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Original article

Comparative Histopathological Changes Between Primary Versus Recurrent Rhinosinusitis with Nasal Polyposis.

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ABSTRACT

Background: Chronic rhinosinusitis associated with nasal polypi [CRSwNP] is one of the two major chronic rhinosinusitis phenotypes. The histopathological changes of such condition may differ between primary and chronic types.

Aim of the work: To differentiate between primary and chronic rhinosinusitis with polypi through detection of the histopathological changes of nasal mucosa.

Patients and Methods: Eighty-five patients with CRSwNP scheduled for functional endoscopic sinus surgery [FESS] were divided into two groups; group [1] 35 patients with primary polyposis, group [2] 50 patients with chronic polyposis. A swab was taken from sinus mucosa during FESS and sent for histopathological investigation.

Results: We studied 12 histopathogical findings of spacemen of sinus mucosa and found 7 of them had a significant value in comparison between primary and recurrent CRSwNP. The significant increases in chronic recurrent group [2] than primary group [1] were eosinophilic cell count [p=0.044], eosinophilic cell aggregation [p=0.049], basement membrane thickness [P=0.021], Mucosal ulceration [p=0.002], hyperplastic or papillary change [p=0.029], fibrosis [p=0.002] and fungal element [p=0.003].

Conclusion: Histopathological findings of sinus mucosa during FESS operation found to be of great value in differentiating between primary and recurrent CRSwNP, however, further studies on large scale groups were recommended to confirm these results.

Keywords: Rhinosinusitis; Nasal; Polyposis; Eosinophilia; Recurrence.

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Chronic rhinosinusitis with nasal polyposis is one phenotype of the two main chronic rhino-sinusitis [CRS] phenotypes and is characterized by the existence of nasal polypi in the middle meatus[1]. CRS specifies a group of heterogeneous, ill-defined conditions of persistent inflammatory conditions of paranasal sinuses, with different responses to the available treatment options. The fundamental pathophysiology of CRS stays unclear, however ongoing advances in our knowledge of the particular inflammatory mechanisms that encourages the progress in improvement of focused biologic pharmacotherapies [2]. In this condition, nasal polyps are normally growing on bilateral sinonasal cavities. Among all patients with CRS, just 25–30% have CRSwNP. CRSwNP is usually related with some morbidities and diminished personal satisfaction making it clinically critical to distinguish, assess, and treat [3]. It is one of the commonest chronic conditions, with a prevalence of 2 - 16% in the US, and is more prevalent in cases with other conditions including asthma and environmental allergies [4].

Although no specific cell or protein expression can entirely differentiate CRSwNP from CRS with absence of nasal polyps [CRSsNP], histopathologic characteristics, such as predominance of specific inflammatory cells, subepithelial edema, Charcot-Leyden crystals, and mucin eosinophil aggregates, have been studied as potential distinguishing markers in patients with CRSwNP vs CRSsNP [5]. CRSsNP is mainly thought to have increased fibrosis, goblet cell hyperplasia, and mononuclear cell infiltration, as CRSwNP can cause more stromal edema with deposition of albumin and formation of pseudocyst [6]. Tosun *et al*. [7] announced that primary CRSwNP tissue enclosing eosinophil concentrations of four cells for every 1000μm^2 volume recur more likely than polypi with eosinophil concentration of < 3 per 1000 μm^2 [81.8% vs 25%].

AIM OF THE WORK

The aim of this study is to differentiate between primary and chronic rhinosinusitis with polypi through detection of the histopathological changes of nasal mucosa.

PATIENTS AND METHODS

This is a prospective research which was conducted at Department of Otorhinolaryngology, Damietta Faculty of Medicine [Al-Azhar University], and Alzahra hospital, Gedda, Kingdom of Saudi Arabia. It included 85 patients with CRSwNP. The study completed in three years [May 2015 to May 2018]. A written informed consent had been signed by the patients for their clinical records to be used in this study. Patients were divided into two groups; group [1] 35 patients with primary polyposis, group [2] 50 patients with chronic [recurrent] polyposis.

