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Structured Histopathologic Profile of Chronic Rhinosinusitis with Nasal Polyposis In Filipino Adult Patients Managed with Endoscopic Sinus Surgery at the Philippine General Hospital: A Retrospective Study

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ABSTRACT

Objective: To describe the histopathologic profile of chronic rhinosinusitis with nasal polyps (CRSwNP) in Filipino patients who underwent endoscopic sinus surgery (ESS) at the Philippine General Hospital from 2019-2023.

Methods: A retrospective study of nasal polyp specimens from adult Filipino CRSwNP patients who underwent ESS in the Philippine General Hospital between January 2019 and December 2023 was conducted. Histopathologic characteristics were evaluated using the structured histopathologic profiling proposed by Snidvongs, *et al.*

Design: Retrospective Study
Setting: Tertiary National University Hospital
Participants: Nasal polyp specimens of 122 patients

Results: Among 122 patients (mean age 45.57 ± 16.87 years; 68.03% male) 43.4% had eosinophilic CRS (ECRS) and 56.6% had non-eosinophilic (non-ECRS). Lymphoplasmacytic inflammatory predominance was observed in 54.7% of cases, occurring most frequently in ECRS (60.38%). Basement membrane thickening was significantly more common in ECRS (33.96%) than in non-ECRS (13.04%). Moderate to severe subepithelial edema was more frequent in ECRS (73.6%) compared with non-ECRS (46.4%), whereas mild edema predominated in non-ECRS (49.3% vs. 24.5%; $p = .018$). Mucosal ulceration was more common in ECRS (18.87%). There was no significant difference between ECRS and non-ECRS in the distribution of neutrophilic infiltrate, hyperplastic/papillary change or squamous metaplasia.

Conclusion: This study provides the first comprehensive local description of the histopathologic characteristics of CRSwNP among Filipino adults who underwent ESS, identifying key characteristics that distinguish ECRS and non-ECRS endotypes. This study highlights the potential value of detailed histopathologic reporting in informing prognosis and therapeutic strategies. Further studies are needed to establish the clinical utility and feasibility of structured reporting of tissue eosinophil count, inflammatory predominance, basement membrane thickening, subepithelial edema, and mucosal ulceration in CRSwNP management.

Keywords: *chronic rhinosinusitis; nasal polyps; eosinophilic chronic rhinosinusitis; endoscopic sinus surgery; Philippines; histopathology*

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Chronic rhinosinusitis (CRS) is a heterogenous inflammatory disease involving the nose and paranasal sinuses present for at least 12 weeks associated with nasal congestion/obstruction, rhinorrhea, and altered sense of smell leading to significant morbidity and decreased health-related quality of life.[1] This is defined clinically as the presence of two or more symptoms, one of which should be either nasal obstruction or congestion, and nasal discharge with or without facial pain or pressure and reduction/loss of smell, lasting for >12 weeks. A key subtype called chronic rhinosinusitis with nasal polyposis (CRSwNP) is defined as CRS with bilateral, endoscopically visualized polyps in the middle meatus.[2] CRS has a significant disease burden with impact on physical and mental health-related quality of life, including daily functioning and sleep. Despite standard therapies recurrence remains to be common. There have since been efforts to study the histopathological profile of this disease to explore more effective treatment methods. CRS has generally been classified into two endotypes: type 2 inflammation and non-type 2 inflammation. Type 2 is characterized by the presence of eosinophils and type 2 cytokines IL-4, IL-5, IL-9, and IL-13, produced by CD4+ T helper 2 (Th2) lymphocytes.[3] Non-type 2 is mainly characterized by neutrophilic predominance due to dysregulation of the innate immune system and activated by the IL-17 pathway and mediated by IL-8.[4] Eosinophilic Chronic Rhinosinusitis (ECRS) is associated with a greater symptom severity, worse olfactory dysfunction, comorbidities and complications of asthma, and bronchial hyperresponsiveness, and a higher recurrence rate after surgery.[5,6,7] Superantigen-induced inflammation, allergic fungal rhinosinusitis, and aspirin-exacerbated eosinophilic rhinosinusitis are known processes in ECRS.[8] Notably, ECRS is associated with a strong tendency for recurrence of nasal polyps after surgery and unresponsiveness to macrolides[2] - both of which were considered the gold standard in the 1990's. However, systemic steroids have significantly reduced the recurrence of ECRS, particularly post-surgery, which highlights the need to identify patients with ECRS.[2]

