

Evaluation and Differential Diagnosis of Hypereosinophilia in Rheumatology Practice

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Keywords

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Abstract

Background: There has been no investigation so far on the prevalence or causes of hypereosinophilia during rheumatic diseases. **Objectives:** The study aimed to identify the prevalence and causes of hypereosinophilia among the patients followed in a rheumatology department. **Methods:** The patients aged 18 years or over followed in our rheumatology department between January 2010 and December 2019 who had at least one AEC $\geq 1,500/\mu\text{L}$ measurement in their peripheral blood count were identified retrospectively. **Results:** Over the 10 years, a total of 130,769 peripheral blood counts were performed, of which 3.9% showed eosinophilia and 0.065% showed hypereosinophilia. Hypereosinophilia was identified in 85 patients. The underlying rheumatic disease was determined in 89.4% ($n = 76$) of patients. Of these, the most frequent one was rheumatoid arthritis at a ratio of 40.8%, followed by eosinophilic granulomatosis with polyangiitis (EGPA) at a ratio of 10.5%. Hypereosinophilia was in primary form in 3.5% of the patients, whereas secondary to

another condition in 91.8% ($n = 78$) of the cases and idiopathic in 4.7% ($n = 4$) of patients. The most common cause of secondary hypereosinophilia was drug induced, as detected in 61.2%, followed by allergic conditions in 11.5% and EGPA in 9.4%. In 15.2% ($n = 13$) of the cases, hypereosinophilia was associated with an underlying rheumatic disease. In the cases with drug-induced hypereosinophilia, most often (in 28.8%) methotrexate was the offending agent. **Conclusions:** Rheumatologists should be cognizant that hypereosinophilia concurrent to rheumatic diseases is usually not due to the underlying rheumatic disease, except for the conventional eosinophil-related rheumatic diseases.

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Introduction

Eosinophils are blood cells of the granulocytic lineage, which also includes basophils. Rather than circulating in the bloodstream, eosinophils are primarily dwelling in extracellular tissues. Production and functioning of eosinophils are regulated by interleukin-5, and eosinophilia

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is associated with diseases characterized by T helper cell type 2-mediated immune response. Eosinophils may, under certain conditions, be severely tissue destructive [1, 2]. Eosinophils play an important role in the pathogenesis of infectious and inflammatory diseases. There are functional differences in eosinophils between those secreted in response to tissue pathologies (allergic, parasitic, neoplastic, and immune) and those playing in hemostasis [3]. Eosinophilic diseases are currently classified according to clinical symptoms including end-organ involvement (eosinophilic dermatitis, gastroenteritis, pneumonia, and fasciitis), the level of eosinophil count in the peripheral blood, and/or pathogenic mechanisms such as cytokine dependent (intrinsic) and/or independent (extrinsic) [4]. In peripheral human blood, eosinophil count varying in the range of 0–500 per μL is considered normal, but it may increase up to 20-fold in certain circumstances [5].

Eosinophilia and hypereosinophilia are distinct entities. Eosinophilia stands for eosinophil levels in peripheral blood or tissues exceeding the normal range and refers to an absolute eosinophil count (AEC) of $\geq 500/\mu\text{L}$. Eosinophilia is classified per cell number as mild (500–1,500/ μL), moderate (1,500–5,000/ μL), and severe ($>5,000/\mu\text{L}$). The term hypereosinophilia, on the other hand, indicates counts of $>1,500/\mu\text{L}$ [6, 7]. When it lasts longer than 6 months and hypereosinophilia associated tissue-damage arises, the condition is called hypereosinophilic syndrome (HES). Eosinophilia may occur in primary/clonal, secondary/reactive, or idiopathic nature. Helminthic parasitic infections are the most commonly identified cause of eosinophilia across the globe, while the most frequent causes in developed industrial countries are atopy, allergic disorders, atopic dermatitis, and asthma. Other causes include medication, hematologic or solid malignancies, rheumatologic, or autoimmune diseases [2, 7]. Only a few studies have described the causes of eosinophilia encountered in the rheumatologic setting. The rheumatic diseases that should be considered in the first place for eosinophilia are eosinophilic granulomatosis with polyangiitis (EGPA), immunoglobulin G4 (IgG4)-related disease, and eosinophilic fasciitis. However, eosinophilia has also been detected during other rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Behcet's disease, albeit rarely [8–11]. On the other hand, depending on our literature search, no study is yet available on hypereosinophilia in rheumatology practice. Our aim here is to identify the prevalence along with the causes of hypereosinophilia in patients followed at the rheumatology department to shed light on its etiology to help rheumatologists or other physicians.

