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Original Research Article

A study of non-neoplastic nasal polypoidal lesions and its relation with local and systemic eosinophilia, peripheral IgE levels and mast cell quantitation

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Abstract: Nasal polyps comprise the most common tumor like, non-neoplastic polypoid masses arising from nasal cavity and paranasal sinuses. The aim of our study was to correlate histopathological diagnosis with local eosinophilia in tissue sections and peripheral IgE levels, and the underlying inflammatory response with clinical presentation. Systemic eosinophilia was calculated along with mast cell quantification. A total of 100 cases clinically diagnosed as nasal polyp, received from the Department of ENT, AIMSR over a period of one and a half year from 1st April 2014 to 30th September 2015 were included in the study. Sections were stained routinely with Haematoxylin and Eosin. Toluidine blue stain was carried out on sections which were diagnosed as non-neoplastic polyps on haematoxylin and Eosin stain. Mast cells in inflammatory polyps were counted in the epithelium and stroma. Age of patients in the study ranged from 5 years to 69years. Out of 110 cases studied, 74% of them were non-allergic and 26% were allergic. Nasal obstruction was the commonest symptom. Mast cells were higher in allergic than in non-allergic polyps. There was a significant correlation between local and systemic eosinophilia. The IgE levels were more in allergic than in non-allergic cases. Different inflammatory cells also correlated with specific clinical presentation. A complete and accurate diagnosis of polypoidal lesions of nose is possible only when histopathological findings were studied along with clinical features. Mast cells should be considered as potential targets for the management of various airway diseases. Histopathological examination remains indispensable for appropriate classification, characterization and treatment of the nasal polyps.
Keywords: Nasal polyp, Non-neoplastic, Eosinophilia, Mast cell, IgE

INTRODUCTION

Nasal polyps were first described more than 3000 years ago and comprise the most common group of mass lesions encountered in the nose [1]. Nasal polyps are a multifactorial disease, with infectious, non-infectious, inflammatory, anatomic and genetic abnormalities. Most theories consider polyps to be the ultimate manifestation of chronic inflammation [2]. A variety of non-neoplastic and neoplastic conditions can present as nasal polyps. Though, inflammatory polyps are the commonest [3, 4]. Nasal polyposis is not a single disease entity, but, instead is a multifactorial disease often associated with asthma, and other respiratory diseases like cystic fibrosis, primary ciliary dyskinesia, and aspirin sensitivity. Inflammatory polyps are fluid filled sacs composed of an oedematous tissue with infiltrating cells including mast cells, eosinophils, lymphocytes and plasma cells surrounded by ciliated airway epithelium.

It is more common in adults than in children under 10 years of age except when associated with cystic fibrosis. The site of polyp origin is a particular narrow area in the upper part of the nose, lateral to the middle turbinate, and around the openings of the ethmoid and maxillary sinuses. This is a part where the mucous membranes come into close contact [5]. The etiology of nasal polyps is still unclear and currently no single theory adequately explains the formation of all nasal polyps. The two most frequently mentioned theories are based on allergic and infectious causes. Although nasal polyp tissue is known to contain a high level of histamine there are hardly any details in the literature regarding the distribution and abundance of mast cells in nasal polyp tissue [6]. The present study is conducted to quantitate and study the localization of mast cells in nasal non-neoplastic polypoidal lesions of varied aetiology.

Idiopathic nasal polyps (NPs) can be distinguished by their presence or absence of eosinophilia and is supported by the observations that these display distinct histological, gene and protein expression patterns. Idiopathic NPs can be divided into distinct subsets characterized by absence (NE) and presence (E) of prominent eosinophilia. The validity of this distinction is supported by the demonstration that NE polyps are further distinguished by glandular hypertrophy, dense collagen deposition, and mononuclear cellular infiltrate. In contrast, eosinophilic nasal polyps display edema, rare glandularity, and minimal collagen deposition except within the basement membrane. Total mast cell numbers were reduced in eosinophilic nasal polyps, whereas connective tissue mast cells were increased in non-eosinophilic nasal polyps. Consistent with the distinctive pattern of increased fibrosis, non-eosinophilic nasal polyps displayed increased transforming growth factor (TGF)-ß and vascular endothelial growth factor transcripts. Similarly, non-eosinophilic nasal polyps had higher concentrations of TGF-ß, fibroblast growth factor-ß, and platelet-derived growth factor protein. The findings suggest that as unique diseases, idiopathic nasal polyps will require distinct therapeutic interventions [7].

