Received: 24 September 2019 | Revised: 10 January 2020 | Accepted: 27 January 2020

DOI: 10.1002/lio2.358

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Histopathological characteristics of surgical tissue from primary vs recurrent chronic rhinosinusitis with nasal polyposis patients

Nathaniel J. Donnell BA[1] | Michael J. Marino MD[2] | Matthew A. Zarka MD[3] | Devyani Lal MD[2]

[1]Creighton University School of Medicine, Phoenix, Arizona

[2]Department of Otorhinolaryngology - Head & Neck Surgery, Mayo Clinic, Phoenix, Arizona

[3]Division of Laboratory Medicine, Mayo Clinic, Phoenix, Arizona

Correspondence
Devyani Lal, MD, Professor & Consultant, Department of Otorhinolaryngology—Head & Neck Surgery, 5777 E Mayo Blvd, Phoenix, AZ 85054.
Email: lal.devyani@mayo.edu

Abstract

Objective: The histopathological characteristics of primary vs recurrent nasal polyps in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) have not been studied comprehensively. Identification of these features may be helpful for prognostication, postoperative management, and consideration of novel eosinophil-targeting biologic therapy. This study investigates the histopathological differences in primary vs recurrent CRSwNP tissue.

Methods: Patients undergoing endoscopic sinus surgery for CRSwNP were included if all 13 histopathological and mucin characteristics on a standardized report were available. Histopathology parameters were compared in surgical tissue and mucin from primary vs recurrent CRSwNP.

Results: Complete structured histopathology reports were available for 96 patients (39 primary polyps and 57 recurrent polyps). Compared to primary polyp tissue, recurrent CRSwNP mucin was significantly more likely to feature eosinophil aggregates (57.9% vs 35.9%; $P = .047$). Tissue eosinophilia (using a threshold >10 per high power field [HPF]) was not significantly different in primary and recurrent CRSwNP tissue. Other histopathologic parameters and clinical characteristics were similar.

Conclusion: Eosinophil aggregates on histopathology are significantly more likely to be present in recurrent CRSwNP. In the limited series, tissue eosinophilia (>10 per HPF) was not significantly different in primary and recurrent CRSwNP. Therefore, in addition to the study of tissue eosinophilia levels, Rhinologic surgeons should also direct attention to CRSwNP mucin. Mucin eosinophilic aggregates are an independent marker of severe inflammation that is associated more likely with recurrent vs

Oral presentation at Rhinoworld 2019, on June 9, 2019, in Chicago, IL.

primary polyposis. Further study of this marker may help determine its role of choice of postoperative medical therapies, including anti-eosinophilic biologics.

Level of Evidence: 4

KEYWORDS

chronic rhinosinusitis, eosinophilic aggregates, histopathology, nasal polyps, tissue eosinophilia

1 | INTRODUCTION

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is one of the two major phenotypes of chronic rhinosinusitis (CRS) and is defined by the presence of nasal polyps in the middle meatus.[1] Studies have shown that CRSwNP negatively affects quality of life and is a common problem worldwide, with prevalence estimates of 0.2%-4%.[2,3] While surgery provides significant benefit in symptomatology and respiratory health,[4,5] as many as 40% of the patients with CRSwNP may develop recurrent polyposis within 12 months postoperatively.[6,7] Clinical factors such as asthma prevalence, as well as aspirin-exacerbated respiratory disease (AERD), appear to be associated with higher recurrence rates of nasal polyps.[6,7] CRSwNP that is recalcitrant to medical and surgical therapies may impact asthma control. [8-10]

There has been increasing interest in studying histopathology and serum inflammatory mediators to identify endotypic and prognosticating features in CRS. Standardized reporting using a structured histopathologic analysis of 13 predefined parameters has been recently described for CRS.[11] Histopathologic features, such as inflammatory cell predominance, subepithelial edema, Charcot-Leyden crystals, and mucin eosinophil aggregates, have been investigated as potential differentiating factors in patients with CRSwNP vs chronic rhinosinusitis without nasal polyposis (CRSsNP).[11,12] Tosun et al. reported that primary CRSwNP tissue containing eosinophil densities of four or more cells per 1000 μm^2 volume were more likely to recur than polyps with eosinophil densities of three or less cells per 1000 μm^2 (81.8% vs 25%).[13]

To our knowledge, no study has investigated differences in primary vs recurrent nasal polyps in CRSwNP using the standardized, structured histopathology report. The current study investigates tissue removed during surgery for primary vs recurrent nasal polyps in CRSwNP patients. In addition to structured histopathology, clinical characteristics of patients undergoing surgery for primary vs recurrent CRSwNP were also analyzed.

