

CORRELATION BETWEEN PERIPHERAL BLOOD EOSINOPHILIA AND THE HISTOPATHOLOGICAL CHANGES IN NASAL MUCOSAL IN CHRONIC RHINOSINUSITIS

ABSTRACT

Background: Chronic rhinosinusitis (CRS) has emerged as one of the major causes of significant morbidity in otorhinolaryngology, as it is often noted to be refractory to medical management and has a tendency to recur post-surgery. Limited research has shown that peripheral eosinophilia is related to the presence of nasal polyps, the extent of the mucosal disease, the severity of tissue eosinophilia, and the risk of recurrence.

Aim: This study aimed to establish the significance of peripheral blood eosinophilia, both differential (EC) and absolute eosinophil counts (AEC) - in adult CRS, to correlate the tissue eosinophilia and peripheral blood eosinophilia, and compare the observations in the two types of CRS with nasal polyp and without nasal polyp.

Material and methods: A total of 50 adult patients with CRS who underwent FESS were included in the study and were divided based on the presence (Group 1) or absence (Group 2) of peripheral blood eosinophilia.

Results: There were equal number of cases of chronic rhinosinusitis with nasal polyp (CRSwNP) and without polyp (CRSsNP); 25 each. With regard to clinical features, Group 1 had a higher number of cases with nasal obstruction (p-value = 0.023), post-nasal drip (p-value = 0.035), and hyposmia (p-value = 0.021) when compared to Group 2. On histopathology, Group 1 had more areas of edema (p-value = 0.027), and mucous gland hyperplasia (p-value = 0.013) while Group 2 had prominent lymphoplasmacytic infiltrates (p-value = 0.035), neutrophilia (p-value = 0.047), and tissue infiltration of macrophages (p-value = 0.027). Tissue eosinophilia was present in 32 out of the total cases; 20 (71.43%) in Group 1 and 12 (53.33%) in Group 2. The group with tissue eosinophilia had significantly higher eosinophil count ($9.24 \pm 4.26\%$ vs $5.32 \pm 2.9\%$; p-value < 0.01) as well as AEC ($823.335 \pm 434.357/\mu\text{l}$ vs $485.128 \pm 285/\mu\text{l}$; p-value < 0.01).

Conclusion: The study demonstrated that CRS cases with tissue eosinophilia exhibit an elevated peripheral eosinophil count when compared to non-eosinophilic CRS.

Keywords: Chronic rhinosinusitis, peripheral blood eosinophilia, tissue eosinophilia, Eosinophils

1. INTRODUCTION

Chronic rhino-sinusitis (CRS) is a clinical syndrome associated with persistent inflammation of the mucosa of the nose and paranasal sinuses.^[1] CRS in adults is defined as inflammation of the nose and paranasal sinuses characterized by the presence of greater than 12 weeks of at least two symptoms like nasal blockage/obstruction/congestion, nasal

discharge (anterior/posterior nasal drip), facial pain/pressure and/or reduction or loss of smell.^[2] The diagnosis should be supported by evidence of disease on nasal endoscopy and/or computerised tomography of the paranasal sinuses.

CRS is one of the most prevalent chronic diseases in the world, comparable to diabetes mellitus and asthma. Among the developed parts of the world, the prevalence of CRS in Europe and the United States of America is about 10.9%^[3] and 12.5%^[4] of the general population, respectively. In India, CRS is known to affect about 15% of the population, which works out to be 1 in 7 people.^[5,6]

This condition affects a noteworthy percentage of the population causing significant functional limitations and loss of workdays. The patients report severe pain, and their social functioning is sometimes reported to be worse than those suffering from COPD, congestive cardiac failure or angina.^[7-10] Quite often, the condition is unmanageable with only medications, necessitating surgical intervention, which levies an economic burden on the patient. Despite many researches being done, the exact nature of the pathophysiology of CRS is still unclear. However, there has been increasing evidence to suggest that eosinophils have an important role in the pathogenesis of CRS.^[11,12] Currently existing studies suggest that the eosinophilic status plays out differently in different types of CRS. CRS with nasal polyp (CRSwNP) has been suggested to be mediated by eosinophils and increased histamine, while CRS without nasal polyp (CRSsNP) are believed to be predominantly mediated by neutrophils with no significant role for eosinophils.^[1] Tissue eosinophilia has also been correlated with a longer duration of medical treatment, postoperative recurrence and severity of the disease in CRS.^[13,14] This has given rise to a more recent classification of CRS into eosinophilic and non-eosinophilic, based on tissue eosinophilia.