The inclusion criteria were: patients' age over 18 years of age, eligibility for FESS operation, and patients were free from hematological diseases. Diagnosis of CRS depends on continuous sinonasal symptoms up to 12 weeks and positive findings for sinusitis on sinus computed tomography scan. Patients were only excluded if they had a known cardiac, malignant, respiratory or autoimmune diseases and patients with known hematological diseases who had bleeding tendency or leukemia. Also, patients who had granulomatosis with polyangiitis, or eosinophilic granulomatosis with polyangiitis and sarcoidosis were also excluded. All patients were evaluated clinically and laboratory before operation. Patients age, sex, occupation, residence and telephone number were recorded for each participant for demographic purposes. General and local examinations were performed also preoperatively as usual.

Hematological analysis including complete blood count [CBC] including differentiated leuco-cytic and lymphocytic cells. Blood glucose level [HbA1c], liver and kidney function tests were evaluated for medical assessment of general health of the included pateints.

CRS diagnosis was achieved according to the American Academy of Otolaryngology clinical practice guidelines on sinusitis, so, all patients had a sinus computed tomography [CT]-scan before surgery [8] and Lund-Mackay Score [LMS] was performed for the studied group. During FESS operation, a biopsy was taken from the tissues of the sinus mucosa and sent to the laboratory for histopathological differentiation in a blind manner. All of the structured pathology reviews

were carried out in a prospective manner as a standard of care for cases undergoing FESS.

Histologic evaluation: Sinus mucosal tissue was gathered from ethmoid cavity before intervention. Labortory investigations were done to all subjects. Tissue samples were speedily fixed, decalcified, and immersed in paraffin. Hematoxylin and eosin stains were performed. Histologic report about cell, epithelial, and stromal markers was done to survey the existence of mucosal inflammation. Assessment of cellular markers including eosinophils, neutrophils, lymphocytes, mast cells, and macrophage counts. The epithelial markers assess squamous metaplasia, basement membrane thickening [BMT], and goblet cells. BMT was assessed in the curettage piece[s] and registered as <5μm, 5 to 10μm, 10 to 15μm, and >15μm. Stromal markers like assessment of subepithelial edema. It was also classified as lack or presence of edema [0 = not present, 1 = marked edema]. Mucosal eosinophilia was diagnosed by count of >10 eosinophils/HPF.

Statistics: All statistical analyses were done by SPSS v23 software [SPSS, Inc, Chicago, Illinois]. Descriptive statistics were calculated for all measures. These include mean and standard deviation for numerical variables; freuqncy and percentages for qualitative variables.

Histopathologic differentiation was calculated for all patients from preoperative to postoperative time points. Wilcoxon signed-rank test was used to identify significant change in cell number. Differences were then compared between those with primary and chronic mucosal eosinophilia by using paired t tests. Independent t tests, Mann Whitney U tests, and Kruskal-Wallis tests were used to examine differences in histopathologic findings. A p value of ≤ 0.05 was statistically significant.

RESULTS

The study included 85 patients with rhino-sinusitis with nasal polyposis referred for FESS. They were classified into two groups; group [1] contained 35 patients with primary polyposis, they were 26 males and 9 females and group [2] contained 50 patients with chronic polyposis, they were 25 males and 25 females. The average age of group [1] patients was 22.7 ± 3.56 years [range, 18 – 29 years] and the mean age of group [2] patients was 23.6 ± 4.12 years [range, 18 – 31 years] as shown in [Table 1]. Data were collected in the following tables.

Patients of the two groups were performed FESS operation. During the operation, swab was taken from the sinus mucosa and sent for histological analysis. Histopathological analysis revealed non-significant values [P> 0.05] as regard inflammatory signs except mucosal ulceration [P <0.0] in comparison between groups [1] and [2] as shown in [Table 2].

However, the rest of histo-pathological findings of showed significant increase in chronic recurrent group 2 than primary group 1 [P < 0.05] regarding eosinophilic cell count, eosinophilic cell aggregation, basement membrane thickness, hyperplastic or papillary change, fibrosis and fungal element [Table 3] and [Figures from 1-4].