Histological diagnosis has been the gold standard of diagnosis. Despite growing interest in out-patient clinical tests, the utility of histological analysis remains useful in assessing the heterogeneous presentation of the disease in each patient and to understand the severity of their condition which may in turn allow for more individualized treatment. To the best of our knowledge, based on a search of HERDIN Plus, the WHO Global Index Medicus, MEDLINE (PubMed) and PubMed Central, local studies have yet to perform a comprehensive histopathological analysis of CRSwNP in the Filipino population.

In order to fill this crucial gap in local literature for better treatment of patients with CRSwNP, this study aims to describe the histopathologic profile of chronic rhinosinusitis with nasal polyps (CRSwNP) in Filipino patients who underwent endoscopic sinus surgery (ESS) at the Philippine General Hospital from 2019-2023.

METHODS

With University of the Philippines Manila Research Ethics Board approval (UPMREB 2024-0649-01), this retrospective analysis examined nasal polyp specimens collected from adult Filipino patients who underwent endoscopic sinus surgery at a tertiary hospital from January 2019 to December 2023.

This study considered for inclusion all adult CRSwNP patients who underwent endoscopic sinus surgery and were admitted to the University of the Philippines - Philippine General Hospital (UP-PGH) under the department of Otolaryngology-Head and Neck Surgery from January 2019 to December 2023.

The sample size was determined based on the number of CRSwNP cases admitted to UP-PGH from January 2019 to December 2023. The sample size was computed to compare the distribution of histopathologic characteristics between ECRS and non-ECRS groups. Using a chi-square test for independence, a total sample size of 298 was determined based on a small-to-medium effect size (Cohen's $w = 0.2$), with 80% statistical power, and a 5% level of significance ($\alpha = 0.05$) .

A total of 354 cases were initially identified through a search query of hospital records for patients who underwent any of the following surgical procedures: Endoscopic Sinus Surgery (ESS), Functional Endoscopic Sinus Surgery (FESS), or Endonasal Sinus Surgery. Procedures that were not considered endoscopic sinus surgery such as diagnostic biopsy, transsphenoidal endoscopic excision, or Caldwell-Luc procedures, as well as surgeries performed by other departments, were excluded. This yielded 253 cases under the Department of Otolaryngology - Head and Neck Surgery. Further exclusions were made for specimens with missing surgical pathology reports, sinonasal pathologies other than inflammatory nasal polyps, and diagnoses inconsistent with CRSwNP such as antrochoanal polyp, mucocele, sinonasal papilloma, malignant neoplasms, and fungal rhinosinusitis yielding 142 cases. Out of the eligible cases, only 122 specimens were successfully retrieved from the Department of Laboratories for review. The remaining 20 specimens could not be located and were considered missing.

As the target sample size was not reached, the study proceeded with the available sample size, acknowledging the potential limitations in statistical power and generalizability of the results. A post-hoc power analysis was performed for the different non-significant variables as follows: Neutrophilic infiltrate – 6.95%, Hyperplastic/papillary change – 28.19%, Squamous metaplasia – 8.10%.

Nasal polyp specimens were retrieved from the records section of the Department of Laboratories. Specimens were first categorized as

eosinophilic (defined as an eosinophil count ≥10 per high-power field [HPF] in two or more fields), or non-eosinophilic (eosinophil count <10 per HPF). For each specimen evaluation, the pathologist (JMC) selected "hotspot" areas for evaluation of the eosinophil count. These were the areas which had the densest infiltration of eosinophil on low-power objective (LPO). After selecting the hotspots on LPO, actual eosinophil count was performed in high-power objective (HPO).