Nasal polyposis is a chronic inflammatory disease of the upper airways. The polyps, which are benign edematous inflammatory masses, arise mainly from nasal or paranasal sinus mucosa and then prolapse into the nasal cavity histologically, nasal polyps are characterized by a large number of inflammatory cells infiltration and structural modifications of the epithelium and lamina propria. Here in this study, we tried to high-lighted the evidence that mast cells play an important role in the development and recurrence of nasal polyps. Clinically, it is quite impossible to distinguish between simple nasal polyps, polypoidal lesions due to specific diseases and polypoidal neoplasms (benign and malignant). For this reason, it becomes important that all polyps and polypoidal lesions of nose should be submitted for histopathogical examination [8].

MATERIAL AND METHODS

The present study was done in the department of ENT, Microbiology and Pathology, AIMSR over a period of one and a half year from 1st April 2014 to 30th September 2015. The patients with nasal polyps taken up for surgery were evaluated clinically and history was taken. Ethical approval from institutional ethical committee of ADESH UNIVERSITY and consent from the patients was taken before the start of the study.

Source of Data: Hospital based study.

Study design: Retrospective study.

Method of study: Only non-neoplastic lesions (eg. allergic, non-allergic like inflammatory, tuberculosis, rhinosporidiosis, fungal polyps etc.) of nose presenting as nasal polyp were taken up for study.

- In this study, we collected information about the age and sex of the patient for demographic analysis of the cases.
- The clinical presentation and laterality of the polyps were noted.
- Blood sample of the patient with nasal polypoidal masses were taken under aseptic conditions for both absolute eosinophil count and IgE levels.
- The biopsy specimens received were fixed in 10% buffered formalin.
- The specimens were examined grossly.
- These samples were then processed through in an automatic tissue processor.
- The paraffin embedded tissue blocks were cut at 3-4 micron thickness by the rotary microtome.
- The slides were stained in Harris haematoxylin and eosin.
- The examination of the hematoxylin and eosin stained slides of non-neoplastic nasal polyps was done using light microscope having a 40x objective and 10 x eyepieces.
- Histopathological diagnosis was made and the polyps were divided into allergic and non-allergic polyps.
- The number of eosinophils in stroma of both allergic and non-allergic polyps was counted and the polyps showing significant eosinophilia were calculated.
- Systemic and peripheral eosinophilias were also correlated.
- Absolute eosinophil count was calculated and the percentages of allergic and non-allergic polyps showing significant peripheral eosinophilia were calculated.
- Mast cell quantitation was done in both epithelium and stroma separately for allergic and non-allergic nasal polyps.
- Peripheral IgE levels were seen and mean IgE levels for both allergic and non-allergic polyps were calculated.
- The percentages of different inflammatory cells in stroma were also correlated with the clinical presentation. Also the number of mast cells was correlated with the clinical presentation.

RESULTS

Distribution of subjects according to histopathological diagnosis:

Table 1: Histopathological Diagnosis

Histopathology	Number	Percentage
Allergic	29	26.36
Non-allergic	81	73.64

P value=0.000

Non-allergic polyps (73.64%) were significantly more than allergic polyps (26.36%).

Distribution according to stromal infiltrate:

Table 2: Stroma Of Nasal Polyps

Infiltrate	Number of cases	Percentage
Predominance of mononuclear cells	64	58.18
Predominance of eosinophils	46	41.82
Total	110	100

58.18% (64 cases) of the nasal polyps showed predominance of mononuclear cell infiltrate and 41.82% (46 cases) showed eosinophil predominance.

