Original Article

Eosinophilia: Clinical experience from a tertiary care center in India

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ABSTRACT

Objectives: Eosinophilia is a prevalent laboratory abnormality that we encounter in day-to-day practice both in outpatient and inpatient settings. The causes range from primary to secondary spanning from an allergic response to clonal neoplastic proliferations. Identifying an etiology may be challenging in many cases and may sometimes require extensive evaluation. We aimed to find the clinical and etiological profile of patients with eosinophilia and the association of eosinophilia with end-organ involvement and IgE levels.

Material and Methods: The study was designed as a cross-sectional study over a period of two years (2019 to 2020). The study setting was outpatient and inpatient medical wards of a tertiary care center in north India. A detailed history and clinical examination were done on patients with eosinophilia detected in blood counts. Standard diagnostic protocols guided by positive clinical and diagnostic tests were followed to find etiologies in patients with eosinophilia.

Results: In our study, the most common cause overall and in each category of eosinophilia was parasitic infections (35%) followed by allergic disorders (29.3%). The most frequent symptoms were cough (32%), generalized weakness (25.5%), dyspnoea (24%), and a history suggestive of atopy (21%). On clinical examination, the most common finding was rhonchi or wheeze (24.5%). The most commonly affected end-organ was the lungs (13.2%) followed by the skin (4.7%).

Conclusion: Parasitic infections are the most common cause of eosinophilia in our population. IgE levels correlate with a diagnosis of atopy or asthma and do not show a correlation with AEC. The lungs were the most frequently involved as end-organ in eosinophilia followed by the skin. We found no significant association between end-organ involvement and the degree of eosinophilia which highlights the importance of working up symptomatic patients for end-organ damage irrespective of the eosinophil count.

Keywords: Eosinophilia, Immunoglobulin E, Hypereosinophilic syndrome, Parasitic infection

INTRODUCTION

Eosinophilia is a frequently encountered abnormality in clinical practice. In a healthy individual, eosinophils constitute 3-5% of the total leukocyte count (350-500 cells/μL). A differential eosinophil count of more than 5% or an absolute eosinophil count (AEC) of 500 cells/μL or higher constitutes eosinophilia and merits further evaluation.[1]

Although clinical history guides an approach for patients with eosinophilia, sometimes a significant set of investigations are required to determine the cause and the possible role in disease presentation. A disorder presenting with a raised eosinophil count may be primary, where there is disordered growth and replication of eosinophils, or secondary, as a response to drugs, malignancy, allergy, or infections.[2]

Identifying an etiology for eosinophilia can be challenging in some cases; the cause of eosinophilia remains unknown in one-third of the cases despite extensive evaluation. Additionally, the etiological spectrum may change according to social and geographical variations. We studied the clinical and etiological profiles of patients with eosinophilia to identify the spectrum of etiology. At the same time, we also analyzed the organ systems commonly affected in cases of eosinophilia in Indian patients. Our study also analyzed the distribution of IgE levels among the severity of eosinophilia.

MATERIAL AND METHODS

We conducted a cross-sectional study over a period of 2 years (2019–2020) in the outpatient clinics and medical wards at a

tertiary care center in Delhi, India. Consecutive patients with peripheral blood eosinophilia (AEC > 500/µL or a differential count > 5%) with the age of 14 years or above were included after informed consent.

Eosinophilia was categorized based on the AEC into mild (≤1500/µL), moderate (1500–5000/µL), and severe (≥5000/µL) eosinophilia.[1] Hypereosinophilia (HE) was defined as an AEC ≥ 1500/µL on two consecutive occasions at least 1 month apart, or the demonstration of tissue HE on pathological examination.[2] Hypereosinophilic syndrome was defined as the presence of severe eosinophilia with organ damage attributable to tissue eosinophilia, after the exclusion of other diagnoses.[3] Standard guidelines were followed for the diagnosis of asthma,[4] allergic bronchopulmonary aspergillosis (ABPA),[5] immunoglobulin G4-related disease,[6] allergic rhinitis,[7] atopic dermatitis,[8] and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.[9] Histopathological diagnoses such as Kimura disease were based on slide reviews by experienced pathologists.[10] Drug-induced eosinophilia was diagnosed in patients who developed eosinophilia during hospitalization temporally correlating with prescription of implicated drugs and confirmed by resolution of eosinophilia on stopping suspected drugs (if feasible).[11] Drug-induced eosinophilia was diagnosed only if the criteria for DRESS were not met.