The following histopathologic characteristics using the structured histopathologic profiling proposed by Snidvongs, *et al*.[8] were then reviewed and recorded:

1. Tissue eosinophilia (<10 per HPF, ≥10 per HPF)
2. Degree of inflammation (absent, mild, moderate, severe)
3. Neutrophilic infiltrate (absent, focal, diffuse)
4. Inflammatory cell predominance (lymphocytic, lymphoplasmacytic, eosinophilic, lymphohistiocytic, neutrophilic, others)
5. Basement membrane thickening (absent, present)
6. Subepithelial edema (absent, mild, moderate, severe)
7. Hyperplastic/papillary change (absent, present)
8. Mucosal ulceration (absent, present)
9. Squamous metaplasia (absent, present).

All features of interest were then reviewed by a single board-certified pathologist (JMC). The primary outcomes of interest were the aforementioned histopathologic features of nasal polyps in patients with CRS. These features were then compared between ECRS and non-ECRS groups to identify significant differences in their distribution.

Data Analysis

Histopathologic features were described by frequencies and percentages. The CRSwNP patients were grouped into ECRS and non-ECRS categories. Significant differences in distribution of the histopathologic features between the two groups were determined by chi-square test or Fisher exact test of homogeneity, as appropriate. Computations were performed using Stata Statistical Software version 17 (StataCorp LP, College Station, TX, USA). All variables of interest were categorical, and there were no missing values in the dataset. Tests of hypothesis were evaluated with significance level set at α=0.05. No correction for multiple comparisons was applied given the exploratory nature of the analysis.

RESULTS

Nasal polyp specimens from a total of 122 patients aged 18-91 years, with a mean age of 45.57 years (SD = 16.87) were assessed. Among them, 83 patients (68.03%) were male and 39 (31.97%) were female and 53 patients (43.4%) had ECRS while 69 (56.6%) had non-ECRS. The frequencies of key histopathologic features are summarized in *Table 1*.

Table 1. Distribution of Histopathologic Features in Eosinophilic and Non-eosinophilic Nasal Polyp Specimens from CRSwNP Patients (n=122)

Histopathologic feature	Frequency (%)			*p*-value
	Full cohort n = 122	*Eosinophilic* n = 53	*Non-eosinophilic* n = 69	
Inflammatory predominance				<.001
Lymphocytic	43 (35.25)	11 (20.75)	32 (46.38)	
Lymphoplasmacytic	67 (54.92)	32 (60.38)	35 (50.72)	
Eosinophilic	7 (5.74)	7 (13.21)	0	
Lymphohistiocytic	5 (4.10)	3 (5.66)	2 (2.90)	
Neutrophilic infiltrate				.682
Absent	92 (75.41)	39 (73.58)	53 (76.81)	
Focal	30 (24.59)	14 (26.42)	16 (23.19)	
Diffuse	0	0	0	
Basement membrane thickening				.006
Absent	95 (77.87)	35 (66.04)	60 (86.96)	
Present	27 (22.13)	18 (33.96)	9 (13.04)	
Sub-epithelial edema				.018
Absent	4 (3.28)	1 (1.89)	3 (4.35)	
Mild	47 (38.52)	13 (24.53)	34 (49.28)	
Moderate	51 (41.80)	27 (50.94)	24 (34.78)	
Severe	20 (16.39)	12 (22.64)	8 (11.59)	
Hyperplastic/papillary change				.167
Absent	107 (87.70)	44 (83.02)	63 (91.30)	
Present	15 (12.30)	9 (16.98)	6 (8.70)	
Mucosal ulceration				.025
Absent	108 (88.52)	43 (81.13)	65 (94.20)	
Present	14 (11.48)	10 (18.87)	4 (5.80)	
Squamous metaplasia				.606
Absent	97 (79.51)	41 (77.36)	56 (81.16)	
Present	25 (20.49)	12 (22.64)	13 (18.84)	

Among the different histopathological features, significant differences in distribution between eosinophilic and non-eosinophilic CRS were observed in: (1) Inflammatory predominance; (2) Basement membrane thickening; (3) Subepithelial edema; and (4) Mucosal ulceration.