Materials and Methods

The patients aged 18 years and older followed in our rheumatology department between January 2010 and December 2019 who had at least one occasion of $\text{AEC} \geq 1,500/\mu\text{L}$ (hypereosinophilia) measured in their peripheral blood count were identified. For patients with >1 occasion of $\text{AEC} \geq 1,500/\mu\text{L}$, the highest measurement was included in the study. Patients younger than 18 years of age and those with $\text{AEC} < 1,500/\mu\text{L}$ were excluded. Patient demographics, presence of any rheumatic disease at the time of hypereosinophilia, their symptoms, detailed results of complete blood count, erythrocyte sedimentation rate (mm/h), levels of C-reactive protein (normal range: 0–5 mg/L), blood urea nitrogen (normal range: 6–20 mg/dL), creatinine (normal range: 0.5–0.9 mg/dL), aspartate aminotransferase (normal range: 0–31 U/L), alanine aminotransferase (normal range: 0–33 U/L), lactate dehydrogenase (normal range: 135–214 U/L), total protein (normal range: 6.4–8.3 g/dL), and albumin (normal range: 3.5–5.2 g/dL) as well as the results of complete urinalysis, parasite screen, antinuclear antibody test, anti-neutrophil cytoplasmic antibody test result(s), if any, from organ and tissue biopsies, bone marrow (BM) exam, and cytogenetic analysis toward primary hypereosinophilia were extracted and recorded.

Causes of eosinophilia were classified into primary/clonal, secondary/reactive, or idiopathic groups [4, 5]. Secondary eosinophilias were further classified as infections, allergic states, drug reactions/effects, dermatological diseases, rheumatic diseases, solid tumors, lymphoma, pulmonary diseases (asthma and eosinophilic pneumonia), gastrointestinal diseases, and others [4, 5, 7]. Written approval of the local ethics committee bearing the decision number 2021-19 has been obtained for this study.

Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation. Categorical variables are presented in percentage (%). The Shapiro-Wilk test was used to investigate whether a set of data has a normal distribution. For groups where data had a normal distribution, an independent sample *t* test was used to compare the 2 groups. In the event of nonnormal distribution, groups were compared using the Mann-Whitney U test, in the case of 2 groups, and the Kruskal-Wallis *H* test was used in cases with 3 or more groups. Cross tabulation was implemented and analyzed using Pearson χ^2 , Pearson exact χ^2 , and Fisher's exact χ^2 tests. For independent markers, receiver-operating characteristic analyses were applied to identify appropriate cutoff values and to calculate their specificities and sensitivities. Analyses were carried out using the software IBM SPSS Statistics 21.0 (Released 2012, IBM SPSS Statistics for Windows, Version 21.0; IBM Corp., Armonk, NY, USA). A *p* value of <0.05 was considered to have statistical significance.

Results

During the study period, a total of 130,769 peripheral blood counts were ordered, of which 3.9% showed eosinophilia and 0.065% showed hypereosinophilia. The number of tests with $\text{AEC} \geq 500/\mu\text{L}$ was 5,107. Of them, in 89.1%, AEC was 500 to $<1,000/\mu\text{L}$; in 6.5%, AEC was 1,000 to $<1,500/\mu\text{L}$; and in 4.2%, AEC was $\geq 1,500/\mu\text{L}$, respectively.