2 | MATERIALS AND METHODS

The study was approved by the institutional review board of the Mayo Clinic, Phoenix, AZ. Adult patients undergoing endoscopic sinus surgery (ESS) for the treatment of CRSwNP in the senior author's (DL) practice between July 1, 2011 and December 31, 2016 were considered for study inclusion. Diagnosis of CRS was made in accordance with the American Academy of Otolaryngology clinical practice guideline on adult sinusitis,[14] and all patients had a sinus computed tomography (CT) scan prior to surgery. Patients that had complete data for all 13 tissue and mucin elements in the structured histopathology report were included.[11] Patients with diagnoses of granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis (EGPA), and sarcoidosis were excluded.

Sinonasal tissue and mucin collected during surgery were examined by the reviewing pathologist, and structured histopathology reports were generated (Table 1). Of note, ethmoidal tissue is specifically studied in addition to nasal polyp tissue at the time of surgery. Any mucin noted at surgery is suctioned out and sent separately if macroscopically visible to the naked eye. However, the pathologists also identify mucin in the "background" of surgical tissue sample. The surgical tissue sample is collected both by a trap that collects tissue and mucin removed by the microdebrider, as well as tissue removed using through-cutting instruments. If there is no mucin identified in the background the categories of fungal elements, Charcot-Leyden crystals and eosinophil aggregates are reported as "not assessable." If mucin is detected in the background, then fungal elements, Charcot-Leyden crystals, and eosinophil aggregates are recorded as absent or present. Eosinophil Count in tissue were reviewed and categorized

TABLE 1 Structured histopathology variables and reported categories

Variable	Reported categories
Degree of inflammation	Mild, moderate, severe
Eosinophil count	≤10 per HPF, >10 per HPF
Neutrophil infiltrate	Absent, present
Inflammatory predominance	Lymphocytic, lymphoplasmacytic, eosinophilic, other
Basement membrane thickening	<7.5 μm, 7.5-15 μm, >15 μm
Subepithelial edema	Mild, moderate, severe
Hyperplastic/papillary change	Absent, present
Mucosal ulceration	Absent, present
Squamous metaplasia	Absent, present
Fibrosis	Absent, present
Fungal elements	Absent, present
Charcot-Leyden crystals	Absent, present
Eosinophil aggregates	Absent, present

Abbreviation: HPF, high power field.

TABLE 2 Primary vs revision surgery according to structured histopathology

Histopathology parameter	Primary surgery[a]	Revision surgery[a]	*P* value
Degree of inflammation			.344
Mild	11 (28.2%)	13 (22.8%)	
Moderate	22 (56.4%)	28 (49.1%)	
Severe	6 (15.4%)	16 (28.1%)	
Eosinophil count			.789
≤10 per HPF	8 (20.5%)	13 (22.8%)	
>10 per HPF	31 (79.5%)	44 (77.2%)	
Neutrophil infiltrate			1.000
Absent	26 (66.7%)	38 (66.7%)	
Present	13 (33.3%)	19 (33.3%)	
Inflammatory predominance			.050
Lymphocytic	8 (20.5%)	5 (8.8%)	
Lymphoplasmacytic	11 (28.2%)	20 (35.1%)	
Eosinophilic	14 (35.9%)	30 (52.6%)	
Other	6 (15.4%)	2 (3.5%)	
Basement membrane thickening (μm)			.734
<7.5	7 (17.9%)	7 (12.3%)	
7.5–15	11 (28.2%)	18 (31.6%)	
>15	21 (53.8%)	32 (56.1%)	
Subepithelial edema			.222
Mild	16 (41.0%)	23 (40.4%)	
Moderate	18 (46.2%)	19 (33.3%)	
Severe	5 (12.8%)	15 (26.3%)	
Hyperplastic/papillary change			.708
Absent	32 (82.1%)	45 (78.9%)	
Present	7 (17.9%)	12 (21.1%)	
Mucosal ulceration			1.000
Absent	35 (89.7%)	51 (89.5%)	
Present	4 (10.3%)	6 (10.5%)	
Squamous metaplasia			.297
Absent	32 (82.1%)	51 (89.5%)	
Present	7 (17.9%)	6 (10.5%)	
Fibrosis			.959
Absent	7 (17.9%)	10 (17.5%)	
Present	32 (82.1%)	47 (82.5%)	
Fungal elements			.735
Absent	36 (92.3%)	50 (87.7%)	
Present	3 (7.7%)	7 (12.3%)	
Charcot-Leyden crystals			.054
Absent	30 (76.9%)	33 (57.9%)	
Present	9 (23.1%)	24 (42.1%)	
Eosinophil aggregates			.034[b]
Absent	25 (64.1%)	24 (42.1%)	
Present	14 (35.9%)	33 (57.9%)	