1. Inflammatory predominance: Non-ECRS cases had a higher proportion of lymphocytic predominance (46.38%) compared to ECRS (20.75%). ECRS were more likely to present with an eosinophilic cell type pattern (13.2% vs 0%). For both ECRS and non-ECRS, Lymphoplasmacytic inflammatory predominance was the most common pattern at 60.38% and 50.72%, respectively (Fisher exact $p < .001$).

2. Basement membrane thickening: Basement membrane thickening was significantly more common in ECRS (33.96%) than in non-ECRS (13.04%) ($\chi^2(1) = 7.61$, $p = .006$).

3. Subepithelial edema: Moderate and severe subepithelial edema were more frequently observed in ECRS (73.58%) compared to non-ECRS (46.37%). Conversely, mild subepithelial edema was more frequently observed in non-ECRS (49.28%) than in ECRS (24.53%). Overall, these comparisons were statistically significant at a Fisher exact $p = .018$.

4. Mucosal ulceration: Mucosal ulceration was present in 10 ECRS cases (18.87%) compared to only 4 non-ECRS cases (5.8%), with a statistically significant difference ($\chi^2(1) = 5.04$, $p = .025$).

DISCUSSION

This study aimed to describe the histopathologic profile of CRSwNP Filipino adult patients that underwent ESS and compare these features among eosinophilic and non-eosinophilic endotypes. This is the first local report describing histopathologic characteristics of CRSwNP specimens and their association with ECRS versus non-ECRS endotypes. Among the 122 CRSwNP cases that underwent ESS, 56.6% of patients presented with non-eosinophilic CRS which is consistent with studies that Asians present with a non-type 2 endotype.[2] This finding, however, contrasts with the local retrospective study by Nable-Llanes[9] which reported a predominantly eosinophilic endotype (54.55% ECRS) among Filipino patients with CRSwNP. Several factors may account for this discrepancy. First, tissue eosinophilic count cutoffs used to define eosinophilic endotype still lack international consensus, and cutoff variability can shift classification, particularly for cases near the borderline. Second, differences in institutional referral patterns and patient populations, along with variation in antibiotic and corticosteroid prescribing practices, may have influenced the inflammatory profile observed at the time of tissue sampling. These methodological differences highlight the need for standardized, multicenter data to better characterize the true local prevalence of ECRS among Filipino patients with CRSwNP.

Four histopathologic characteristics were found to have a statistically significant difference between ECRS and non-ECRS - inflammatory predominance, basement membrane thickening, subepithelial edema, and mucosal ulceration. There were no significant differences in the distribution of characteristics between ECRS and non-ECRS in Neutrophilic infiltrate, Hyperplastic/Papillary change, and Squamous metaplasia.

Lymphoplasmacytic predominance was the most common (54.92%) type of inflammatory predominance for both ECRS and non-ECRS. This may imply that most of the chronic inflammation among Filipino patients with CRSwNP is driven by lymphocytes and plasma cells, reflecting a heterogenous inflammatory pattern rather than purely neutrophilic or eosinophilic profile. Previous evidence from Lou *et al.*[10] suggests that CRSwNP exists along a spectrum rather than as distinct endotypes, with mixed and eosinophilic-dominant clusters presenting with worse symptom severity and higher recurrence rates.[10] The predominance of lymphoplasmacytic inflammation in this study aligns more closely with these mixed inflammatory patterns. These findings suggest that lymphoplasmacytic inflammatory patterns in CRSwNP patients may respond suboptimally to standard corticosteroid therapy.

Basement membrane thickening was significantly more frequent in ECRS (33.96%) supporting previous studies demonstrating that eosinophilic infiltration correlates with epithelial damage BM remodeling.[11] BM thickening has been correlated positively with duration of symptoms, especially in patients with comorbid asthma and aspirin sensitivity.[12] This supports the inclusion of BM thickness in histopathologic evaluation, as it reflects long-standing tissue remodeling and may serve as a potential prognostic indicator.

