parasites, bacterial, fungal and mycobacterial cultures and/or PCR testing, *FIP1L1/PDFGRA, PDGFRB, BCR-ABL, KIT, FGFR1* and *JAK-2* mutation status], imaging procedures [which were carried out depending on the patients' symptoms, including pulmonary function test, chest radiography, computed tomography (CT), magnetic resonance (MR), electrocardiography, echocardiography, electromyography, and endoscopic imaging], and histopathology (in case of indication, bone marrow aspiration and biopsy, and the associated organ biopsy) results were recorded from the patients' medical files.

Statistical analysis

The SPSS 25.0 package program (SPSS Inc., Armonk, NY, USA) was used for statistical analyses. The descriptive characteristics of the patients are presented as mean± standard deviation, median (range), or frequency (%). The normality of data was verified by the Kolmogorov-Smirnov test. The chi-square test and Mann-Whitney U test were used to compare categorical and continuous variables, respectively. The statistical significance level was set at a p-value less than 0.05. The graphical analyses were performed using the GraphPad Prism software (San Diego, CA, USA).

RESULTS

Clinical and demographical characteristics of the study population

There were 71 females (49.7%) and 72 males (50.3%), with a mean±SD age of 45.25±16.89 years (range 18-88) (Table 1). The patients did not live in a geographical residence endemic to any parasite and had no travel history before eosinophilia was detected. There were no patients with an HIV infection. Approximately 57.3% (n=82) of the patients had at least one comorbidity at admission that was previously diagnosed, and 36.8% of patients were current smokers (Table 1). A total of 79 (55.2%) patients had an additional drug use and the distribution of the drugs used was long-acting beta-agonist and inhaled corticosteroids (n=28), leukotriene receptor antagonist (n=25), beta-blocker (n=14), nasal corticosteroid (n=12), acetylsalicylic acid (n=12), calcium channel blocker (n=9), statin (n=9), angiotensin-receptor blockers (n=9), levothyroxine (n=9), metformin (n=8), angiotensin-converting-enzyme inhibitors (n=8), antihistamine (n=6), ipratropium bromide (n=6), PPI (n=6), clopidogrel (n=5), dipeptidyl peptidase-4 inhibitors (n=4), prednisolone (n=3), mesalazine (n=2), colchicine (n=2), methotrexate (n=2), and adalimumab (n=1). And also, patients with malignancies were receiving relevant treatments. 17 (11.9%) patients had nasal polyposis, and three of these patients had non-steroidal anti-inflammatory drug hypersensitivity. The detailed demographic characteristics of these 143 patients are shown in Table 1.

Table 1: The demographic characteristics of the study population at admission

Parameter	Number (%)
Age, mean±SD (year)	45.25±16.89
Gender	
Female	71 (49.7)
Male	72 (50.3)
Smoking status (current)	54 (36.8)
Comorbidities	
Allergic rhinitis	16 (11.2)
Asthma	31 (21.7)
Cardiovascular diseases	12 (8.4)
Diabetes mellitus	12 (8.4)
Hypertension	20 (14)
Hypothyroidism	9 (6.3)
Ulcerative colitis	3 (2.1)
Psoriasis	1 (0.7)
Rheumatoid arthritis	2 (1.4)
Systemic lupus erythematosus	1 (0.7)
Urticaria and angioedema	6 (4.2)
Malignancies	
Lung	2 (1.4)
Hodgkin lymphoma	1 (0.7)
Atopy	
House dust mite	16 (11.2)
Pollens	19 (13.2)
Mold	1 (0.7)
Animal dander	6 (4.2)
Food	2 (1.4)

Data are presented as n (%) unless otherwise stated.