As of now, the gold standard for detecting tissue eosinophilia is the histological criterion. However, obtaining samples for histopathological analysis is an invasive and expensive procedure, usually done during endoscopic sinus surgery. Thus, there is a need for an easier and less invasive tool for detecting tissue eosinophilia. Recent studies have suggested the role of peripheral blood eosinophilia as a marker of disease severity in CRS. Studies done by Yildirim A et al.^[15] and Hu Y et al.^[16] showed a significantly higher peripheral blood eosinophil counts in cases of CRS when compared to control groups. Zadeh et al have also pointed out that elevated serum eosinophilia correlates with higher rates of refraction to medical and surgical treatments.^[17] Therefore, peripheral eosinophilia can potentially be used as a marker for assessing disease severity and response to treatments. Although previous studies have assessed the relationship between peripheral eosinophilia and CRS; and tissue eosinophilia and CRS, very few have assessed the correlation between peripheral and tissue eosinophilia. Hence, this study aims to establish the correlation between peripheral blood eosinophilia and eosinophilia in the nasal mucosa in adult patient with CRS.

2. MATERIAL AND METHODS

A retrospective analysis was done on adult patients (≥ 18 years) with CRS, who underwent FESS over a 2-year period (January 2015-December 2016) in Saveetha Medical College, a tertiary care hospital. The cases of CRS were defined as per the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS), **2012 2020** as inflammation of the nose and paranasal sinuses with the presence of two or more symptoms; one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior /posterior nasal drip), facial pain and pressure, reduction or loss of smell for >12 weeks.^[18] In addition, the diagnosis was supported by either: endoscopic signs of polyps; oedema, or mucopurulent discharge; and/or CT PNS showing mucosal changes within the osteomeatal complex and/or sinuses.

The inclusion criterion was all patients with CRS who underwent FESS after failing previous maximum medical therapy during the study period. The exclusion criteria included: patients under 18 years of age; patients with systemic illnesses affecting the nasal mucosa such as immunodeficiency, cystic fibrosis, granulomatous conditions, or vasculitis. The demographic data regarding age and gender, clinical symptoms, total WBC count, differential WBC count, eosinophils percentage, absolute eosinophil counts, and the histopathology reports of nasal mucosa following FESS were collected from medical records of the hospital and histopathology registers in the department of pathology for each case and systematically recorded in a proforma. Serum eosinophilia was defined as an absolute eosinophil count $>0.5 \times 10^9$ cells/L.^[19] On histopathology, tissue eosinophilia was defined as tissue eosinophil count >10 /HPF.^[20, 21]

2.1 STATISTICAL METHODS

The cases were divided based on the presence (Group 1) or absence (Group 2) of peripheral blood eosinophilia. The results were subsequently tabulated by entering into Microsoft Excel and analysed. The data was interpreted in terms of percentage, mean values and chi-square test. Comparison of the means of continuous variables between the two groups was done using independent sample's t-test/Mann-Whitney U test. A probability value (p-value) less than or equal to 0.05 was taken to be statistically significant.

3. RESULTS AND DISCUSSION

The study population included a total of 50 cases of CRS which had undergone FESS. This included 35 cases with peripheral blood eosinophilia (Group 1); and 15 without peripheral blood eosinophilia (Group 2). The overall age group ranged from 18 to 69 and the mean age was 35.5 ± 13.6 years. Out of this, 57% (N = 27) of the case were in the age group between 21-40 years; 14 were in group 1 and 13 were in group 2. There was no significant difference in the age distribution between the two groups (p-value = 0.480). With respect to gender, there were a total of 23 (46%) males and 27 (54%) females. There was no gender predominance in either of the groups, with 13 (48.15%) males and 14 (43.48%) females in group 1; and 10 (51.85%) males and 13 (56.52%) females in group 2 (Table 1).