Radiographic CT scores according to Lund-Mackay Score [LMS] of the two studied groups was evaluated [Table 4] and showed a significant difference between the two studied groups as regard degree of inflammation, eosinophilic count and aggregates, neutrophil infiltrate, fibrosis, mucosal ulceration & Charcot-Leyden crystals.

Table [1]: Demographic data of the studied patients

		Group [1] Primary polyposis[n=35]		Group [2] Chronic polyposis[n=50]		Test of significance	
		n.	%	n.	%	Test	P
Gender	Males	26	74.29	25	50.0	0.0254	0.2510
	Females	9	25.71	25	50.0	0.2934	0.0835
Age [years] [mean±SD]		22.7±3.56		23.6±4.12		0.0035	0.8062

Table [2]: Inflammatory characteristics of the two studied groups.

Findings		Group [1] Primary polyposis[n=35]		Group [2] Chronic polyposis[n=50]		Test of significance	
		n.	%	n.	%	χ^2	*p*
Inflammatory cells	Lymphocytes. Lymphoplasmacytes. Eosinophils. Others	7 9 12 7	20.0 25.7 34.3 20.0	5 19 23 3	10.0 38.0 46.0 6.00	1.652	0.072
Degree of inflammation	Mild Moderate Severe	9 20 6	25.7 57.1 17.1	10 30 10	20.0 60.0 20.0	1.772	0.069
Subepithelial edema	Mild Moderate Severe	14 17 4	40.0 48.6 11.4	20 18 12	40.0 36.0 24.0	0.922	0.117
Mucosal ulceration	Absent Present	33 2	94.3 5.71	32 18	64.0 36.0	6.231	0.002*

χ^2 = Chi square test, * P <0.05= significant.

Table [3]: Histopathological findings of the two studied groups.

Findings		Primary polyposis [n= 35]		Chronic polyposis [n= 50]		Test of significance	
		n.	%	n.	%	χ^2	P
Eosinophilic count	< 5 per HPF 5-10 per HPF >10 per HPF	8 14 13	22.6 40.0 37.1	11 14 25	22.0 28.0 50.0	***3.211***	***0.044****
Eosinophil aggregates	Absent Present	23 12	65.7 34.3	23 27	46.0 54.0	***2.925***	***0.049****
Neutrophil infiltrate	Absent Present	24 11	68.6 31.4	34 16	68.0 32.0	0.095	0.222
BM thickening [µm]	<7.5 7.5–15 >15	6 19 10	14.1 54.3 28.6	8 12 30	16.0 24.0 60.0	***4.262***	***0.021****
Hyperplastic/papillary change	Absent Present	30 5	85.7 14.3	40 10	80.0 20.0	***3.867***	***0.029****
Squamous metaplasia	Absent Present	29 6	82.9 14.1	41 9	82.0 18.0	1.966	0.092
Fibrosis	Absent Present	9 26	25.7 14.1	15 35	30.0 70.0	***6.116***	***0.002****
Fungus	Absent Present	34 1	97.1 2.90	38 12	76.0 24.0	***5.367***	***0.003****
Charcot-Leyden crystals	Absent Present	26 9	14.1 25.7	31 19	62.0 38.0	1.345	0.096

BM: Basement membrane, HPF: High power field.

Table [4]: Radiographic computed tomography scores [Lund-Mackay Score [LMS]] of the two studied groups.