Mast cell count in Epithelium and Stroma:

Table 3: Mast Cell Counts In Epithelium And Stroma.

Site	Epithelium			Stroma					
	Mast cells per 10 Hpf			Mast cells per 10 Hpf					
	0-5	6-10	>10	0-10	11-20	21-30	31-40	41-50	>50
Non-allergic polyp	78	3	-	53	24	2	1	1	-
Percentage	96.29	3.70	0.00	65.43	29.63	2.46	1.23	1.23	0.00
Allergic polyp	24	4	1	7	6	9	3	3	1
Percentage	82.76	13.79	3.45	24.14	20.69	31.03	10.34	10.35	3.44
Total	102	7	1	60	30	11	4	4	1
Percentage	92.73	6.36	0.91	54.55	27.27	10.00	3.64	3.64	0.91

The distribution of mast cells in the epithelium and stroma of non-allergic and allergic polyps were different as shown in table. When both types of polyps were taken into consideration, in the epithelium, 0–5 mast cells per 10 high power field (hpf) were seen in 92.73% of the cases. $P < 0.000$, confirming that in the majority of cases mast cells in the epithelium were seen in the range of 0–5 cells per 10 hpf. In stroma, 0–10 mast cells per 10 hpf were seen in 54.54%, 11–20 in 27.27%, 21–30 in 10.00% of the cases. $P < 0.005$, confirming that in the majority of cases mast cells in the stroma were seen in the range of 0-10 cells per 10 hpf.

Inflammatory cells in nasal polyps:

The type and density of inflammatory cell population was observed. Majority of the polyps had lymphocytes, plasma cells, eosinophils, neutrophils and macrophages. Most polyps had a dense infiltrate of eosinophils, lymphocytes and plasma cells. Neutrophils and macrophages were scanty in most polyps. Average number of cells / 5 hpf was taken to approximately quantitate the inflammatory cell population as dense (> 50) moderate (30-50) or scanty (<30). Lymphocytes, plasma cells and eosinophils were having moderate density in majority of the polyps. Mast cells, neutrophils and macrophages were scanty in majority of the polyps.

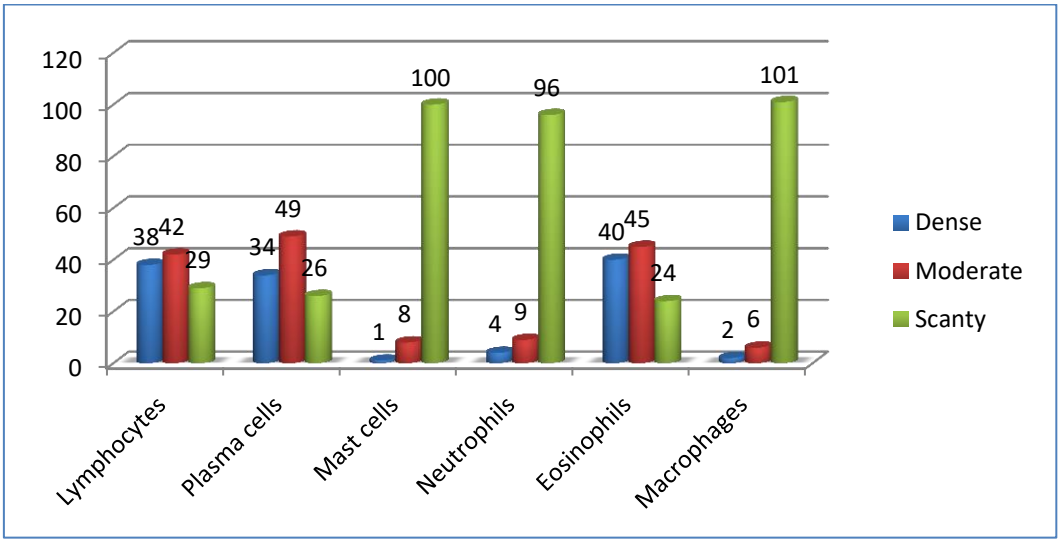

Fig 1: Inflammatory cells in nasal polyps

Distribution according to absolute eosinophil count:

Table 4: Absolute Eosinophil Count in Patients of Nasal Polyps

AEC	Allergic		Non-allergic	
	Number	Percentage	Number	Percentage
0-500	4	13.79	78	96.30
501-1000	21	72.41	2	2.47
1001-1500	3	10.34	0	0.00
1501-2000	1	3.45	1	1.23
Mean	789.83		220.26	
SD	328.17		223.43	

P value=0.000

Significant peripheral eosinophilia was seen in 72.4% (21 cases) of allergic polyps with most common range of 501-1000eosinophils per mm^3. Maximum absolute eosinophil count was 1824eosinophils/mm^3 and minimum was 248 eosinophils per mm^3. In case of non-allergic polyps, eosinophils were in range of 0-500eosinophils per mm^3 in 96.3% (78 cases), with a maximum of 1632eosinophils/mm^3, seen in only one fungal polyp.

Peripheral eosinophilia levels:

Absolute eosinophil count was determined in blood sample of both study and control groups. More than or equal to 500eosinophils per micro litre is considered as systemic eosinophilia. So, in our study, 86.21% (25 cases) of allergic polyps and 3.7% (3 cases) of non-allergic polyps showed significant peripheral eosinophilia.

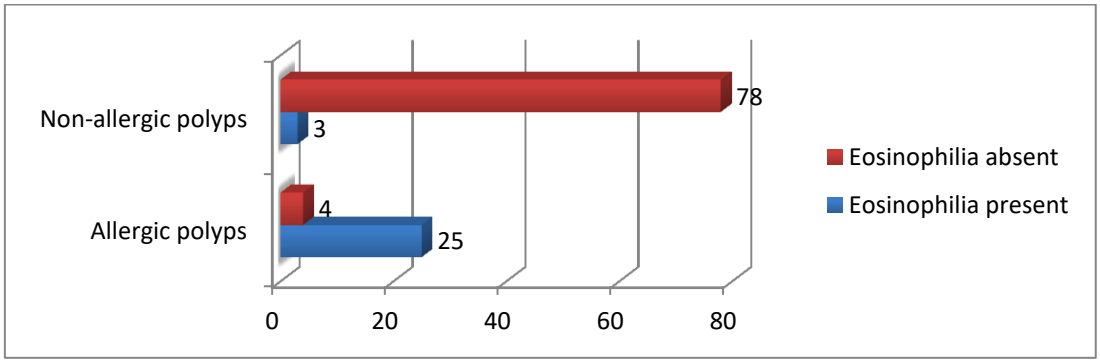

Fig 2: Peripheral eosinophilia levels

Peripheral IgE levels:

In our study, the IgE levels were elevated in 100% of patients with allergic nasal polyps. In these cases, the mean value was 2200IU/ml. In non-allergic polyps, mean IgE value was 258.58. When the sino-nasal polyposis was associated with fungal elements (*i.e.* polyps with sinusitis), the IgE values ranged from 2499 IU/ml to more than 4000 IU/ml.

Table 5: Peripheral Ig-E Levels In Nasal Polyps

	Allergic polyps	Non-allergic polyps
Patients	29	81
Mean IgE levels	2200.07	258.58
SD	1200.36	736.82

P value=0.000

In our study, peripheral IgE levels are significantly higher in allergic nasal polyps (that is 2200.07±1200.36IU/ml) as compared to non-allergic nasal polyps (that is 258.58±736.82IU/ml).