Table 1. Demographic characteristics of study population

	N	%
Age, mean $\pm$ SD (min–max)	52.07 $\pm$ 13.9 (26–80)	
Age at diagnosis of rheumatological disease, mean $\pm$ SD (min–max)	42.6 $\pm$ 15.1 (16–77)	
Age at diagnosis of hypereosinophilia, mean $\pm$ SD (min–max)	46.5 $\pm$ 14.8 (20–77)	
Gender, female	51	59.3
Clinical signs		
Asthma	11	12.9
Sinusitis	3	3.5
Fever	4	4.7
Urticaria	4	4.7
Cutaneous vasculitis	5	5.9
Pulmonary infiltrate	6	7
Cardiomyopathy	2	2.4
Renal involvement	2	2.4
Peripheral neuropathy	5	5.9
Investigations		
Cytopenia	30	35.3
Anemia	29	34.1
Thrombocytopenia	1	1.2
Serum protein electrophoresis results		
Monoclonal gammopathy	3	3.5
Polyclonal gammopathy	6	7.1
Patients undergoing BM examination, <i>n</i>	17	19.8
Diagnoses		
Primary	3	3.5
Secondary	78	91.8
Idiopathic	4	4.7
Rheumatologic diseases	13	15.1

BM, bone marrow; SD, standard deviation.

Hypereosinophilia (AEC $\geq$ 1,500/ μ L) was identified in 85 patients, who were 52.07 ± 13.9 years old (26–80), on average, and 59.3% of them were female. Pathological findings were present in 30% of patients with hypereosinophilia. Out of these patients, 12.9% had asthma, 4.7% had urticaria, 5.9% had cutaneous vasculitis, 7% had pulmonary infiltration, and 5.9% had peripheral neuropathy. Laboratory assays indicated 34.1% of the patients had anemia, whereas only 1 patient had thrombocytopenia. BM aspiration biopsy was done in 17 (19.8%) patients (the demographic characteristics of patients with hypereosinophilia are provided in Table 1).

Rheumatic Diseases in the Study Population

Among the patients who were referred to and assessed/followed up in the rheumatology department, 89.4% (*n* = 76) of those with hypereosinophilia had an underlying rheumatic disease. The most frequent disease was RA which was determined in 40.8%, followed by ankylosing spondylitis in 14.5% and EGPA in 10.5%, respectively

Table 2. Rheumatologic diseases in the study population

	N	%
Rheumatoid arthritis	31	40.8
Ankylosing spondylitis	11	14.5
EGPA	8	10.5
Behcet's disease	6	7.9
FMF	5	6.6
Polymyositis	3	3.9
Gout arthritis	3	3.9
Psoriatic arthritis	2	2.6
SLE	2	2.6
IgG4-related disease	1	1.3
Eosinophilic fasciitis	1	1.3
Takayasu's arteritis	1	1.3
GPA	1	1.3
Systemic scleroderma	1	1.3

EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; SLE, systemic lupus erythematosus; FMF, familial Mediterranean fever.

Table 3. Causes of secondary hypereosinophilia

	N	%
Drug related	52	61.2
Rheumatologic diseases		
EGPA	8	9.4
IgG4-related disease	1	1.2
NERDS	1	1.2
Eosinophilic fasciitis	1	1.2
Polymyositis	1	1.2
GPA	1	1.2
Others		
Asthma	3	3.5
Atopic dermatitis	3	3.5
Eosinophilic pneumonia	2	2.4
Allergic rhinitis	2	2.4
Bullous pemphigoid	1	1.2
Urticaria	1	1.2
Lymphoma	1	1.2

EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; NERDS, nodules-eosinophilia-rheumatism-dermatitis and swelling syndrome.

(Table 2 provides the breakdown of rheumatic diseases in the study population). Out of a total of 76 patients with rheumatic diseases, in 78.9%, eosinophilia was detected during the follow-up phase of the rheumatic disease.

Causes of Hypereosinophilia

Hypereosinophilia was classified as primary in 3.5% ($n = 3$), secondary in 91.8% ($n = 78$), and idiopathic in 4.7% ($n = 4$) of patients. The most common cause of secondary hypereosinophilia was medication, as detected in 61.2%, followed by allergic conditions in 11.5% and EGPA in 9.4% (details on causes of secondary hypereosinophilia are provided in Table 3). Only in 15.2% ($n = 13$) of the cases, hypereosinophilia was associated with an underlying rheumatic disease. The majority of this subset was composed of EGPA patients. Drug-induced hypereosinophilia was most often (in 28.8%) caused by methotrexate (MTX), and nonsteroidal anti-inflammatory drugs ranked as the second most common (in 13.5%) offending agent. Other common causes were anti-tumor necrosis factor (TNF)- α agents, antibiotics, and sulfasalazine (the drugs which were identified to possibly cause hypereosinophilia are listed in Table 4).