		Primary polyposis [N = 35]	Chronic polyposis [N = 50]	Significance	
				t-test	P
Degree of inflammation	Mild Moderate Severe	7.02 ± 3.56 8.44 ± 4.82 12.8 ± 5.22	8.12 ± 3.58 9.95 ± 4.92 16.6 ± 5.21	0.466	0.025*
Eosinophilic count	< 5 per HPF 5-10 per HPF >10 per HPF	5.24 ± 3.63 7.64 ± 3.54 9.03 ± 3.97	10.2 ± 5.14 11.3 ± 5.32 14.2 ± 5.95	0.371	0.044*
Neutrophil infiltrate		9.97 ± 5.64	11.85 ± 6.24	0.029	0.182
Basement membrane thickness		8.63 ± 5.15	13.81 ± 5.76	0.396	0.049*
Subepithelial edema		9.62 ± 5.84	11.83 ± 5.77	0.037	0.196
Hyperplastic/papillary changes		9.51 ± 5.83	14.31 ± 4.52	0.109	0.097
Squamous metaplasia		8.29 ± 4.84	12.32 ± 5.55	0.196	0.065
Fibrosis		6.95 ± 4.25	12.49 ± 4.29	0.535	0.013*
Eosinophil aggregates		7.95 ± 3.88	14.37 ± 5.64	0.502	0.011*
Mucosal ulceration		7.42 ± 3.94	15.11 ± 5.41	0.597	0.009*
Charcot-Leyden crystals		8.24 ± 4.27	14.15 ± 4.46	0.488	0.008*

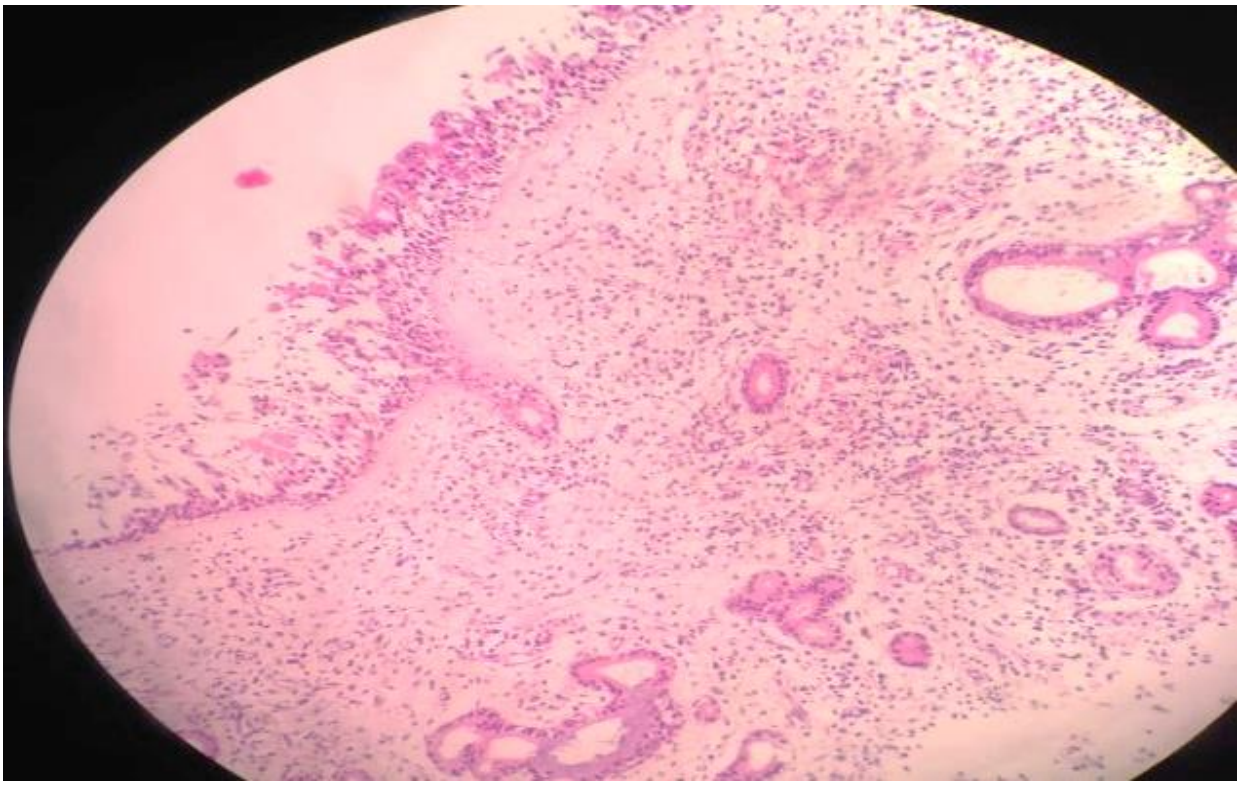

Figure [1] Primary rhinosinusitis, H&E [x20], Respiratory lining with moderately edematous subepithelial tissue with insignificant eosinophilic infiltration.