Relation between inflammatory response and clinical presentation:

Table 6: Relation between Inflammatory Cells and Clinical Symptoms in Nasal Polyps

Symptoms	Lymphocytes		Eosinophils		Plasma cells		Neutrophils	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
NO	54.07	15.09	10.43	9.40	27.93	8.53	7.14	5.29
NO+E	47.50	17.68	17.50	10.61	25.00	0.00	10.00	7.07
NO+H+DB	36.56	19.81	28.74	21.02	30.00	5.77	5.00	4.83
NO+R+S	14.76	6.80	54.76	13.74	27.38	9.70	3.10	3.35
EP	35.00	-	20.00	-	20.00	-	25.00	-
P-value	0.000		0.000		0.701		0.000	

There was a significant relation between the percentage of lymphocytes in stroma and clinical presentation of nasal obstruction. Similarly, significant relation was also seen between the percentage of eosinophils and clinical presentation of nasal obstruction, rhinorrhea and sneezing. There was no relation between the percentage of plasma cells and any of the specific clinical presentations. Also, significant relation was seen between percentage of neutrophils and ear pain.

Relation between mast cells and clinical presentation:

Table 7: Relation between Mast Cells and Clinical Symptoms in Nasal Polyps

Symptoms	Number	Mast cells	
		Mean	SD
NO	70	1.61	1.31
NO+E	2	2.00	0.00
NO+H+DB	16	2.44	1.75
NO+R+S	21	3.29	2.43
EP	1	4.00	-
P-value		0.001	

Mast cell count also showed a significant relation with the clinical presentation of ear pain.

DISCUSSION

This study was done in the Department of Pathology at Adesh Institute of Medical Sciences and Research, Bathinda in patients of non-neoplastic nasal polyps from 1st April 2014 to 31st September 2015. One hundred ten patients of non- neoplastic nasal polyps were included in the study. The histopathology of polyps was studied. The surface epithelium, inflammatory cell infiltrate and stroma were analyzed. Histopathological findings were correlated with the peripheral eosinophilia, IgE levels and clinical presentation of the cases.

HISTOPATHOLOGICAL FINDINGS IN COMPARISON TO OTHER STUDY GROUPS:

Inflammatory cells in stroma of nasal polyps:

Table 8: Comparison of Inflammatory Cells Population in the Stroma of Polyps

Cells	Dandapath *et al.;* [9]			Present study		
	Plenty	Moderate	Poor	Dense	Moderate	Scanty
Lymphocytes	29 (25.7%)	69 (61.0%)	15 (13.3%)	38(34.55%)	42(38.18%)	29(26.36%)
Plasma cells	22 (19.5%)	80 (70.8%)	11 (9.7%)	34(30.91%)	49(44.54%)	26(23.63%)
Macrophages	11 (9.7%)	76 (67.25%)	26 (23%)	2(1.82%)	6(5.45%)	101(91.81%)
Polymorphs (neutrophils)	-	33 (29.2%)	80 (70.8%)	4(3.64%)	9(8.18%)	96(87.27%)
Eosinophils	55 (48.7%)	33 (29.2%)	25 (22.1%)	40(36.36%)	45(40.91%)	24(21.81%)
Mast cells	33 (29.2%)	33 (29.2%)	25 (22.1%)	1 (0.91%)	8 (7.27%)	100(90.91%)

Various attempts to subgroup nasal polyps on a histological basis were totally unsuccessful. In the present study, significant feature was the constant presence of inflammatory cells in the stroma of nasal polyps. Most polyps in present study showed varying degree of cellular infiltrate consisting of eosinophils, lymphocytes, plasma cells and mast cells. Macrophages and neutrophils were scanty in majority of cases. Histopathologists often face difficulty in subgrouping the nasal polyp as allergic and non-allergic [10] or as inflammatory polyp and allergic polyp [11]. Patients with polyps have about the same prevalence of positive skin tests as does the normal population. Additional evidence against the hypothesis of allergy as a causal factor is that polyps seldom occur in children or young adults with atopic dermatitis, hay fever and allergic asthma. Nasal polyps arising in non-allergic group also showed significant number of eosinophils [12].