Laboratory Findings

In peripheral blood counts of the patients, mean leukocyte count was $11,267 \pm 5,157/\mu\text{L}$, AEC was $3,522 \pm$

Table 4. Drugs that are possible causes of hypereosinophilia

	N	%
MTX	15	28.8
NSAIDs	7	13.5
Anti-TNF α	5	9.6
Antibiotics	4	7.7
Sulfasalazine	4	7.7
Pregabalin	3	5.8
Allopurinol	3	5.8
Azathioprine	3	5.8
Rituximab	2	3.8
Antidepressant	2	3.8
Leflunomide	1	1.9
Tacrolimus	1	1.9
Tocilizumab	1	1.9
Antituberculous drugs	1	1.9

MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; anti-TNF α , tumor necrosis factor alpha inhibitors.

$3,799/\mu\text{L}$, C-reactive protein value was $2.9 \pm 5 \text{ mg/dL}$, and erythrocyte sedimentation rate was $33 \pm 24.9 \text{ mm/h}$. In 13 patients (15.2%) with AEC $\geq 5,000/\mu\text{L}$ (mean level: $9,870/\mu\text{L}$), 4 had EGPA, 4 had a drug-induced condition, 2 had primary HES, 1 had nodules-eosinophilia-rheumatism-dermatitis and swelling syndrome, 1 case was asthma associated, and the last one was idiopathic. In our cohort, mean AEC was higher in the EGPA group compared to the non-EGPA group ($7,620 \pm 8,794/\mu\text{L}$ vs. $3,096 \pm 2,623/\mu\text{L}$, $p = <0.0001$).

Clinical symptoms and laboratory findings were compared between groups of drug-related, rheumatic disorder-related, or other causes of hypereosinophilia and given in Table 5. AEC level of $>2,700/\mu\text{L}$ had a sensitivity of 87.5% and a specificity of 66.2% to decide the diagnosis of EGPA (95% CI: 0.646–0.839, $p = 0.0294$).

Discussion

The role of eosinophils in the pathogenesis of rheumatic diseases other than eosinophilic diseases such as EGPA and eosinophilic fasciitis has not been elucidated [10]. But, eosinophilia may also arise during such rheumatic diseases. Although there have been a few studies which investigated the prevalence of eosinophilia (AEC $\geq 500/\mu\text{L}$) in a rheumatology setting, this study is the first of its kind to figure out the prevalence and causes of hypereosinophilia (AEC $\geq 1,500/\mu\text{L}$) in presence of rheumatic diseases.

Table 5. Clinical and laboratory findings comparison of patients with secondary hypereosinophilia according to etiological causes

	Group I (drug related) (n = 52)		Group II (rheumatologic disease related) (n = 13)		Group III (other secondary causes) (n = 13)		p values
Age, mean ± SD (min–max)	54.4±14		49.6±14		48.3±12		0.266
Age at diagnosis of hypereosinophilia, mean ± SD (min–max)	49.3±14		42.3±16		42.6±12		0.157
Gender, female, n, %	33	63.5	4	30.8	9	69.2	0.072
Pathological clinical findings							
Asthma, n, %	0	–	8	61.5	2	15.4	<0.0001
Sinusitis, n, %	0	–	2	15.4	1	7.7	0.032
Fever, n, %	1	1.9	3	23.1	0	–	0.029
Urticaria, n, %	1	1.9	0	–	2	15.4	0.138
Cutaneous vasculitis, n, %	0	–	5	38.5	0	–	0.001
Pulmonary infiltrate, n, %	1	1.9	3	23.1	1	7.7	0.027
Cardiomyopathy, n, %	1	1.9	0	–	0	–	1
Renal involvement, n, %	0	–	1	7.7	0	–	0.551
Peripheral neuropathy, n, %	0	–	5	38.5	0	–	0.001
Investigations							
Cytopenia, n, %	20	38.5	4	30.8	4	30.8	0.890
Anemia, n, %	19	36.5	4	30.8	4	30.8	0.886
Thrombocytopenia, n, %	1	1.9	0	–	0	–	1
Serum protein electrophoresis results, n, %							
Monoclonal gammopathy, n, %	0	–	3	23.1	0	–	0.001
Polyclonal gammopathy, n, %	3	5.8	2	15.4	0	–	
Patients undergoing BM examination, n, %	4	7.7	9	69.2	1	7.7	<0.0001
Laboratory findings							
Hemoglobin level, mean ± SD, g/dL	12.4±1.8		13±1.6		13.2±2.1		0.318
Leukocyte count, mean ± SD, /μL	9,954±2,671		15,280±8,561		10,846±3,444		0.147
Absolute eosinophil count, mean ± SD, /μL	2,665±1,146		6,501±7,569		2,295±1,234		0.016
CRP, mean ± SD, mg/dL	3.1±5.8		4.2±3.8		0.9±1.2		0.012
ESR, mean ± SD, mm/h	32±22		45±31		21±19		0.061