Detailed history and clinical examination relevant to the etiological assessment and organ dysfunction were performed. Patients were investigated with complete blood counts, peripheral blood smear, stool examination for parasites (repeated for 3 days), and testing for microfilariae infection.[12] The latter included peripheral blood smear staining using acridine orange and giemsa, microfilariae antigen detection, and a quantitative buffy coat. Further, the diethylcarbamazine (DEC) provocation test was performed for increasing sensitivity of detection of microfilaria antigen.[13] All cases of moderate or severe eosinophilia (and mild eosinophilia if clinically indicated) were evaluated with a rationalized second set of investigations for etiology and organ dysfunction [Table 1]. Renal involvement

was accessed using kidney function test, urine eosinophils and, if indicated, kidney biopsy. Serum immunoglobulin E (IgE) (Phadiatop technology), bone marrow study, cytogenetics, Janus Kinase 2, and screening for platelet-derived growth factor receptor alpha and platelet-derived growth factor receptor beta by fluorescent *in situ* hybridization were done where required.[14] Eosinophilia was considered idiopathic when the first set of investigations was non-contributory, bone marrow examination and cytogenetics were normal, and drug-induced eosinophilia was unlikely.

The normality of distributions was confirmed using the Shapiro–Wilk test. If the data were normally distributed, it was expressed as mean ± standard deviation (SD), otherwise, it was presented as median with interquartile range. Association between qualitative variables was tested using the Chi-squared/Fisher's exact test. For comparing the quantitative variables between the three groups, one-way analysis of variance or Kruskal–Wallis tests were used as appropriate, and subsequently, multiple comparison tests (with Bonferroni correction) were performed to identify the pairs of groups having significantly different results. Correlation among quantitative variables was measured using Pearson's correlation coefficient or Spearman's correlation coefficient. $P = 0.05$ or less was considered significant. All statistical analysis was done using STATA.

RESULTS

A total of 106 patients were recruited during the study period, of whom the full baseline workup could be done in 97 patients, while partial workup was available for the rest. The mean age of the study population was 35.4 (±1.3) years and included 60 males (56%). The mean ± SD AEC was 2569 ± 188 cells/µL (range 382–27,588 cells/µL). Among a total of 106 patients with eosinophilia, 62 (58.8%) patients had mild eosinophilia, 31 (29.2%) had moderate, and 13 (12%) patients had severe eosinophilia.

Among the study population, the most frequent symptoms were cough, generalized weakness, dyspnea, and a history

Table 1: Diagnostic investigations for end-organ involvement assessment.		
Symptoms and signs assessed	**Organ system accessed**	**Investigations performed**
Dyspnea, wheeze, rhonchi, and crepitations	Lungs, and pulmonary system	PFT, CXR, CT scan, BAL, and lung biopsy
Orthopnea, PND, abnormal apex, LPH S3, S4, and murmur	Heart and cardiovascular system	ECG, ECHO, MRI, and serum cardiac markers
Dyspepsia, gastritis, hemoptysis, and hepatomegaly	GI system	UGI endoscopy and USG abdomen
Splenomegaly	Reticuloendothelial system	Bone marrow
Focal neurological deficits	CNS	Brain and spinal cord MRI, CSF studies, NCV, EMG, and muscle biopsy
Rash	Skin	Biopsy
PFT: Pulmonary function test, CXR: Chest X-ray, CT: Computed tomography, BAL: Bronchoalveolar lavage, PND: Paroxysmal nocturnal dyspnea, LPH: Left parasternal heave, ECG: Electrocardiogram, ECHO: Echocardiography, GI: Gastrointestinal, UGI: Upper gastrointestinal, USG: Ultrasound, MRI: Magnetic resonance imaging, CNS: Central nervous system, CSF: Cerebrospinal fluid, EMG: Electromyography, NCV: Nerve conduction velocity		

suggestive of atopy [Table 2]. On clinical examination, the most common finding was rhonchi or wheeze. A minor percentage of the population had nasal polyp, crepitations, and abdominal mass [Table 2]. Of the 106 patients analyzed, two had diabetes mellitus, three had hypothyroidism, and one had chronic kidney disease as well as hypertension.