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis without nasal polyposis; HPF, high power field.
[a]Values are count with percentage.
[b]Significant value.

based on numbers per high power field (HPF) and designated as ≤10 per HPF or >10 per HPF. Eosinophilic aggregates were defined as a minimum of two distinct aggregates of at least 10 cells each/HPF within the mucin removed at time of surgery. The preoperative SNOT-22 scores and Lund-Mackay CT scores were retrospectively acquired from the medical record. Associated diagnosis of asthma, AERD, and allergic fungal rhinosinusitis (AFRS) were also noted. Patients were divided into two cohorts according to whether they were being treated with surgery for primary vs recurrent nasal polyps in the setting of CRS. Study data were stored in a Research Electronic Data Capture (REDCap) database (version 8.10.5, Nashville, Tennessee). Two-sample independent *t* test was used to compare continuous variables. Chi-square test was used to compare categorical variables, except when frequency counts were <5, in which case Fischer exact test was used. Multivariable logistic regression analysis was used to assess statistically significant findings. Statistical analysis was performed using JMP Pro, version 14.1.0 (SAS Institute Inc., Cary, North Carolina), and *P* values less than .05 were considered significant.

3 | RESULTS

From a total of 125 CRSwNP patients that had at least some components of the structured histopathology report completed, 20 patients did not have mucin reported on pathology, while an additional eight patients had some other component of the structured histopathology report missing and these were excluded. One patient with EGPA was excluded from further analysis. A total of 96 CRSwNP patients with complete structured histopathology for tissue and mucin met inclusion criteria, with 39 in the primary nasal polyp cohort and 57 in the recurrent nasal polyp cohort. Of the 20 patients where mucin variables were not reported, 13 were in the recurrent polyp group and 7 were in the primary group. This was not statistically different from the patients were mucin was report (P = .640). Histopathologic features of primary and recurrent CRSwNP are demonstrated in Table 2. Eosinophil aggregates were more common in recurrent CRSwNP mucin (57.9%, n = 33) compared to primary CRSwNP tissue (35.9%, n = 14), and this difference was statistically significant (P = .034). Other parameters were not statistically different between the two groups.

TABLE 3 Demographic and baseline characteristics of study population

Characteristic	All patients (n = 96)[a]	Primary surgery (n = 39)[a]	Revision surgery (n = 57)[a]	*P* value
Age (years)	50.9 ± 15.7	50.5 ± 17.1	51.1 ± 14.9	.861
Male	51 (53.1%)	21 (53.8%)	30 (52.6%)	.907
Female	45 (46.9%)	18 (46.2%)	27 (47.4%)	
AFRS	16 (16.7%)	5 (12.8%)	11 (19.3%)	.403
AERD	26 (27.1%)	4 (10.3%)	22 (38.6%)	.005[b]
Asthma	62 (64.6%)	20 (51.2%)	42 (73.7%)	.042[b]
Preoperative SNOT-22	43.7 ± 20.2	45.9 ± 19.2	42.1 ± 20.9	.367
Preoperative LMS	13.9 ± 4.7	13.1 ± 4.5	14.4 ± 4.8	.182

Abbreviations: LMS, Lund Mackay score; AFRS, allergic fungal rhinosinusitis.
[a]Values are count with percentage or mean ± SD.
[b]Significant values.