CRP, C-reactive protein; BM, bone marrow; ESR, erythrocyte sedimentation rate.

Hypereosinophilia is clinically classified as primary (myeloid and stem cell neoplasms), secondary/reactive, and idiopathic. Secondary/reactive eosinophilia may emerge due to helminthic infections, toxic and allergic drug reactions, chronic inflammatory disorders, autoimmune diseases, and atopic conditions [12]. Diagnostic approach should consist of a detailed history taking (especially drugs and travel history), physical examination, and extensive laboratory and imaging studies, if necessary, in hypereosinophilia [12] (a diagnostic algorithm regarding differential diagnosis of hypereosinophilia from rheumatology perspective is given in Fig. 1).

In the scarce number of studies that explored the prevalence of eosinophilia, various thresholds were accepted to define eosinophilia, and there were methodological differences which in turn have led to variances in epidemiological results. In a study evaluating 1,000 patients ad-

mitted to an outpatient department of rheumatology between the years 2001 and 2002, the limit for eosinophilia was set to 500 cells/μL. In that study, the prevalence of eosinophilia was 7.7%, but the etiologic causes of eosinophilia were not classified [8]. In another study carried out in Argentina, only 109 RA patients were recruited for whom eosinophilia threshold was taken as 350/mm³, and thus prevalence of eosinophilia was 7.3% [13]. In our study, contrary to former studies, we have applied an AEC threshold of ≥1,500/μL. During the 10-year study period, a total of 130,769 peripheral complete blood counts were done, of which 3.9% showed eosinophilia and 0.065% showed hypereosinophilia.

Etiology may also vary by the center to where the patient was admitted. In the study which addressed the etiology of hypereosinophilia in patients seen in the hematology department, the rheumatic diseases which induced