Hematological and biochemical parameters, except for TLC, were within reference range for the majority of the study population and did not differ across the severity groups [Table 3]. We calculated non-eosinophil leukocyte count (TLC-AEC) to estimate if the difference in TLC between the groups is entirely attributable to the difference in AEC. This

was significantly different across the groups, and *post hoc* analysis identified that those with moderate eosinophilia had higher non-eosinophil leukocyte counts ($P = 0.01$). Levels of immunoglobulin IgE were measured in 50 patients and were elevated in 44 patients (88%). Sixteen of these 50 patients had an allergy, with a trend toward higher IgE levels in these patients (median 1630 vs. 851 IU/mL, $P = 0.06$) compared to those without allergy. The median IgE levels (IU/mL) were not significantly different between mild, moderate, and severe eosinophilia ($P = 0.325$) [Figure 1].

Parasitic infestations were found to be the most common identified cause of eosinophilia [Table 4]. Even when the

Table 2: Clinical signs and symptoms in eosinophilic patients.

Symptom	Frequency in number and percentage *n* (%)	Sign	Frequency in number and percentage *n* (%)
Cough	34 (32.1)	Rhonchi	26 (24.53)
Generalized weakness	27 (25.5)	Pallor	17 (16.04)
Dyspnea	26 (24.5)	Pedal edema	5 (4.71)
Allergic rhinitis	23 (21.7)	Lymph node swelling	4 (3.78)
Wheeze	21 (19.8)	Icterus	3 (2.83)
Fever	17 (16)	Nasal polyp	3 (2.83)
Abdominal pain	12 (11.3)	Crepitations	3 (2.83)
Swelling	10 (9.4)	Splenomegaly	1 (0.94)
Rash	9 (8.5)		
Diarrhea	8 (7.6)		
Itching	7 (6.6)		
Headache	6 (5.6)		
Asymptomatic	13 (12.3)		

Table 3: Laboratory investigations in patients of eosinophilia.

Investigation	Overall	Mild eosinophilia (*n*=62)	Moderate eosinophilia (*n*=31)	Severe eosinophilia (*n*=13)	*P*-value for comparison across groups
Age (years)	35.4±1.3	32.2±1.6	42.42±2.2	34.2±4.8	0.36
Male (%)	60 (56%)	39 (63%)	16 (52%)	5 (38%)	0.26
Hb (gm/dL)	12.51±2.46	12.69±2.4	12.6±2.26	11.24±3.03	0.385
TLC (/mL)	8730 (6860–8730)	6980 (5600–9100)	11100 (7950–16200)	21400 (18060–29520)	<0.001 (*P*<0.05 for all comparisons)
Leucocyte count (/µL) excluding eosinophils	6771 (5224–9630)	6270 (5096–8200)	8040 (5760–13028)	7782 (5137–10370)	0.028 (*P*=0.01 for mild vs. moderate; 0.56 for mild vs. severe; 0.49 for moderate vs. severe)
Platelet (^108/mL)	2.14±0.96	2.19±0.87	2.2±0.77	1.96±1.54	0.492
Total bilirubin (mg/dL)	0.40 (0.3–0.7)	0.5 (0.3–0.7)	0.5 (0.3–0.4)	0.35 (0.3–0.4)	0.148
AST (IU/L)	28 (20–38)	26 (19–38)	28 (22–41)	32 (27–37)	0.645
ALT (IU/L)	26 (15–47)	24 (15–44)	37 (16–57)	35 (21–40)	0.442
ALP (IU/L)	241 (186–327)	235 (185–300)	251 (190–394)	286 (254–377)	0.134
Urea (mg/dL)	21 (18–31)	21 (18–30)	22 (19–31)	23 (19–28)	0.903
Creatinine (mg/dL)	0.8 (0.7–0.9)	0.8 (0.65–0.9)	0.7 (0.7–0.9)	0.8 (0.7–1)	0.786
IgE level (IU/mL) (*n*=49)	1014 (518–3106)	951 (504–2812	1193 (127–5000)	4000 (662–5709)	0.32

AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, Hb: Hemoglobin, TLC: Total leukocyte count, IgE: Immunoglobulin E

Table 4: Etiological distribution in patients of eosinophilia.