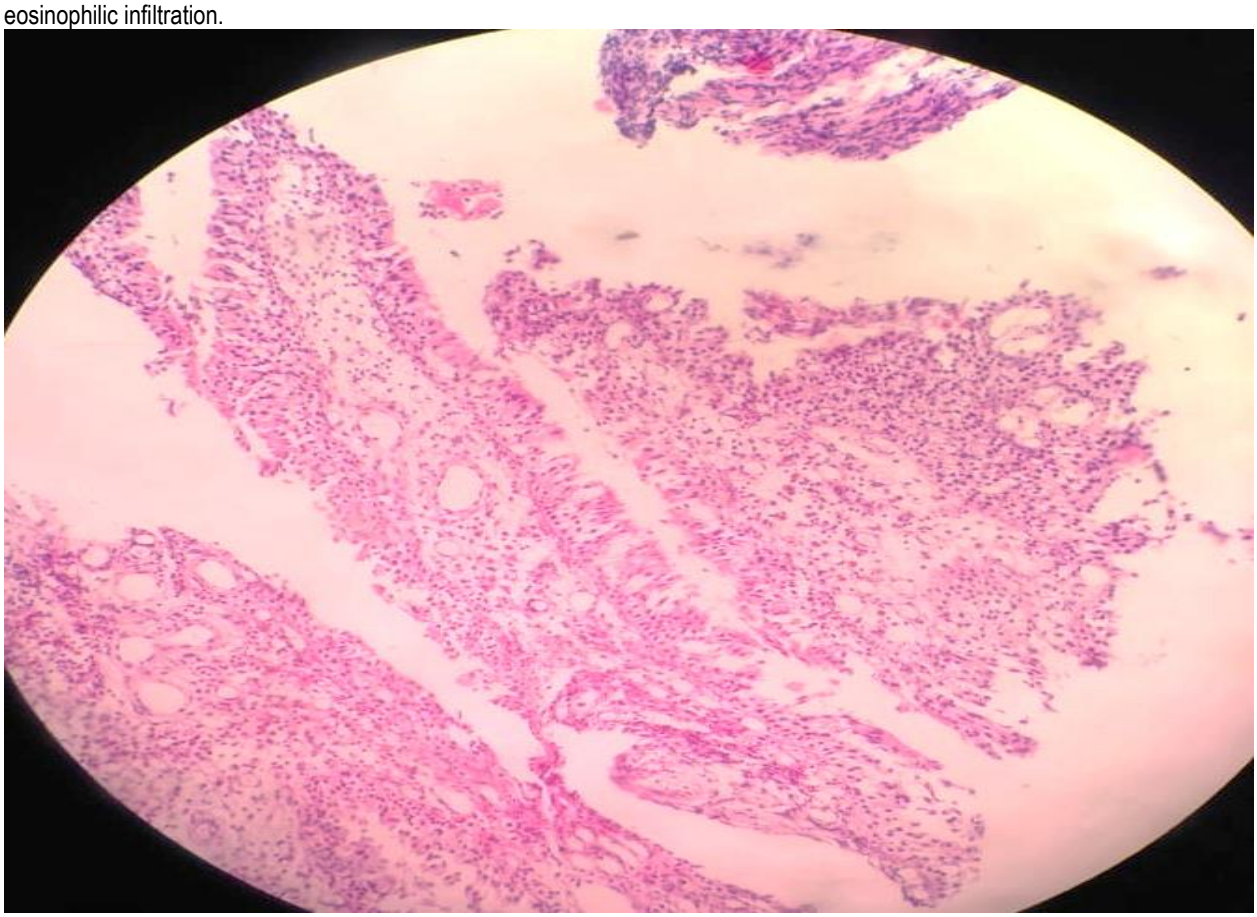

Figure [2] Primary rhinosinusitis, H&E [x40], Respiratory lining with mucosal hyperplastic papillary changes and thin basement membrane.