Not all patients with eosinophilic predominance were found to have eosinophil aggregates. Conversely, some patients with other types of inflammatory predominance did have eosinophil aggregates present. Overall patients with eosinophilic predominance were more likely to have eosinophil aggregates ($P < .001$), although patients with both eosinophilic predominance and eosinophil aggregates were not different between primary and recurrent nasal polyps ($P = .923$).

Patient demographics, preoperative SNOT-22, and Lund-Mackay CT scores are detailed in Table 3. There were no statistical differences in age ($P = .861$), gender ($P = .907$), preoperative SNOT-22 score ($P = .367$), Lund-Mackay CT score ($P = .182$), and AFRS diagnosis ($P = .403$) between the two cohorts. Patients in the revision group had a higher prevalence of asthma (n = 42, 73.7%) compared to those who underwent primary surgery (n = 20, 51.2%). While this difference was statistically significant ($P = .042$) on univariate analysis, it regressed on multivariable logistic analysis ($P = .103$). Diagnosis of AERD was also significantly higher ($P = .005$) in recurrent CRSwNP (n = 22, 38.6%) compared to primary disease (n = 4, 10.3%), and multivariable logistic regression analysis found AERD to be statistically significant ($P = .008$). Eosinophil aggregates were associated with recurrent nasal polyps on multivariable logistic regression analysis ($P = .047$), when accounting for AERD and asthma.

4 | DISCUSSION

Most published studies have focused on using histopathologic markers to assess the general features of CRS or differentiate between CRSwNP and CRSsNP.[11-13,15-18] Various studies investigating histopathologic markers in CRSwNP have identified the presence of eosinophilia as an important factor.[11-13,15-18] Moreover, eosinophilia has been suggested as a marker for worse decrease in smell,[15] disease severity,[16] and recurrence.[17] One study comparing risk of polyp recurrence used a volume-based analysis of tissue eosinophilia.[13] Typically this has been subdivided into local tissue eosinophilia[11,13,18] and eosinophil aggregates,[11,12] which may be a sign of eosinophilic activity.

Structured histopathology evaluation of CRS is a relatively new endeavor that aims to capture and report on 13 inflammatory characteristics of sinonasal tissue and mucin removed during ESS.[11] Prognostic implications of this report have yet to be comprehensively established. To our knowledge, this is the first study to investigate histopathologic differences in primary and recurrent CRSwNP tissue using the detailed structured report format. We found that eosinophil aggregates were more common in recurrent nasal polyp mucin but did not find differences in tissue eosinophilia levels between primary and recurrent CRSwNP tissue using a threshold value of 10 eosinophils per HPF.[18] There were no statistical differences in the detected amount of fungal elements between both groups. This report suggests that eosinophilic aggregates in the mucin, which are hallmarks of hyperactive eosinophilic inflammation, are an important consideration that needs to be further evaluated.

Eosinophilic aggregates have been reported in patients with CRSwNP in only three prior studies.[11,12,19] A study conducted by Kuhar et al. posited that the presence of tissue eosinophilic aggregates may be a useful predictor of polyposis and may also indicate a more severe disease process.[12] The current study finds that eosinophil aggregates are more prevalent in recurrent CRSwNP mucin compared to primary disease. This further supports previous studies' findings that activated eosinophils may play role in more severe (recurrent) CRSwNP and indicate disease that is difficult to treat with standard therapies. A recent study also suggests that tissue eosinophil aggregates were the most substantial driving factor for increased cumulative prednisone doses following sinus surgery.[19] In this study, patients with eosinophilic predominance were more likely to have eosinophil aggregates ($P < .001$), although patients with both eosinophilic predominance and eosinophil aggregates were not different between primary and recurrent nasal polyp tissue.

The presence of local tissue eosinophilia in primary and recurrent CRSwNP has been studied more extensively than eosinophilic aggregates.[11,13,18] For example, a study conducted by Bassiouni et al. in 2015 evaluated local tissue eosinophilia in patients who had recurrent CRSwNP compared to those who did not require revision surgery. That study found that increased local eosinophilia (≥10 per HPF)

correlated with higher rates of recurrence and increased likelihood of requirement for further ESS.[18] Our study did not find a difference between primary and recurrent CRSwNP when evaluating local tissue eosinophilia. This suggests that investigating higher thresholds for tissue eosinophilia (eg, >100 per HPF) may be an additionally important differentiator. Eosinophil aggregates, markers of severe eosinophilic inflammation, are a distinguishing characteristic more likely to be associated with recurrent CRSwNP mucin. Other elements on the structured histopathology report were not different in primary vs recurrent CRSwNP. The authors therefore propose that if resources do not permit a formal 13-item structured report, otolaryngologists could potentially request a report on the presence or absence of eosinophilic aggregates in the mucin removed in patients, in addition to tissue eosinophil levels. The presence of mucin eosinophilic aggregates may mark eosinophilic activity and provide clinically relevant information for the surgeon.