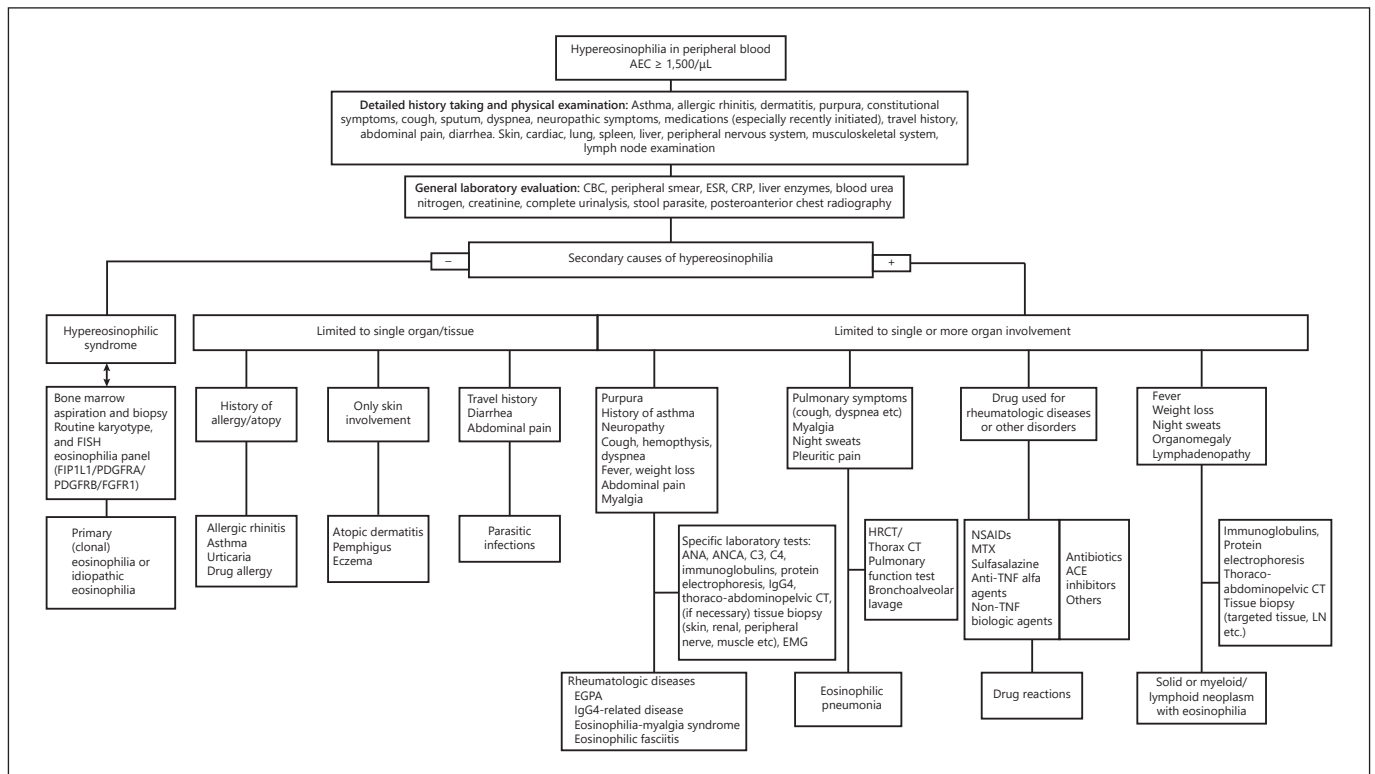


Fig. 1. Diagnostic approach regarding hypereosinophilia from rheumatology perspective. ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; C, complement; CBC, complete blood count; CRP, C-reactive protein; CT, computerized tomography; EGPA, eosinophilic granulomatosis with polyangiitis; EMG, electromyography; ESR, erythrocyte sedimentation rate; HRCT, high-resolution computed tomography; Ig, immunoglobulin; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs.

hypereosinophilia were ranked as EGPA in 9%, IgG4-related disease in 9%, and autoimmune diseases in 4% [14]. In our series, hypereosinophilia was detected in 85 patients, of whom 76 had a background rheumatic disease. The rheumatic diseases with hypereosinophilia in our patients were EGPA, IgG4-related disease, RA, polymyositis, eosinophilic fasciitis, GPA, Behçet's disease, gout, SLE, and scleroderma subtypes. On the other hand, underlying rheumatic diseases were not the most frequent cause of secondary hypereosinophilia. Merely in 13 (15.1%) cases, hypereosinophilia was associated with an underlying rheumatic disease. Of these patients, 8 had EGPA, 1 had IgG4-related disease, 1 had nodules-eosinophilia-rheumatism-dermatitis and swelling syndrome, 1 had eosinophilic fasciitis, 1 had polymyositis, and 1 had GPA-induced hypereosinophilia.

It is stated in a review article that although eosinophilia may develop in virtually all rheumatic diseases, albeit rarely, merely a few of them characteristically incorporate it. In the same review, authors have argued eosinophilia

may infrequently accompany RA; but rather than the RA disease itself, this condition is due to medications used to treat RA [10]. Another review points out that rheumatologic or vascular conditions associated with peripheral or tissue eosinophilia are rare. Such that, EGPA, IgG4-related disease, eosinophilic fasciitis, eosinophilia-myalgia syndrome, and eosinophilic myositis are commonly associated with peripheral or tissue eosinophilia. The authors have also highlighted that when eosinophilia occurs in rheumatic diseases where this is not generally considered to be an integral part of the clinical picture, clinicians need to rule out the presence of other factors, particularly including medications, allergic diseases, infections, and hematologic conditions [7].