Out of the total of 50 cases, 25 were with nasal polyp (CRSwNP) and 25 without nasal polyp (CRSsNP). In group 1, there were 15 with CRSwNP and 12 with CRSsNP; and within group 2 there were 10 with CRSwNP and 13 with CRSsNP. There was no statistically significant correlation between the incidence of nasal polyposis in Groups 1 and 2 (p-value = 0.395) (Table 2). Cross-tabulation between nasal polyposis and tissue eosinophilia also showed no significant correlation between the two (p-value = 0.556). (Table 6)

Analysis of the clinical features revealed that the most common symptoms in the cases studied included, nasal obstruction (N=43; 86%) and post-nasal drip (N=41; 82%). The presentation of nasal obstruction, postnasal drip, and hyposmia were higher in Group 1 (Table 1) when compared with Group 2 and the findings were statistically significant; nasal obstruction (96.30% vs 73.91%; p-value = 0.023), post-nasal drip (92.59% vs 69.57%; p-value = 0.035), and hyposmia (88.89% vs 60.87%; p-value = 0.021). (Table 3). CRSwNP cases were found to have significantly higher percentage of nasal obstruction (96% vs 76%; p-value = 0.042), and hyposmia (88% vs 64%; p-value = 0.047). (Table 4)

Among the histopathological features, the most common findings were edema (34, 68%), tissue eosinophilia (32, 64%), mucous gland hyperplasia (31, 62%), and lymphoplasmacytic infiltrate (29, 58%). (Figure 1) Out of these, Group 1 had a significantly higher presence of edema (81.5% vs 52.2%; p-value = 0.027), and mucous gland hyperplasia (77.8% vs 43.5%; p-value = 0.013) compared to Group 2. Group 2 had a statistically significant higher presence of lymphoplasmacytic infiltrate (44.4% vs 73.9%; p-value = 0.035), neutrophilia (37.0% vs 65.2%; p-value = 0.047), macrophages (29.6% vs 60.9%; p-value = 0.027) compared to Group 1. The histopathologic variables of hemorrhage and necrosis did not differ significantly between the two groups. Tissue eosinophilia was present in 20 (74.07 %) of Group 1 cases vs 12 (52.17 %) in group 2. Cross tabulation was done between the presence of tissue eosinophilia in groups 1 and 2 and assessed using the chi-square test. There was no significant correlation between peripheral eosinophilia and tissue eosinophilia (p-value = 0.108) (Table 5).

Analysis of histopathological variables between CRSwNP and CRSsNP cases was done. CRSwNP cases had a significantly higher incidence of lymphoplasmacytic infiltrate (76% vs 40%; p-value = 0.01), neutrophilia (68% vs 63.2%; p-value = 0.01), edema (84% vs 52%; p-value = 0.015), and mucus gland hyperplasia (76% vs 48% p-value = 0.041) when compared to CRSsNP. (Table 6).

The differential eosinophil count (EC) and absolute eosinophil count (AEC) of the samples were analyzed. The mean EC of the 50 cases studied was $7.83 \pm 4.25\%$ and the mean AEC was 701.58 ± 417.86 cells/ μ l. The means of the EC and AEC were compared between three groups – Group 1 and Group 2, CRSwNP and CRSsNP and with tissue eosinophilia and without tissue eosinophilia.

Group 1 showed a significantly higher mean eosinophil count (EC) value ($10.6 \pm 3.74\%$ vs $4.5 \pm 1.48\%$; $P < 0.001$) and mean absolute eosinophil count (AEC) (1004.3 ± 336.96 cells/ μ l vs 346.20 ± 101.09 cells/ μ l; $P < 0.001$). The group with tissue eosinophilia had significantly higher EC ($9.24 \pm 4.26\%$ vs $5.32 \pm 2.91\%$; p-value < 0.01) as well as AEC (823.335 ± 434.357 cells/ μ l vs 485.128 ± 285.907 cells/ μ l; p-value < 0.01) when compared to the group without tissue eosinophilia. The mean AEC and EC were higher in CRSwNP compared to CRSsNP which was however wasn't statistically significant. (Table 7)

Further analysis showed that peripheral eosinophilia had a sensitivity of 62.5% in detecting tissue eosinophilia and specificity of 61.11% and accuracy of 62%. The positive predictive value was 74.07% and the negative predictive value was 52.17%. Using peripheral eosinophilia as a test to detect nasal polyposis was found to have a moderate sensitivity of 60%, a specificity of 52%, and an accuracy of 56%.