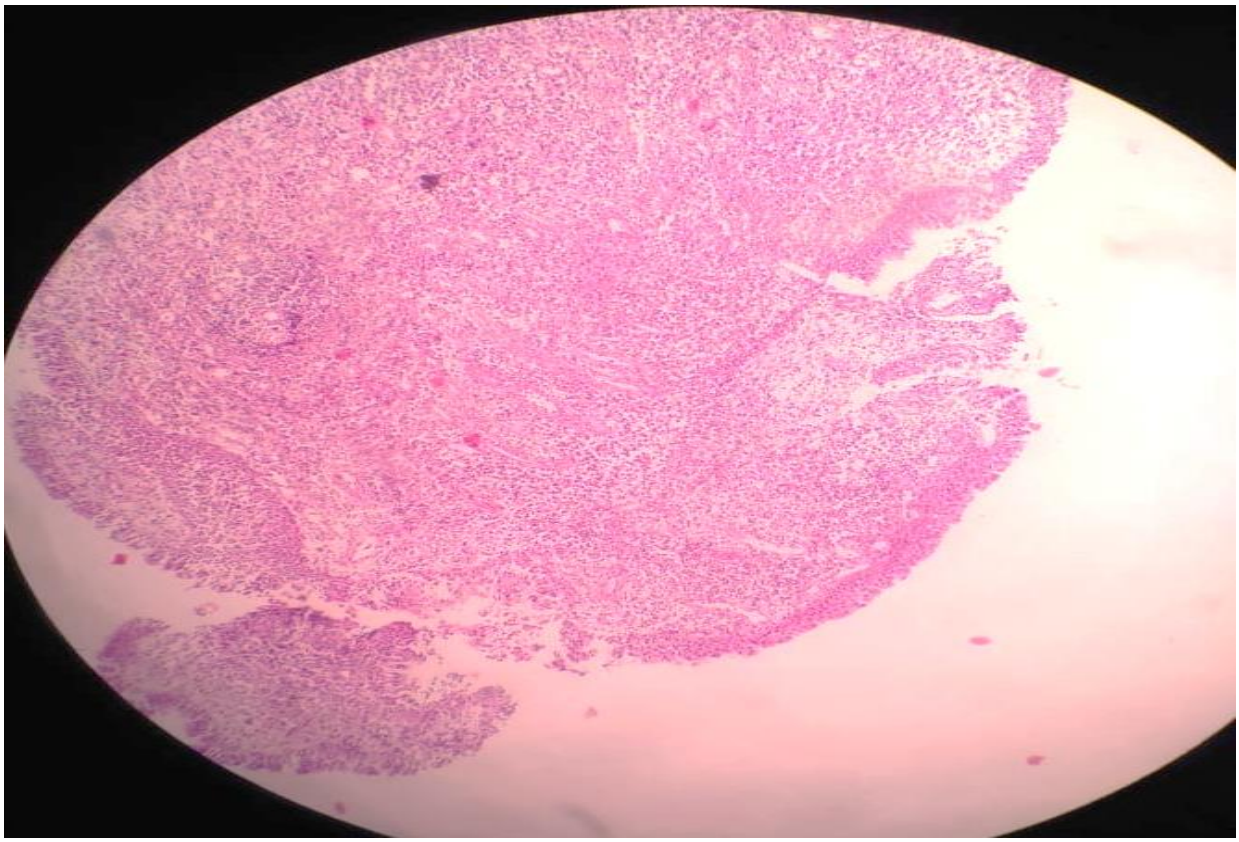

Figure [3] Severe chronic rhinosinusitis, H&E [x20], Respiratory lining with focal ulceration, markedly edematous subepithelial tissue with eosinophilic infiltration more than 10/HPF.