In a study conducted by Friedmann (1982), 10.6% were allergic polyps and 31.9% non-allergic or inflammatory polyps, the rest being mixed type. [10]. According to Friedmann *et al.;* in 1982, non-allergic polyps should have preponderance of polymorphonuclear leucocytes with few mononuclear cells including plasma cells. Presence of eosinophils even in variable concentration indicates allergic nasal polyps [13]. But this was not seen in our study as most of the inflammatory cells in non-allergic polyps (nonspecific inflammatory and specific infectious polyps) were mononuclear cells and not neutrophils. This may be because of early control of infection by the use of effective antibiotics.

Mygind (1985) classified polyps into two groups, those containing large number of eosinophils and those containing large number of neutrophils.[14] In the present study, we could not classify polyps into eosinophilic or neutrophilic polyps as by Mygind, because in majority of the polyps eosinophils were present. It is tempting to classify the eosinophilic polyps as allergic because they were often associated with asthma and perennial rhinitis, but relationship between polyps and allergy is not clear. Sherman stated that allergy was a causal factor in the development of nasal polyps; however other authors, including Kern and Schenck, Pepys, Duveen and Caplin have considered the relationship to be co-incidental.

In a study by Dandapath *et al.;* in 1993, lymphocytes, plasma cells and macrophages were present in moderate number in 61.1%, 70.8% and 67.3% instances respectively. Though these cells were constantly present in stroma of polyps, polymorphs were present in poor numbers in majority of these cases. Eosinophils were present in plenty in 48.7% of cases and rest of polyps showed presence of moderate to poor number of eosinophils. In majority of cases plenty to moderate number of mast cells were present in 58.4% cases [9]. Whereas in our study, only 9% of the cases showed plenty to moderate number of mast cells.

But according to Shanmugarathnam and Sobin (1993), nasal polyp of any type may contain all types of

cells including mast cells although in allergic types, eosinophils predominate. Same was found in our study. According to Drake (1997), eosinophils were present in 90% of polyps.15 Study of Dandapath *et al.;* in 1993 showed eosinophils in moderate numbers in all the polyps [9]. In the present study, eosinophils were seen in majority of nasal polyps. The present study, correlates with the studies of Dandapth *et al.;* Slavin and Drake [9, 15].

POLYPOIDAL LESIONS:

Table 9: Distribution of Mast Cells in Nasal Polyps among Various Studies

Study	No of cases	Epithelium	Stroma
Mysorekar *et al.;* [16](2004)	110	90% - < 5000 cells/cumm	30% - 5000 to 20,000 cells/cumm
Otsuka *et al.;* [17](1993)	n	20, 000 cells/cumm	6000 cells/cumm
Pawliczak [18] (1997)	17	Predominantly in superficial layer of mucosa	
Present study	110	96.2% (0-5/10 hpf) in non-allergic polyps and 82.7% (0-5/10 hpf) in non-allergic polyp.	65.4% (0-10/10 hpf) in allergic polyps and 31.3% (21-30/ 10 hpf) in non-allergic polyps.

In a study conducted by Mysorekar *et al.;* [16] (2004), mast cells were found to be equally increased in allergic and non-allergic polyps. A few more authors such as Ruhno *et al.;* [19] and Otsuka *et al.;* [17] have shown that epithelial mast cells in nasal polyps are equally elevated in non-allergic and allergic patients. The present study also showed that there is a significant difference in the distribution of mast cells in allergic and non-allergic nasal polyps. So our study did not correlate with the studies conducted by Mysorekar *et al.;* in 2004, Ruhnoet *et al.;* and Otsuka *et al.;*

Comparison of local and systemic eosinophilia:

According to Wardlaw *et al.;* in 2000 [20], the hypothesis that eosinophils are important effector cells in allergic disease rests on the evidence that the eosinophils are found in tissues in allergic diseases, their mediators are relevant to the disease process and removal of eosinophils is associated with an improvement in the disease. GCs undoubtedly have a profound effect on eosinophils and their beneficial effects in allergic disease appear to go hand-in-hand with their inhibition of tissue eosinophilia, but they are of course broad-spectrum anti-inflammatory drugs [20].