Table 1: Age and gender distribution of cases in Group 1 and 2

Age	Total n = 50	Group 1 n = 27	Group 2 n = 23	p-value
<20 years	6 (12%)	5 (18.52 %)	1 (4.35 %)	0.480
21-40	27 (54 %)	14 (51.85 %)	13 (56.52 %)	
41-60	13 (26 %)	6 (22.22 %)	7 (30.43 %)	
>60 years	4 (8 %)	2 (7.41 %)	2 (8.70 %)	
Gender	All subjects	Group 1 n = 27	Group 2 n = 23	p-value
Male	23 (46 %)	13 (48.15 %)	10 (43.48%)	0.741
Female	27 (54 %)	14 (51.85 %)	13 (56.52 %)	

Table 2: Correlation of nasal polyps with and without peripheral blood eosinophilia

Nasal polyposis	Total n = 50	Group 1 n = 27	Group 2 n = 23	p-value
CRSwNP	25 (50 %)	15 (55.56 %)	10 (44.44 %)	0.395
CRSSNP	25 (50 %)	12 (43.48 %)	13 (56.52 %)	

Table 3: Comparison of clinical features in groups with/without peripheral blood eosinophilia

Clinical Features	Total n = 50	Group 1 n = 27	Group 2 n = 23	p-value
Nasal block/obstruction	43 (86%)	26 (96.30 %)	17 (73.91 %)	0.023*
Nasal discharge	29 (58%)	14 (51.85 %)	15 (65.22 %)	0.340
Post-nasal drip	41 (82%)	25 (92.59 %)	16 (69.57 %)	0.035*
Paranasal tenderness	29 (58%)	16 (59.26 %)	13 (56.52 %)	0.845
Frequent URTI	31 (62%)	18 (66.67 %)	13 (56.52 %)	0.461
Hyposmia	38 (76%)	24 (88.89 %)	14 (60.87 %)	0.021*
Headache	35 (70%)	20 (74.07 %)	15 (65.22 %)	0.496

Table 4: Comparison of clinical features between CRSwNP and CRSsNP

Clinical Features	Total n = 50	CRSwNP n = 25	CRSsNP n = 25	P-value
Nasal block/obstruction	43 (86%)	24 (96%)	19 (76%)	0.042*
Nasal discharge	29 (58%)	13 (52%)	16 (64%)	0.390
Post-nasal drip	41 (82%)	19 (76%)	22 (88%)	0.269
Paranasal tenderness	29 (58%)	15 (60%)	14 (56%)	0.774
Frequent URTI	31 (62%)	16 (64%)	15 (60%)	0.771
Hyposmia	38 (76%)	22 (88%)	16 (64%)	0.047*
Headache	35 (70%)	18 (72%)	17 (68%)	0.758

Table 5: Comparison of histopathological findings between Group 1 and 2

Histopathology	Total n = 50	Group 1 n = 27	Group 2 n = 23	p-value
Lymphoplasmacytic infiltrate	29 (58%)	12 (44.44%)	17 (73.91%)	0.035*
Tissue eosinophilia	32 (64%)	20 (74.07)	12 (52.17%)	0.108
Neutrophilia	25 (50%)	10 (37.04%)	15 (65.22%)	0.047*
Macrophages	22 (44%)	8 (29.63%)	14 (60.87%)	0.027*
Hemorrhage	3 (6%)	1 (3.70%)	2 (8.70%)	0.459
Necrosis	3 (6%)	2 (7.41%)	1 (4.35%)	0.650
Edema	34 (68%)	22 (81.48%)	12 (52.17%)	0.027*
Mucous gland hyperplasia	31 (62%)	21(77.78%)	10 (43.48%)	0.013*

Table 6: Comparison of histopathological findings between CRSwNP and CRSsNP

Histopathology	Total (n)	CRSwNP (n)	CRSsNP (n)	p-value
Lymphoplasmacytic infiltrate	29 (58%)	19 (76%)	10 (40%)	0.010*
Tissue eosinophilia	32 (64%)	15 (60%)	17 (68%)	0.556

Neutrophilia	25 (50%)	17 (68%)	8 (32%)	0.011*
Macrophages	22 (44%)	13 (52%)	9 (36%)	0.254
Hemorrhage	3 (6%)	2 (8%)	1 (4%)	0.552
Necrosis	3 (6%)	1 (4%)	2 (8%)	0.552
Edema	34 (68%)	21 (84%)	13 (52%)	0.015*
Mucous gland hyperplasia	31 (62%)	19 (76%)	12 (48%)	0.041*

Table 7: Comparison of the mean of eosinophil count (EC) and absolute eosinophil count (AEC) in the presence/absence of tissue eosinophilia and presence/absence of polyps