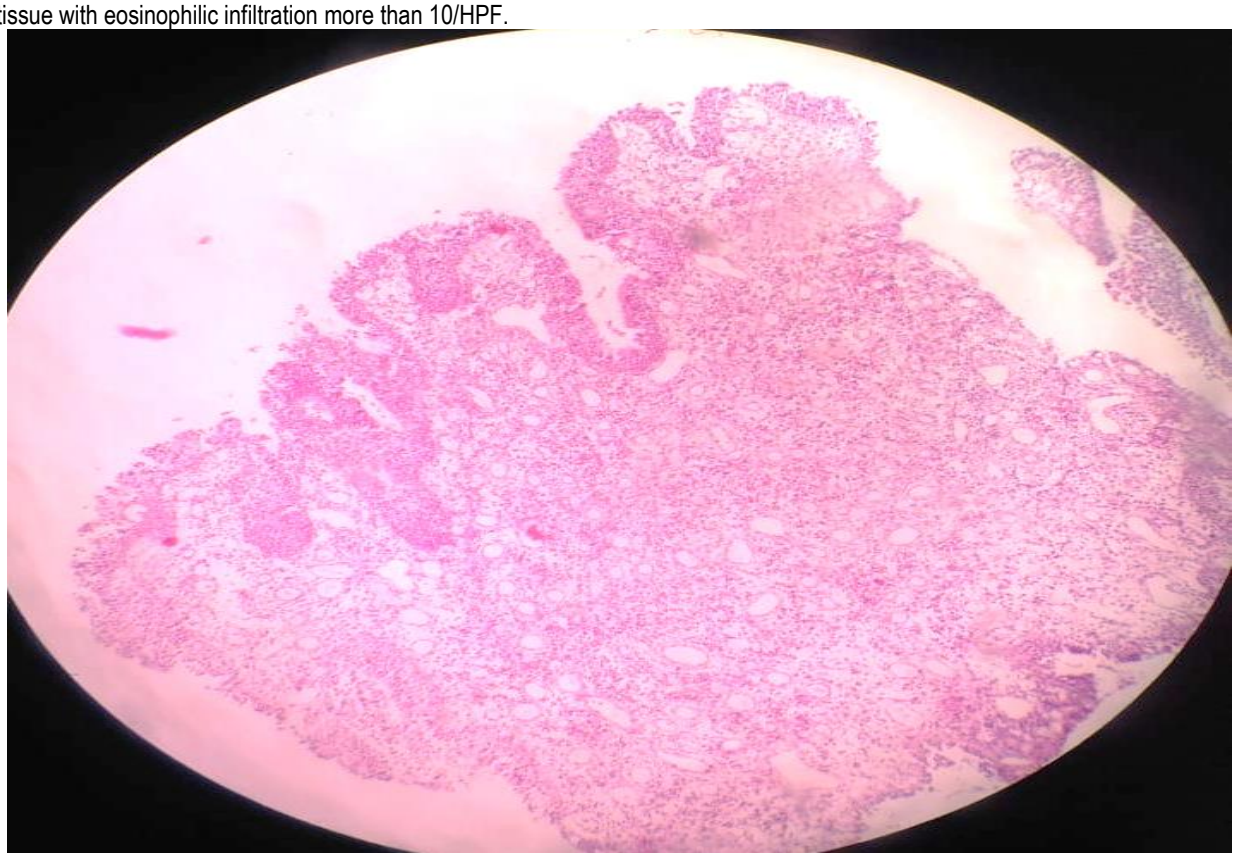

Figure [4] Moderate chronic rhinosinusitis, H&E [x20], Respiratory lining with thick basement membrane, markedly edematous subepithelial tissue with eosinophilic infiltration more than 7/HPF.

DISCUSSION

FESS is most typically reserved for chronic refractory cases of CRS who failed standard medical treatments. Currently, FESS is considered as the standard therapeutic option for CRS [9]. Wynn and Har-El [10] reported a 60% rate of recurrence after endoscopic sinus surgery in 118 patients with severe nasal polyposis in a 12- to 168-month follow-up period. Nonsteroidal anti-inflammatory drug intolerance, asthma, revision surgery, and polyp extension are the most often reported clinical factors associated with a higher rate of polyp recurrence after treatment. The mean recurrence rate was 53.4% for the whole group of patients in the follow-up period [7]. A previous trial prospectively evaluated the relevance of histologic inflammatory indicators in CRS. The presence of mucosal eosinophilia is a signficnt marker for disease severity assessment. It correlates with baseline objective disease severity measures such as olfactory tests, endoscopy and CT [11].