Asthma and AERD have been previously associated with recalcitrant CRSwNP.[4,6,7,10,20] Our study found that patients with recurrent CRSwNP were more likely to have AERD than patients with primary CRSwNP. This finding further supports the unified airway hypothesis as well as prior studies that have shown increased rates of CRSwNP recurrence in patients with AERD compared to patients who did not have AERD.[7,20] Importantly, though, mucin eosinophil aggregates remained associated with recurrent nasal polyps in multivariable analysis accounting for AERD.

There are several limitations to the present study. The study involves a small number of patients; a prospective study with larger sample size is optimal to validate our conclusions. Not all CRSwNP patients have macroscopically visible mucin present at the time of surgery and in these patients, the mucin is studied if present in the background of the surgical tissue sent from a trap; the amount of mucin may have implication on severity of CRSwNP. Additionally, other factors such as tissue IgE staining were not conducted as part of the clinical standard of care. Preoperative data on use of oral corticosteroids and antibiotic use could not be comprehensively gathered. It is not the senior author's practice to use perioperative oral corticosteroids routinely for CRSwNP, restricting its use to patients with unstable asthma. As a standard, all adult patients are given intravenous dexamethasone (8-10 mg) at the time of induction of anesthesia. All patients undergoing ESS are encouraged to use topical nasal steroids, but data on compliance was not gathered or available. While preoperative use of oral steroids, topical nasal steroids, and oral leukotriene inhibitors does not appear to affect histopathological reporting in a previous study, the authors believe that a more optimal study should be prospective and record the use of antibiotics and oral corticosteroids as these may confound the histopathology.[12]

A valid concern is whether the histopathologic study is reproducible by different pathologists. The criteria originally developed by Snidvongs et al. appear to have good interobserver and intraobserver test-retest reliability based on testing at the time of adoption in our institution. At our institution, a single slide per sample is studied, with addition slides cut if further staining is deemed necessary.

The study reviews differences in characteristics of tissue at the time of surgery. The prognostic significance of mucin eosinophil aggregates is not therefore clear. The study did not look at long-term follow-up of the patients. At the submission of the manuscript, we reviewed differences in revision surgery rates, but analyses could not be drawn due to the low number of revisions (3%) performed overall. Prospective studies with larger sample size and long-term follow-up (5-10 years) are necessary to draw definitive conclusions on the prognostic value of finding eosinophil mucin aggregates.

Tissue eosinophilia has been previously recognized as a factor of recalcitrance in CRS. The implications of mucin characteristics in CRSwNP are however under-studied. This study shows that eosinophil aggregates in the mucin may be a novel marker independently associated with more recalcitrant disease, being present in recurrent polyposis more likely than primary polyposis patients. It is unknown at this time as to what the presence of these aggregates represents or what triggers these. This feature may reflect an environmental stressor or biologic process that attracts eosinophils in high numbers to the sinonasal tissue. As novel biologic therapy targeting eosinophilic inflammation have become available, markers that may be used to endotype patients into those most likely to respond to such therapy will become very important. Mucin can be sampled in many patients in the office. Prospective studies that address limitations of the current study are necessary to further define the role of eosinophil aggregates in the mucin of CRSwNP patients.