Variables	EC (%)	AEC (cells/ μ l)
	Mean \pm SD	Mean \pm SD
Group 1	10.6 \pm 3.74	1004.3 \pm 336.96
Group 2	4.5 \pm 1.48	346.20 \pm 101.09
P-value	<0.001*	<0.001*
Tissue Eosinophilia present	9.24 \pm 4.26	823.335 \pm 434.357
Tissue Eosinophilia absent	5.32 \pm 2.91	485.128 \pm 285.907
P-value	<0.001*	<0.001*
CRSwNP	7.87 \pm 4.40	765.23 \pm 454.79
CRSsNP	7.79 \pm 4.18	637.92 \pm 375.79
P-value	0.947	0.286

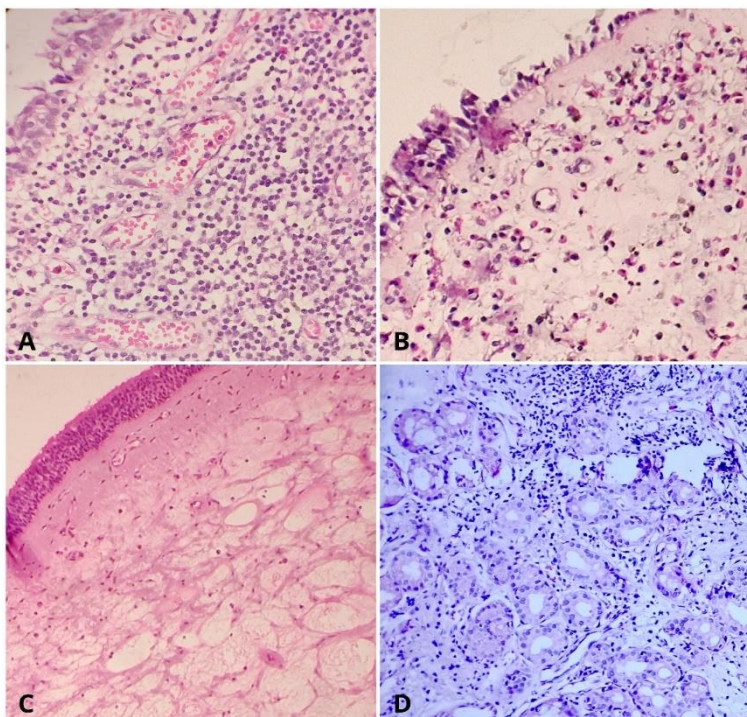


Figure 1: A: Lymphoplasmacytic infiltrate, B: Eosinophilic infiltrate, C: Tissue oedema, D: Mucous gland hyperplasia: (H & E, x 200)

3.1 DISCUSSION

Chronic rhinosinusitis has emerged as one of the causes of significant morbidity in otorhinolaryngology, as it is often noted to be refractory to medical management and has a tendency to recur post-surgery.^[6,9,22] Numerous studies have suggested the possibility that eosinophils play a major role in the pathogenesis of CRS, based on their presence in the nasal mucosa.^[1,11,12,22,23] It is yet to be established whether it is a definite causative factor or merely a bystander, being at the wrong place at the wrong time. Limited research has shown that peripheral eosinophilia is related to the presence of nasal polyps, the extent of the mucosal disease, the severity of tissue eosinophilia, and the risk of recurrence.^[2,24,25] However, there is insufficient data to prove this relation, particularly in India.

In our short-term observational study, we have found that there was no gender predilection overall. The majority of the cases presented between the ages of 20-40 years, with relative sparing of extremes of age. On dividing the cases into those with and without peripheral blood eosinophilia and labeling them as Groups 1 and 2 respectively, demographic distribution remained the same in both the groups, comparable with a study done by Hu Y et al, and D Jain.^[16,6] Since the commonly affected age group comprises the most productive years in life, this can contribute to the increased financial burden and social functioning of the patients.

Nasal polyposis was present in 50% of the study population. Group 1 had 15 (55.56%) with nasal polyps and group 2 had 10 (44.44%) with nasal polyps. This study did not show any significant association between nasal polyposis and peripheral eosinophilia (p-value = 0.395), which was in contrast to the findings of A Ganti et al.^[28] Both tissue (p-value = 0.556) and peripheral blood eosinophilia (p-value = 0.395) did not correlate with the presence of nasal polyps, another contrasting finding to other studies such as J.M.Bryson et al^[29] and McHugh et al,^[22] and Kuhar HN et al^[24] which suggested that the presence of eosinophilic aggregates was associated with an increased presence of polyp disease.

Symptoms such as nasal obstruction, postnasal drip, and hyposmia were significantly more in those patients with peripheral eosinophilia, having a p-value of <0.05. Other common symptoms included nasal discharge and paranasal tenderness and were equally distributed among both groups.