The departments that most frequently referred patients were examined, it was observed that the department of internal medicine (with all divisions) (34.2%), chest diseases (37.1%), and dermatology (14.7%) constituted the vast majority (Figure 1). While the most common clinical symptoms at presentation were cough, dyspnea, pruri-

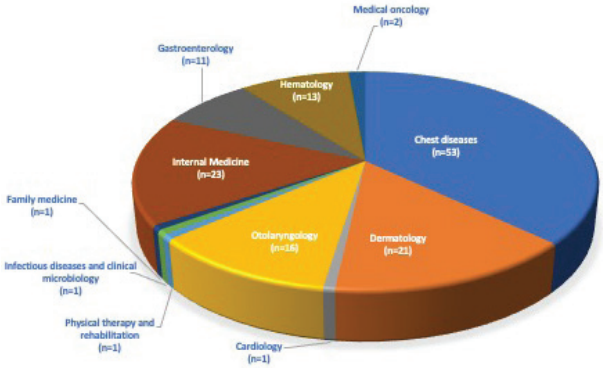


Figure 1: Departments where patients are consulted

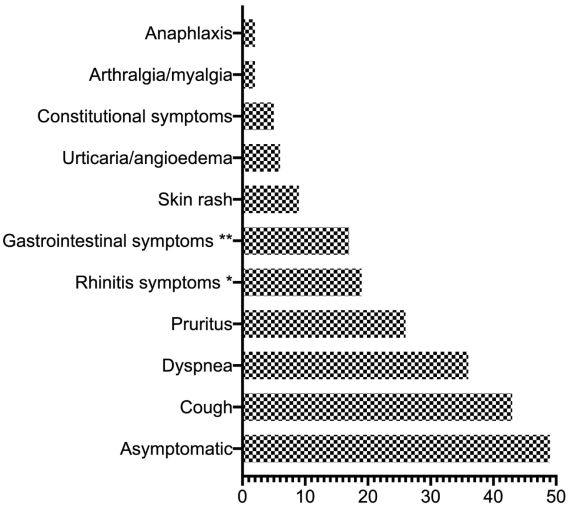


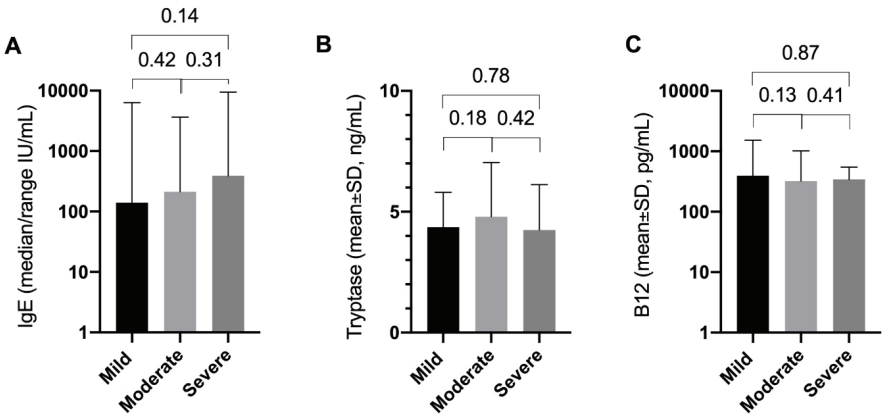
Figure 2: Clinical symptoms of patients

tus, rhinitis symptoms (sneezing, a runny nose, a blocked nose, and/or itchy nose, eyes, ears, and throat), and gastrointestinal symptoms (abdominal pain, dyspeptic symptoms, or diarrhea), the skin rashes, urticaria/angioedema, constitutional symptoms, arthralgia /myalgia, or anaphylaxis were the less common symptoms (Figure 2). In addition, 49 (34.3%) patients were asymptomatic when they were referred (Figure 2). The eosinophilia was detected in those patients either during the follow-up of their comorbid diseases or incidentally on routine CBC measurement.

Diagnostic test results of the study population

The median (range) eosinophil count was 2456 cells/mm^3 (520-42920). When patients were grouped according to the severity of eosinophilia, 86 (60.1%) patients were classified as mild (500 to 1500 cells/mm^3), 44 (30.8%) patients as moderate (1500 to 5000 cells/mm^3), and 13 (9.1%) patients as severe (≥5000 cells/mm^3). The median (range) duration of eosinophilia was 12 (2-82) months. There was no difference between males and females with respect to age (47±15.1 vs 43.5±18.4, p=0.20) and AEC [1020 cells/mm^3 (520-16410) vs 1310 cells/mm^3 (530-42920), p=0.39].