5 | CONCLUSION

Eosinophil aggregates on histopathology are significantly more likely to be present in recurrent CRSwNP mucin. We did not identify any other differences in recurrent vs primary CRSwNP tissue on the 13-item structured histopathology report. In this limited series, tissue eosinophilia (10 per HPF threshold) was not significantly different in primary and recurrent CRSwNP. The presence of eosinophilic aggregates in the mucin may mark eosinophilic activity and potentially more severe disease. Therefore, in addition to the attention devoted to tissue eosinophilia, rhinologic surgeons should also direct attention to sampling mucin in CRSwNP. Mucin eosinophilic aggregates may be an independent marker of severe inflammation that is more likely to be associated with recurrent versus primary CRSwNP.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Nathaniel J. Donnell https://orcid.org/0000-0003-1636-9219
Michael J. Marino https://orcid.org/0000-0002-8672-0310
Devyani Lal https://orcid.org/0000-0002-7593-2385

REFERENCES

1. Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6:S22-S209.
2. Sharma R, Lakhani R, Rimmer J, Hopkins C. Surgical interventions for chronic rhinosinusitis with nasal polyps. *Cochrane Database Syst Rev*. 2014;11:CD006990.
3. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg*. 1995;113:104-109.
4. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal outcome test. *Clin Otolaryngol*. 2009;34:447-454.
5. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope*. 2017;127:550-555.
6. Miglani A, Divekar RD, Azar A, Rank MA, Lal D. Revision endoscopic sinus surgery rates by chronic rhinosinusitis subtype. *Int Forum Allergy Rhinol*. 2018;8:1047-1051.
7. Mendelsohn D, Jeremic G, Wright ED, Rotenberg BW. Revision rates after endoscopic sinus surgery: a recurrence analysis. *Ann Otol Rhinol Laryngol*. 2011;120:162-166.
8. Hopkins C, Andrews P, Holy CE. Does time to endoscopic sinus surgery impact outcomes in chronic rhinosinusitis? Retrospective analysis using the UK clinical practice research data. *Rhinology*. 2015;53:18-24.
9. Hopkins C, Rimmer J, Lund VJ. Does time to endoscopic sinus surgery impact outcomes in chronic rhinosinusitis? Prospective findings from the National Comparative Audit of surgery for nasal polyposis and chronic rhinosinusitis. *Rhinology*. 2015;53:10-17.
10. Benninger MS, Sindwani R, Holy CE, Hopkins C. Impact of medically recalcitrant chronic rhinosinusitis on incidence of asthma. *Int Forum Allergy Rhinol*. 2016;6:124-129.
11. Snidvongs K, Lam M, Sacks R, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int Forum Allergy Rhinol*. 2012;2:376-385.
12. Kuhar HN, Tajudeen BA, Mahdavinia M, Gattuso P, Ghai R, Batra PS. Inflammatory infiltrate and mucosal remodeling in chronic rhinosinusitis with and without polyps: structured histopathologic analysis. *Int Forum Allergy Rhinol*. 2017;7:679-689.
13. Tosun, F., Arslan, H. H., Karslioglu, Y., Salih Deveci, M., & Durmaz, A. Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. *Ann Otol Rhinol Laryngol* 2010; 119:455–459.
14. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): Adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152:S1-S39.
15. Soler ZM, Sauer DA, Mace JC, Smith TL. Ethmoid histopathology does not predict olfactory outcomes after endoscopic sinus surgery. *Am J Rhinol Allergy*. 2010;24:281-285.
16. Soler ZM, Sauer DA, Mace J, Smith TL. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2009;141:454-461.
17. Soler ZM, Sauer D, Mace J, Smith TL. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg*. 2010;142:64-71.
18. Bassiouni A, Ou J, Rajiv S, Cantero D, Vreugde S, Wormald PJ. Subepithelial inflammatory load and basement membrane thickening in refractory chronic rhinosinusitis with nasal polyposis: a histopathological study. *Int Forum Allergy Rhinol*. 2016;6:248-255.
19. Tajudeen BA, Ganti A, Kuhar HN, et al. The presence of eosinophil aggregates correlates with increased postoperative prednisone requirement. *Laryngoscope*. 2019;129:794-799.
20. Amar YG, Frenkiel S, Sobol SE. Outcome analysis of endoscopic sinus surgery for chronic sinusitis in patients having Samter's triad. *J Otolaryngol*. 2000;29(1):7-12.

How to cite this article: Donnell NJ, Marino MJ, Zarka MA, Lal D. Histopathological characteristics of surgical tissue from primary vs recurrent chronic rhinosinusitis with nasal polyposis patients. *Laryngoscope Investigative Otolaryngology*. 2020;5:5–10. https://doi.org/10.1002/lio2.358