There is no doubt that eosinophils are intimately associated with asthma and the other atopic diseases. As there is virtually no evidence that eosinophils can ameliorate disease, we presume they must either be bystander cells or actively involved in pathogenesis. The current evidence is consistent with a role for eosinophils simply as markers of the inflammatory process. Perhaps eosinophils are part of a complex inflammatory process in which they favour some aspect of the pathophysiology. So, more work needs be done to determine the extent to which the eosinophilia might guide management of nasal polyps. [20]. Zhang *et al.;* in 2008 [21] also assessed the infiltration and activation of eosinophils in nasal polyps immunohistochemically. They concluded eosinophilia is a prominent histological feature of nasal polyps, which indicates that the activated eosinophils may play vital role in the pathogenesis of nasal polyps. According to Pradhananga *et al.;* in 2008 [22], there is significant correlation between local and systemic eosinophilia. Thus this study correlated with our findings.

Table 10: Comparison of IGE levels

Study	Ig-E levels IU/ml	
	Allergic nasal polyps	Non-allergic nasal polyps
Aleksandar *et al.;* in 2011[23]	328.93±46.25	68.71±31.84
Present study	2200.07±1200.36	258.85±736.82

According to Wittig *et al.;* in 1980 healthy, non-allergic adults have an expected IgE concentration up to 120 IU/ml. In the study by Chowdary *et al.;* in 2003 [24], it was observed that the normal IgE levels in Indian population were relatively higher than the western values. They proved that the IgE levels were elevated in more than 90% of patients with allergic rhinitis with sinonasal polyposis, the value was more than 1000 IU/ml. When the sino-nasal polyposis was associated with fungal elements (*i.e. Aspergillus* induced allergic rhinitis with sinusitis), the IgE values ranged from 2323 IU/ml to more than 4000 IU/ml, and

our study also supported the above findings. According to a study by, Aleksandar *et al.;* in 2011 [23], All patients with allergic rhinitis and atopic nasal polyposis were positive to the skin-prick test and had increased serum IgE. Histology showed that plenty of eosinophils were seen in the samples taken from patients with atopic nasal polyposis, while in non-atopic patients eosinophil infiltration was scarce. So, this study correlated with our study.

Relation between inflammatory response and clinical presentation:

Whether allergy is a cause of nasal polyposis is a controversial issue. The fact that polyps are characterized by mast cell degranulation and high local levels of IgE and of histamine and that there is an eosinophil dominated inflammation driven by cytokines (which are also operative in allergic inflammation), is compatible with an allergic aetiology [25]. In a study by Aleksanda *et al.;* in 2011 [23], it was found that allergic nasal polyposis patients showed a higher level of eosinophilic inflammation than non-allergic patients with nasal polyps. This study was in concordance with our study.

CONCLUSION

Airway epithelial cells serve as the first barrier of host defense against bacterial, viral, or airborne particles. Continuous exposure to these agents may be a primary etiologic factor predisposing to disease development. So, it is important to remember that there is no single etiological factor that is responsible for the development of nasal polyposis, but the inflammation still remains to be the central major factor in all nasal polyps. Activation of epithelial cells, mast cells, and macrophages by various factors like bacteria, virus in addition to altered aerodynamics also plays a major role in the development of non-specific inflammatory polyps which comprise of 74% of the cases in our study.

In our study we have highlighted the evidence that mast cells play more diverse and crucial roles as both effector and immune-regulatory cells in causing allergic conditions. Therefore mast cells should be considered as potential targets for the management of various airway diseases. Different treatment modalities are in use now days for various types of polyps. So, histopathological examination remains indispensable for proper classification, characterization and treatment of the nasal polyps.

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