There was no association between the degree of eosinophilia and the presence of symptoms, sex, age, skin prick test positivity, current smoking status, or the presence of allergic diseases (p>0.05). In contrast, we found that end-organ damage was significantly higher in patients with moderate and severe eosinophilia than in patients with mild eosinophilia (p=0.021). Atopy (positive skin prick test or allergen sIgE) was identified in 26.6% (n=38) of the patients (Table 1). The mean±SD vitamin B12 and tryptase levels were 424.2±240.5 pg/mL, and 4.48±1.76 ng/mL, respectively. The median (range) total IgE level was 150 IU/mL (1.5-9464). The IgA, M, and G levels of patients were normal. When the laboratory findings were compared depending on the degree of eosinophilia, no statistically significant difference was found between the groups in terms of vitamin B12, tryptase, and total IgE levels (p>0.05) (Supplement Figure 1). It was found that two patients had positive troponin test results and one



Supplement Figure 1: Comparison of laboratory findings according to the severity of eosinophilia.

patient had elevated aspergillus sIgE and IgG. While ANCAs were negative in all patients, ANA and RF/anti-CCP were positive in 17 (one had SLE diagnosis) and two patients (both had RA diagnosis), respectively. Parasitic infections such as giardiasis and entamoeba histolytica were positive in one patient each.

In addition, 27 patients had abnormal chest CT scans including bronchial wall thickening, ground-glass opacities, bronchiectasis, pulmonary nodules, or consolidation areas. Of these 27 patients, three patients had lung cancer and 1 had eosinophilic pleural effusion. In 17 patients, nasal polyposis was confirmed by a CT scan. Abnormalities in echocardiography and/or cardiac MR were observed in three patients, while only two had elevated troponin. Hydatid cysts were detected in the liver of only two patients by CT scan and serologic test (indirect hemagglutination). Electromyography showed sensory-motor axonal mononeuritis multiplex in only one patient.

In our cohort, 47 patients with HE were investigated for bone marrow morphology and karyotype, *FIP1L1-PDGFRA, PDGFRB, BCR-ABL, KIT, FGFR1,* and *JAK-2* mutations. All karyotypes appeared normal and no mutation was detected in any patient. All patients had an increased level of eosinophils on bone marrow examination and approximately 20% of the bone marrow samples showed hypercellularity, but only three patients had a percentage of eosinophils in the bone marrow that exceeded 20% of all nucleated cells.

Active gastritis and H. pylori positivity were detected in eight of the patients who applied with gastrointestinal system symptoms and underwent gastroscopy and/or colonoscopy. In addition, extensive eosinophilic infiltration (>40%) was detected in liver biopsy in two patients, and peritoneal nodule and eosinophilic infiltration were detected in one patient. Besides, eosinophilic esophagitis in one patient, eosinophilic gastroenteritis in two patients, and eosinophilic colitis in one patient were confirmed by biopsy. Skin biopsy results confirmed the diagnosis of atopic dermatitis in six patients, drug hypersensitivity in three patients, and HES in two patients. The diagnosis of scabies was confirmed in two patients by identifying the mite or mite eggs, and similarly, the diagnosis of dermatophytosis was confirmed in two patients by microscopic examination.

The final eosinophilia-related diagnosis of the study population

While there were no patients diagnosed with myeloproliferative or lymphocytic variants of HES, eight patients were diagnosed with idiopathic HES. In addition, idiopathic eosinophilia and idiopathic HE were diagnosed in five and eight patients, respectively. Among the remaining 122 patients, the most common underlying causes were asthma (n=39) and allergic rhinitis (n=19). In particular, the underlying non-allergic causes of eosinophilia in 38 of the remaining 122 patients were as follows; chronic eosinophilic pneumonia (n=8), H. pylori infection (n=8), autoimmune/inflammatory disorders (n=7), parasitic infection (n=6), neoplasms (n=4), EGPA (n=3), and fungal infection (n=2), respectively. The underlying diagnoses of eosinophilia according to the consulting departments and eosinophil severity are detailed in Table 2.

DISCUSSION

Eosinophil-related disorders can affect almost any tissue and organ in the body regardless of the severity of eosinophilia. Peripheral eosinophilia has become one of the common problems faced by different disciplines in clinical practice, and thus it has become one of the important reasons for consultation requests. To our knowledge, this is the first study in our country to evaluate the consultations requested from the immunology and allergy department due to peripheral eosinophilia. In our study, the overall prevalence of eosinophilia, which was consulted to the immunology and allergy department, was 10.5% (143/1366). It was observed that the departments that most frequently requested consultations were chest diseases, internal medicine, dermatology, and otolaryngology (139/143). In addition, of the 143 patients evaluated for eosinophilia in the current study, the underlying cause of eosinophilia could be determined in approximately 91% of patients.