Subepithelial edema was identified to be moderate to severe in 57.38% of cases and a significantly higher proportion among ECRS (73.58%) compared to non-ECRS (46.37%, $p = .018$). This finding is consistent with prior literature emphasizing the role of subepithelial edema in the pathophysiology of CRSwNP, particularly in tissue remodeling and eosinophilic inflammation.[13] It is linked with nasal polyposis, asthma, aspirin-exacerbated respiratory disease, and worse preoperative CT and endoscopy scores.[14] The predominance of moderate to severe edema among ECRS may reflect the association between tissue eosinophilia and mucosal remodeling in CRS.[13]

Mucosal ulceration, although less frequently observed overall (11.48%), was significantly more associated in ECRS (18.87%) compared to non-ECRS (5.8%, $p = .025$). Mucosal ulceration serves as an indicator of advanced epithelial damage, a consequence of prolonged inflammatory insult and possibly compounded by local microbial invasion.[15] Mucosal ulceration predisposes to secondary infection due to epithelial barrier disruption, which contributes to chronic inflammation.[4] Its association with ECRS mirrors previous findings showing higher mucosal damage in polypoid and eosinophilic disease.[13] Clinically, this could account for the higher recurrence rates and relative refractoriness of ECRS to standard therapy.

On the other hand, no significant differences were observed in neutrophilic infiltrates ($p = .682$), hyperplastic/papillary change ($p = .167$), or squamous metaplasia ($p = .606$). However, given the reduced statistical power due to the smaller sample size, definitive conclusions regarding the discriminatory value of these features between ECRS and non-ECRS endotypes cannot be made. Previous Asian studies have reported a higher prevalence of neutrophilic inflammation in CRSwNP compared to Western cohorts.[2,9] The absence of a significant difference in the current study may reflect the mixed eosinophilic-

neutrophilic inflammatory pattern reported in severe CRS, [16] as well as the heterogeneity of inflammatory pathways across ethnic populations. Likewise, squamous metaplasia, while a marker of severe epithelial remodeling, may occur independently of the underlying endotype.

Our study limitations include a small sample size, which reduced the statistical power to detect differences between ECRS and non-ECRS groups. As the target sample size was not achieved, the generalizability of the findings is limited, given the exploratory nature of the study. In addition, the study period (2019-2023) spans the COVID-19 pandemic, during which elective ESS were significantly reduced due to hospital restrictions and patient hesitancy. This is a potential source of selection bias, as it may have affected which cases underwent surgery and had specimens available for review. Moreover, as this was conducted in a single institution, these results may not be representative of all Filipino populations. In addition, some slides and/or blocks were not available for review despite best efforts of specimen retrieval due to archival limitations. We performed analysis of all available specimens to decrease selection bias. We restricted the analyses to those with available information and findings were interpreted with caution given these known limitations. Another limitation is that the histopathologic review was performed by a single surgical pathologist in our institution, without intra-rater reliability testing. Ideally, multiple pathologists would independently review the cases, with discrepancies resolved by consensus or by an arbiter. Recommendations for future studies include incorporating intra-rater and inter-rater reliability testing to strengthen the consistency and reproducibility of histopathologic scoring, incorporating additional clinical characteristics such as comorbid asthma and aspirin hypersensitivity, symptom severity and quality-of-life measures such as the Sino-Nasal Outcome Test (SNOT-22), imaging findings from preoperative CT scans, and post operative recurrence rates, and correlating these with the histopathologic characteristics. Larger multicenter studies are also recommended to improve statistical power, enhance external validity, and determine whether these histopathologic characteristics have prognostic implications for treatment outcomes in CRS.

In conclusion, our present findings support the utility of standard grading not only tissue eosinophilia, but also inflammatory predominance, basement membrane thickening, subepithelial edema, and mucosal ulceration in routine histopathologic assessment of post-ESS CRSwNP. These parameters may serve as potential prognostic markers in personalized, endotype-driven management, and may also guide the rational use of emerging biologic therapies.

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