The current research aimed to evaluate cellular, epithelial and stromal inflammatory indicators in cases with primary and recurrent chronic nasal polyposis. Despite a variety of inflammatory markers being used in this study after FESS, mucosal eosinophilia and basal membrane thickness [BMT] showed a statistically significant difference between primary and recurrent chronic polyposis in rhinosinusitis cases, however, eosinophilia showed weak significant values [P = 0.044] and eosinophil aggregates [P = 0.049] which was similar to Donnell *et al*. [12] who found that increasing eosinophils have more eosinophil aggregates [P < 0.001]. The presence of eosinophilia in primary and recurrent CRSwNP were studied extensively more than eosinophilic aggregates[7,13-14]. The overall mean percentage of tissue eosinophil [number of inflammatory cells per HPF] is often 50% in CRSwNP, compared to 2% of CRSsNP **[13]**. In our study, the presence of eosinophils of more than 10 per high power field [HPF] showed a statistically significant difference [P = 0.044] as the current cutoffs proposed in the literature to define the presence of eosinophil count in a tissue <5 cells/HPF for mild, >5 cells/HPF for moderate and >10 cell/HPF for severe cases [5]. Eosinophils are the most prevalent inflammatory cells in nasal polyp tissues, except in cases of cystic fibrosis. Steroids diminish eosinophilic infiltration of the upper airway by decreasing eosinophil viability [7- 15]. The increase in eosinophils in chronic recurrent polyposis can be explained because These cells release mediators such as eosinophil-derived neuro-toxin and eosinophil cationic protein and can also synthesize a number of regulatory molecules such as transforming growth factor β and interleukin-4, which can directly or indirectly contribute to the further recruitment and activation of eosinophils capable of causing cellular injury and tissue damage [16]. Eweiss *et al*. [17] investigated the influence of eosinophilia and vascular cell adhesion molecule–1 expression on postoperative diffuse nasal polypi recurrence among 50 patients underwent FESS followed by the use of local steroids for a year and found that, infiltrating eosinophils did not significantly differ between the group of recurrence and those without recurrence of nasal polypi.

Other inflammatory markers found in histo-pathology were also recorded to be significant in chronic recurrent rhinosinusitis than primary ones such as BMT [P <0.021], mucosal ulceration [p < 0.002], hyperplastic/papillary change [p <0.029], and fibrosis [P <0.002] in our study. This was also agreed by other studies [5,12,14,18]. Neutrophilic infiltrates showed non-significant value [P >0.05] in our study which was confirmed by others [5,11,12,14] that found no role of neutrophilic infiltrates in rhinosinusitis with polyposis.

In our study, fungal rhinosinusitis showed significant increase in chronic recurrent rhinosinusitis [P = 0.003], that was parallel to Carney *et al*. [19] who found a close relation between fungal and CRS [P <0.01]. In comparison of the histological findings, radiographic sings of CRSwNP showed comparable results between primary and recurrent rhinosinusitis as regard stage of inflammation, BMT, eosinophilic count, fibrosis, eosinophil aggregates, mucosal ulceration and Charcot-Leyden crystals found to be significant in comparison between groups. Radio-graphic sings of CRSwNP was evaluated by other studies who found similar results [5,20,21].

Our results have confirmed our initial hypothesis that patients with CRSwNP would exhibit a higher tissue inflammatory load than primary ones. This was confirmed by other studies such as Bassiouni *et al*.[14]

Conclusion: Histologic inflammatory indicators [markers] can provide an important predictive data to estimate disease severity. Current results reflect the signficance of histopathologic analysis of sinus tissue in differentiation between primary and recurrent chronic polyposis in rhinosinusitis patients usually mucosal eosinophilia and thickness of BM. As an observational study, future investigations should be performed to assess the role of inflammatory markers of histological origin in defining disease severity and predicting its outcome.

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None

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