In a study evaluating HE, 6% of patients had primary HES and 14% of patients were diagnosed with idiopathic HE or idiopathic HES (6). On the other hand, in a previous study, the diagnosis of idiopathic HES was reported as the most common cause of HE (47%) (7). In this study, approximately 14% of patients with HE were diagnosed with idiopathic HES. There was no patient diagnosed with primary or reactive (lymphocytic) HES in our study.

The etiology of eosinophilia varies by geographic regions or the presence of a travel history (8, 9). Parasitic, bacterial, viral, and fungal infections are among the most common etiologies of reactive eosinophilia in both children and adults (9-11). A previous study showed that parasite infestation is the most common cause of secondary eosinophilia (52%) (12). In another study, parasitic infections were found to be responsible for eosinophilia in 15.7% of patients (8). Similarly, in a previous study investigating the causes of pediatric and adult HE showed that parasitic infections were the underlying cause in 14% of children and 10% of adults (7). Conversely, in this study, we found that parasitic infection as the cause of reactive eosinophilia in only 2.8% of patients. In addition, in this study non-parasitic infections (aspergillus, dermatophyte, and H. pylori) were found in 8.4% of patients. The H. pylori infection was found as the cause of eosinophilia in 5.6% of our patients and similarly, the previous studies have

Table 2: The final diagnosis of patients according to the consulting departments and severity of eosinophilia (n=143)

Departments requesting consultation	Severity of eosinophilia			Final diagnosis
	Mild	Moderate	Severe	
Chest diseases (n=53)	33	18	2	- ABPA (n=1) - Allergic rhinitis (n=5) - Asthma (n=35) - Chronic eosinophilic pneumonia (n=8) - EGPA (n=2) - AERD (n=2)
Internal medicine (n=23)	12	11	-	- Asthma (n=2) - Drug hypersensitivity (n=1) - EGPA (n=1) - Food allergy (n=1) - HES (n=2) - Hodgkin Lymphoma (n=1) - H. pylori infection (n=5) - Urticaria/angioedema (n=4) - Ulcerative colitis (n=2) - Parasitic infections (n=4)
Dermatology (n=21)	15	5	1	- Allergic rhinitis (n=2) - Dermatitis (n=6) - Dermatophytosis (n=2) - Drug hypersensitivity (n=2) - Food allergy (n=1) - HES (n=2) - Systemic lupus erythematosus (n=1) - Urticaria/angioedema (n=2) - Psoriasis (n=1) - Scabies (n=2)
Otolaryngology (n=16)	12	2	2	- Allergic fungal rhinosinusitis (n=1) - Allergic rhinitis (n=12) - Asthma (n=2) - AERD (n=1)
Hematology (n=13)	4	6	3	- Idiopathic eosinophilia (n=4) - Idiopathic HE (n=8) - HES (n=1)
Gastroenterology (n=11)	4	2	5	- EGID (n=4) - H. pylori infection (n=3) - HES (n=3) - Ulcerative colitis (n=1)
Medical oncology (n=2)	2	-	-	- Lung cancer (n=2)
Cardiology (n=1)	1	-	-	- Idiopathic eosinophilia (n=1)
Infectious diseases and clinical microbiology (n=1)	1	-	-	- Lung cancer (n=1)
Physical therapy and rehabilitation (n=1)	1	-	-	- Rheumatoid arthritis (n=1)
Family medicine (n=1)	1	-	-	- Rheumatoid arthritis (n=1)

ABPA: Allergic bronchopulmonary aspergillosis, EGID: eosinophilic gastrointestinal disorders (eosinophilic esophagitis, eosinophilic gastroenteritis, and eosinophilic colitis), EGPA: Eosinophilic granulomatosis with polyangiitis, HE: Hypereosinophilia, HES: Hypereosinophilic syndrome, PSC: Primary sclerosing cholangitis

reported that eosinophil counts increase in the stomach during H. pylori infection (13-15).