With regard to histopathological findings, lymphoplasmacytic infiltrate (p-value= 0.035), neutrophilia (p-value = 0.047), macrophages (p-value = 0.027) were significantly higher in those without peripheral eosinophilia, whereas edema (p-

value= 0.05), and mucous gland hyperplasia (p-value = 0.021) were significantly higher in those with peripheral blood eosinophilia. Between CRSwNP and CRSsNP, CRSwNP showed a higher proportion with lymphoplasmacytic infiltrate (p-value = 0.01), neutrophilia (p-value = 0.01), edema (p-value = 0.02), and mucus gland hyperplasia (p-value = 0.047). The results suggest a multimodal pathogenesis of CRS, including different inflammatory mediators like lymphocyte, neutrophils, macrophages in non-ECRS.

In addition to tissue oedema and mucus gland hyperplasia on histopathology, the group with peripheral eosinophilia showed increased presence of symptoms of nasal obstruction, postnasal drip, and hyposmia. This could indicate a possible underlying pathological process, but requires more focused research to support it.

A major aim of this study was to determine the association between peripheral eosinophilia and tissue eosinophilia in CRS patients. A significant association would indicate that blood eosinophilia can be used as a screening tool to detect tissue eosinophilia in CRS patients, which in turn is associated with worse disease prognosis. Tissue eosinophilia has been defined as >10 eosinophils/HPF according to studies done by Soler et al^[21] and Snidvongs et al^[20]. Cases that met the above criteria have been referred to as Eosinophilic CRS, or ECRS. ECRS encompassed 64 % of our total cases, similar to the study by Stephan Vlaminc et al.^[26] Our results clearly showed that both the EC and AEC were significantly elevated in those with tissue eosinophilia (p < 0.01), similar to A Sreeparvathi et al. However, this study did not show any remarkable association between the two (p=0.107). This was similar to the study by S Gitomer^[27] which showed no correlation between tissue and serum eosinophil levels in CRSwNP.

The absence of an association even in the presence of elevated blood eosinophil counts could also implicate the role of mediators other than eosinophils in CRS behaviour and progression. Moreover, peripheral blood eosinophilia is not exclusive to CRS. It's well known to be present in other conditions like allergy, autoimmune disorders, malignancies, and parasitic infestations; which were not factored in in this study. The existence of these confounding factors, which were not accounted for in this study, can contribute to the association between peripheral blood eosinophilia, tissue eosinophilia, and nasal polyps. The variation between the various studies could also indicate that different inflammatory mediators like neutrophils also play a role in the pathogenesis.

As per this study, peripheral eosinophilia had moderate sensitivity (62.5%), specificity (61.11%), and accuracy (62%) in detecting tissue eosinophilia. And, peripheral eosinophilia also had only moderate sensitivity (60%), specificity (52%), and accuracy (56%) in detecting nasal polyposis. This was in contrast to Hu Y et al^[16] who showed that AEC $\geq 0.215 \times 10^9/L$ had a sensitivity of 74.2% and a specificity of 86.5%, and EC $\geq 3.05\%$ had a sensitivity of 80.3% and a specificity of 75.3% in diagnosing eosinophilic CRSwNP. However, their cut-off value for the blood eosinophil level was lower than ours (AEC $> 0.5 \times 10^9/L$), which could have contributed to the higher sensitivity and specificity.

A major limitation of our study is that we only included a small subset of patients who underwent FESS and so a large portion of those being managed medically and with mild disease remained excluded. Further large scale studies are needed to analyse blood and tissue eosinophil levels by including those medically managed as well.

4. CONCLUSION

The study demonstrated that cases of CRS with tissue eosinophilia exhibit an elevated peripheral blood eosinophil count when compared to those without tissue eosinophilia. Significantly more clinical symptoms, tissue oedema and mucus gland hyperplasia were observed in those with peripheral blood eosinophilia. Based on this study, we conclude that blood eosinophil count may be a useful indicator of nasal mucosal eosinophilic infiltration and hence a more severe disease process. However, histological examination still remains the gold standard for the detection of tissue eosinophilia. Currently, there is a paucity of significant research in this area in India. We hope that this study will pave way for studies on a larger scale to study the burden of CRS in the Indian population.

ETHICAL APPROVAL

Ethical clearance- Institutional ethics committee approval was obtained SMC/AEC/2017/039.

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