Etiology	Number of patients (%)	Sub-type
Parasitic infestations	37 (35)	Identified organisms include: Filaria (*n*=22), *Giardia* (*n*=4), *Endolimax nana* (*n*=3), *Ancylostoma* (*n*=3), *Entamoeba histolytica* (*n*=3), *Ascaris* (*n*=2), coccidian parasites (*n*=1), and *Strongyloides* (*n*=1)
Allergic disorders	31 (29.3)	Identified disorders include bronchial asthma (*n*=8), allergic dermatitis (*n*=8), allergic bronchopulmonary aspergillosis (*n*=8). The most common offending allergen were mites, followed by dermatophagoides, animal fur, and Bermuda grass.
Autoimmune disease	7 (6.6)	Scleroderma (*n*=1), SLE, IgG4 related disease (*n*=2)
Malignancy	1 (0.9)	Small cell lymphoma
Drug associated	7 (6.6)	
Kimura disease	1 (0.9)	
Idiopathic	14 (13.2)	Seven patients were found to have *Entamoeba coli**
Incomplete evaluation	9 (8.5)	

*Likely incidentally detected and is not associated with eosinophilia. SLE: Systemic lupus erythematosus, IgG4: Immunoglobulin G4

causes were analyzed in groups of eosinophilia, parasites were still the most common cause. All the allergic disorders were distributed among mild and moderate eosinophilia. Idiopathic eosinophilia was mostly distributed among severe cases, followed by moderate cases, both of which were classified as idiopathic HE [Figure 2].

When organ involvement was accessed on patients with persistent eosinophilia, the most common organ involvement was lungs in the form of obstructive/restrictive pattern on pulmonary function test (PFT) [Table 5]. When analyzed with AEC, end-organ involvement had no direct association with the increase in AEC, nor was varied significantly among the three severity groups of eosinophilias ($P = 0.07$) [Table 6].

DISCUSSION

Our study found that eosinophilia commonly occurred in the third decade (mean ± SD, 35.44 ± 1.35 years). Overall, it was almost slightly more common in males (56%) with a female preponderance in the group with severe eosinophilia. Similar findings have been seen in the previous studies from India.[15] However, studies in developed nations have shown eosinophilia to be more common in the fifth and sixth decades and have a female preponderance.[16,17] The younger age group of presentation of the disease in India may be due to the relatively early presentation of parasitic infections, allergic disorders, and autoimmune disorders which contributed to the majority of cases.

In our study, as in the previous studies from developing nations, the most common cause overall and in each category of eosinophilia was parasitic infestations.[2,15,18,19] This is linked to both the socioeconomic status of the region and the higher diagnostic accuracy with strict emphasis placed on three consecutive stool samples and four simultaneous methods on samples to detect filarial larvae. In a study from
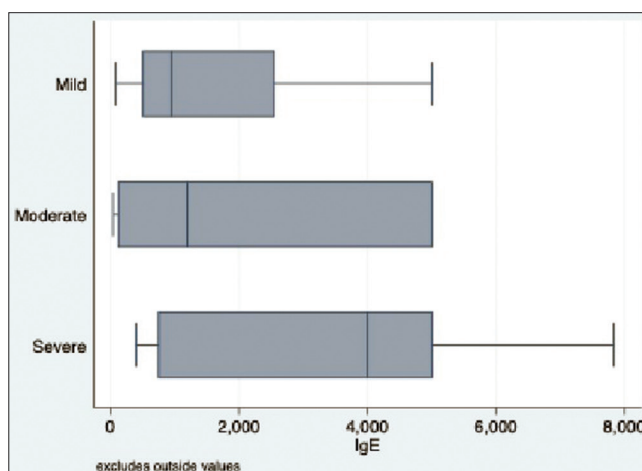
Figure 1: Distribution of immunoglobulin E levels among severities of eosinophilia.
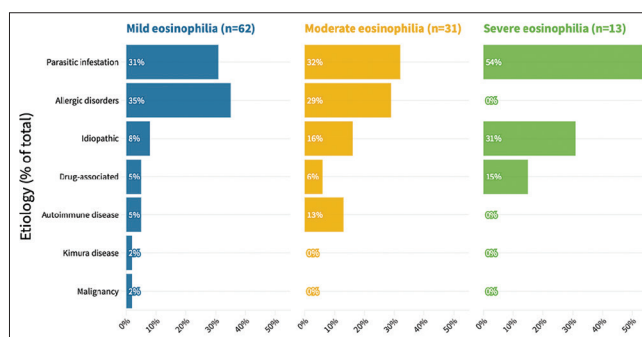
Figure 2: Comparison of the group of etiology among severities of eosinophilia. The overall comparison was significantly different between the groups ($P = 0.046$, Fischer's exact test).

north India, parasites were the most common cause (16%), followed by bronchial asthma and allergic rhinitis (6%).[19] In our study as well, the second most common etiology was

Table 5: Frequency of end-organ involvement by eosinophilia.