Common causes of mild to moderate eosinophilia are allergic diseases such as atopic dermatitis, drug hypersensitivity, urticaria/angioedema, allergic rhinitis, and asthma (10). Mild-to-moderate eosinophilia was also more common in our study, and we identified allergic diseases including asthma and allergic rhinitis are the most common cause of this mild-to-moderate eosinophilia. Presence of atopy (OR:1.64, 95% CI:1.50-1.80), active smoking (OR:1.72, 95% CI:1.52-1.96), and diagnosis of asthma (OR:2.05, 95% CI:1.70-2.51) were found to be significantly associated with high blood eosinophil counts in a large cohort study (16). In line with these results, 26.6% of our patients had atopy, 36.8% were active smokers, and 30% had asthma. On the other hand, persistent and severe eosinophilia or end-organ damage cannot be explained by asthma, smoking, or atopy alone and requires a good differential diagnosis. In addition, sinonasal and pulmonary involvement was prominent in clinical symptoms in our cohort. In the case of eosinophilia with sinonasal and pulmonary symptoms overlapping clinical, laboratory, and radiological features, many underlying diseases should be evaluated such as allergic rhinitis, asthma, chronic rhinosinusitis, EGPA, ABPA, AERD, CEP, HES, or COPD (17, 18). In this study, 13.3% of patients had pulmonary involvement (except asthma), and were as follows; CEP (n=8), HES (n=3), EGPA (n=3), AERD (n=3) and ABPA (n=1), respectively. Antibiotics, NSAIDs, and hypersensitivity reactions to anti-epileptic drugs are cited as common causes of eosinophilia, but almost any drug, herbal remedy, or supplement can be a trigger (19, 20). Drug-related eosinophilia was reported as the most common cause of eosinophilia (24.5%) in a previous study (8). Besides, in a pediatric cohort, 2.8% of patients had DHRs as a cause of eosinophilia (21). Similarly, in our study, only three patients had DHRs.

EGIDs, which are rare conditions characterized by high levels of eosinophilic infiltration of different parts of the GIS in the absence of an identifiable secondary cause, include eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis (22, 23). The prevalence of eosinophilic esophagitis is more common than other EGIDs and is approximately 57 cases/100,000 people (24). However, the prevalence of these other EGIDs were found around 3.3-8.4 cases/100,000 people (22). Whereas, in our cohort, the diagnosis of EGIDs was higher and 2.8% of the patients were diagnosed. In addition, the less common etiologies of secondary HE, which includes neoplasms, vasculitis, and autoimmune disorders, should be kept in mind. In our study, these etiologies were found in 9.8% of patients.

Although a relationship between blood eosinophil levels and end-organ damage symptoms has not yet been proven, we observed in this study that eosinophil levels were higher in patients with end-organ damage. In a large cohort study, risks of respiratory (OR: 2.11, 95% CI:1.96-2.27, p<0.001) and skin (OR:1.88 95% CI:1.64-2.15, p<0.001) end-organ damage at an eosinophil count of 750 cells/mm^3 were found increased about two-fold (25). Consistent with the findings of this study, the eosinophil count of all patients with end-organ damage was over 750 cells/mm^3 in our cohort.

In conclusion, although parasitic infections and allergic diseases are the first etiologies that come to mind when eosinophilia is detected in a patient, a specific anamnesis and advanced diagnostic tests for differential should be performed in order to detect other underlying or accompanying conditions apart from these diseases. Treatment of the underlying disease will prevent organ damage that may occur at any eosinophil levels.

Ethics Committee Approval: This study was approved by Ankara City Hospital Ethics Comittee (Date: 01.09.2021 No: E2-21-790).

Informed Consent: Written consent was obtained from the participants

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Ş.B., Z.Ç.S., Ş.S.; Data Acquisition- Ş.B., Z.Ç.S., Ş.S.; Data Analysis/Interpretation- Ş.B., Z.Ç.S., Ş.S.; Drafting Manuscript- Ş.B., Z.Ç.S., Ş.S.; Critical Revision of Manuscript- Ş.B., Z.Ç.S., Ş.S.; Approval and Accountability- Ş.B., Z.Ç.S., Ş.S.; Material and Technical Support- Ş.B., Z.Ç.S., Ş.S.; Supervision- Ş.B., Z.Ç.S., Ş.S.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

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