At the practice, an essential question is: "Whether the eosinophilia determined amid the follow-up of a rheumatic disease is induced by the underlying disease or the anti-rheumatic drugs?" Of note, one of the major causes of eosinophilia is the drug reaction/effect. Particularly, anti-convulsants, antibiotics, antirheumatic drugs, and other

drugs such as allopurinol have a well-known potential to cause eosinophilia [7]. Beyond them, the possibility that immunosuppressive agents such as MTX, anti-TNF agents, tocilizumab, and tacrolimus may cause eosinophilia was also documented in the medical literature [6, 15–17]. Although reports demonstrate eosinophilia may occur during rheumatic diseases RA, SLE, Behçet's disease, etc., it is not accurate to attribute eosinophilia directly to such diseases. These studies have identified the rheumatic diseases which existed at the time of eosinophilia detection [8]. In none of the mentioned studies, it has been clarified as to whether the patients were drug naïve. Provided that eosinophilia is determined in a drug-naïve rheumatology follow-up patient, the condition is attributable to the disease. It is, however, difficult to pinpoint the exact cause of eosinophilia when the patient is on medication. If a patient with a normal blood count before the initiation of medication has been detected to have eosinophilia once started taking medication, and other possible causes were ruled out, then it is likely the patient has drug-induced eosinophilia. The cause of secondary hypereosinophilia was drug reaction in 4% of cases in the study by Moller et al. [14]. Overall, in our study, the most frequent cause of hypereosinophilia was drugs, causing 61.2% of the cases. The most widely used hypereosinophilia-inducing agents were MTX or nonsteroidal anti-inflammatory drugs followed by biological agents at various ratios, anti-TNFs coming in the first place, immunosuppressive agents, antibiotics, antidepressants, allopurinol, and pregabalin. In concert with the former literature, none of our RA patients' eosinophilia was due to the disease itself.

The second essential question for rheumatologists/specialists is "Whether the level of AEC may help us predict the underlying rheumatic disease or hypereosinophilic cause?" Connective tissue/autoimmune disease might be associated with peripheral eosinophilia up to a varying degree. Eosinophils are not necessarily of the cell types engaged in disease pathogenesis, but they exist as a part of the overall inflammatory milieu. In such cases, the degree of eosinophilia is not elaborated [11]. While allergic diseases lead to a mild degree of eosinophilia, moderate to severe eosinophilia may arise from exacerbation of EGPA and asthma flare-ups [2, 7]. In the medical literature, no AEC cutoff value has been described toward differentiation of hypereosinophilia causes. In our study, an AEC level of $>2,700/\mu\text{L}$ had a sensitivity of 87.5% and a specificity of 66.2% for EGPA diagnosis. Verification of this result warrants further studies covering a larger sample size. Nevertheless, rheumatologists/specialists should

consider requesting a BM exam and cytogenetic analysis along with the clinical findings for differential diagnosis of primary HES and the secondary causes, including EGPA, in case of severe eosinophilia or eosinophilic organ damage as their treatment would be different as well.

Our study has some limitations. It is mainly limited by its retrospective design. Furthermore, it only covers data from a single center. The relatively small sample size might also be recognized as a limitation. Another aspect is the fact that our data are from a tertiary care rheumatology unit and therefore are not representative of the regular public. On the other hand, the strongest aspect of this study is that it is the first of its kind to delineate the causes along with the prevalence of hypereosinophilia in rheumatic disease, thus providing insight to rheumatologists or to other physicians in their practice.

In rheumatology practice, the clinical picture at diagnosis or during the follow-up of rheumatic diseases may involve eosinophilia or hypereosinophilia. For patients on medication, however, it may occasionally be challenging to differentiate whether it results from the disease itself or rather from the medication. In conclusion, most of the time eosinophilia concurrent to rheumatic diseases is usually not due to the underlying rheumatic disease, except for the conventional eosinophil-related rheumatic diseases (e.g., EGPA, IgG4-related disease, and eosinophilic fasciitis). Therefore, other causes of secondary eosinophilia, which primarily refer to drug reaction, should be considered and searched in such patients.

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Statement of Ethics

The study protocol was reviewed and approved by the Eskisehir Osmangazi University Ethics Committee, Approval No. 26 Jan 2021 under Decision No. 19. Written and informed consent for participation in the study was not required due to retrospective design by local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.U.C. and H.U.T. contributed to the design of the research. D.U.C., H.U.T., R.Y., and M.D. collected the data. D.U.C., H.U.T., R.Y., M.D., and C.K. contributed to the analysis of the data. D.U.C., H.U.T., and C.K. contributed to drafting of the manuscript. D.U.C., H.U.T., R.Y., M.D., and C.K. approved the final version.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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