Organ/organ system	Frequency of occurrence *n* (%)
Lungs	14 (13.2)
Skin	5 (4.7)
Kidney	1 (0.9)
Oral and maxillofacial area	1 (0.9)

Table 6: Distribution of end-organ involvement among different categories of eosinophilia.

Categories of eosinophilia	Frequency of patients with end-organ involvement *n* (%)	Frequency of patients with no end-organ involvement *n* (%)
Mild eosinophilia	8 (12.9)	54 (87.1)
Moderate eosinophilia	10 (32.26)	21 (67.74)
Severe eosinophilia	3 (23.08)	10 (76.92)
Total	21 (19.81)	85 (80.19)

allergic disorders. Malignancy-associated eosinophilia was rare in our population compared to previous populations; this may be attributed to our small sample size.[16]

Patients with eosinophilia present most commonly with constitutional symptoms such as fever, cough, and dyspnea. Specific symptoms such as rashes and itching may be seen in some patients, while others may present with non-specific symptoms like abdominal pain.[15,16,18] This was similar to our findings, where cough, generalized weakness, and fever were the most common complaints. The presence of wheeze or rhonchi was the most common clinical finding in our study, which may be explained by underlying asthma or ABPA in these cases.[16,20,21]

The median IgE level in our study was 1014 ± 1983.2. When the stratified analysis was done with respect to eosinophil counts, there was no significant association between IgE level and AEC. There was a set of patients with IgE within the normal range also. This suggests an alternate pathway in clonal proliferation and distribution of eosinophils apart from IgE mediated.

Elevated IgE levels were found to be associated with a diagnosis of allergic disorders. This is similar to the previous literature, where allergic disorders and asthma are strongly associated with elevated IgE levels.[22]

In our study, the most commonly affected organs were the lungs, followed by skin, while other sites of damage such as kidneys and mass lesions were relatively rare. The previous studies have demonstrated abnormal PFTs, chest X-rays, and CT scans in patients with eosinophilia, indicating significant pulmonary involvement.[16,18-21] We found no significant level

of prediction between end-organ involvement and degree of eosinophilia. This highlights the importance of working up symptomatic patients for end-organ damage irrespective of the eosinophil count.[23]

The previous studies had also shown a high incidence of thromboembolism (~8%) in patients of eosinophilia, which was relatively rare in our population.[16] This may be due to mainly in-hospital recruitment in the previous studies where patients may have presented with the complaint of thromboembolism.

Our study provides insight into common etiologies of eosinophilia in India. Since a complete workup for eosinophilia was done in almost all of the patients, our findings can be reported with confidence. Only 13.2% of cases in our population were idiopathic, compared to previous estimates of nearly one-third. This indicates that our panel of testing was more comprehensive than in the previous studies. After the review of the literature, it was found that there are no recent data from North India on etiologies of eosinophilia. Furthermore, there is no recent data on the correlation of eosinophilia with organ system involvement in North India.

Our study had a few limitations. Since this was a single-center study with a small sample size of about 100 patients, the generalizability of the findings may be limited. Due to a cross-sectional design, further clinical courses of the patients could not be determined. Patients with primary eosinophilic disorders were referred and managed at the Hematology and Medical Oncology services and were thus underrepresented in our study. Longitudinal studies with larger sample sizes may shed light on the same. A correlation with organ system involvement is limited by the small sample size.

CONCLUSION

Eosinophilia is a commonly encountered abnormality in clinical practice. In our population, parasitic infestations are the most common cause of eosinophilia, followed by allergic disorders. The symptomatology of eosinophilia includes constitutional symptoms, cough, itching, and rashes. IgE levels correlate with a diagnosis of atopy or asthma and do not show a correlation with AEC. The lungs are the most frequently damaged organ, followed by the skin. There is no correlation between end-organ damage and the degree of eosinophilia, and thus, even patients with mild eosinophilia should be evaluated for evidence of end-organ damage.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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