

Endotyping of nasal polyps in a multiracial Asian population*

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Abstract

Background: Chronic rhinosinusitis is a heterogenous disease with variation in the endotypes of nasal polyps, with type 2 inflammation being more prevalent in Caucasian populations whereas Chinese populations are more heterogenous. We aim to describe the variation in endotypes for patients with chronic rhinosinusitis with nasal polyposis in our unique multiracial population.

Methodology: Demographic, clinical and structured histopathological data of 66 patients who underwent sinus surgery for nasal polyposis were evaluated retrospectively.

Results: 54.6% had eosinophilic disease, and 45.4% had non-eosinophilic disease with no significant demographic differences between the 2 populations. There were significantly higher peripheral eosinophil levels in patients with eosinophil-predominant inflammation on tissue histology (mean absolute eosinophil count $0.59 \pm 0.18 \times 10^9$) compared with non-eosinophilic disease (mean absolute eosinophil count $0.24 \pm 0.11 \times 10^9$). Structured histopathological reporting revealed that patients with eosinophilic disease had higher degree of inflammation and eosinophil aggregates.

Conclusions: Our population is shown to have a slight preponderance toward eosinophilic disease, however the Chinese majority tended to have non-eosinophilic disease. Serum eosinophilia and the presence of asthma seems to correlate well with tissue eosinophilia, which can potentially be utilised as markers of type 2 inflammatory disease

Key words: Chronic rhinosinusitis, nasal polyps, endotyping, eosinophilic, non-eosinophilic, Asian, Type 2 inflammation

Introduction

Chronic rhinosinusitis (CRS) is defined as inflammation of the sinonasal mucosa lasting for more than 12 weeks. Beyond the cardinal symptoms of purulent nasal discharge, nasal congestion, facial pain and smell disturbance, a large proportion of patients also report fatigue (11-79%)⁽¹⁾ and poor sleep (50-90%)⁽²⁾, leading to an overall decreased quality of life⁽³⁾. The societal and financial burden of disease from both loss of productivity and healthcare costs are significant^(4,5). Therefore, there is a need to better understand the disease so that patients can be better informed of their disease prognosis, and eventually receive effective personalised therapy.

The traditional phenotypical dichotomy of CRS into CRS with

polyps (CRSwNP) and without nasal polyps (CRSsNP) has been reclassified as primary and secondary CRS in the European Position Paper on Rhinosinusitis (EPOS) 2020 guidelines⁽⁶⁾. Primary CRS is further classified into inflammatory endotypes, classically described as Type 2 and non-Type 2. Type 2 disease (eosinophilic) is driven by activation of TH2 inflammatory pathways producing cytokines IL 4, -5 and -13 and non-Type 2 (non-eosinophilic) involves activation of TH1 or TH17 pathways. CRSsNP is typically characterized by a predominant TH1 milieu with high IFN- γ and TGF- β 1 concentrations, whereas CRSwNP shows a TH2 skewed eosinophilic inflammation with high levels of IL-5 and IgE and low TGF- β 1⁽⁷⁾.

With increasing international efforts toward better understand-

ding of CRS, there is emerging data showing that the relationship between phenotypes and endotypes is more complex. They suggest an interplay between genetics and environmental exposure, as there is variation in inflammatory predominance amongst different geographical locations, ethnicity, and even evolution with time. Wang et al. compared TH2/TH1/TH17 cytokine patterns and markers of eosinophilic and neutrophilic inflammation in patients with CRS from 6 regions covering Europe, Asia, and Australia⁽⁸⁾. They found that greater than 50% of patients with CRSwNP in Benelux, Berlin, Adelaide, and Tochigi demonstrated a predominantly eosinophilic endotype, whereas less than 30% patients in Beijing and Chengdu had eosinophilic disease. A Korean centre compared polyp samples from 1993 and 2010, and using 5 eosinophils/hpf as a threshold, found that there was a significant increase in proportion of eosinophilic disease from 24.0% to 50.9% over 17 years⁽⁹⁾. Mahdavinia compared second generation Asian Americans with Caucasians with CRSwNP as a depiction of patients with the same environmental exposure but different ancestry and found that there was significantly lower prevalence of eosinophilic disease amongst the Asian Americans⁽¹⁰⁾.

Singapore has a multi-ethnic, culturally diverse population comprising 74.3 % Chinese, 13.5% Malays and 9% Indians, with a 30% migrant population⁽¹¹⁾. We aim to describe the variation in endotypes for patients with chronic rhinosinusitis with nasal polyposis in our unique heterogenous population and associated demographic and clinical biomarkers.

Materials and methods

This study was approved by the SingHealth Centralised Institutional Review Board. A retrospective review of consecutive adult patients (>21 years old) who underwent endoscopic sinus surgery between Jan 2016 to May 2021 by the senior author in Singapore General Hospital was performed. Patients who fulfilled diagnostic criteria for chronic rhinosinusitis with nasal polyposis as stipulated in the EPOS 2020 guidelines⁽⁶⁾, had failed medical therapy and underwent ESS were included. Those with neoplastic or non-inflammatory sinonasal disease were excluded, e.g. sinonasal tumours and antrochoanal polyps. History of asthma, NSAID allergy, smoking status and previous sinus surgeries were retrieved from existing electronic medical records. Preoperative serum markers including eosinophil count ($\times 10^9$) and total IgE were documented. Preoperative CT paranasal sinuses findings were recorded. Intraoperative findings of nasal polyp grade and presence of mucopus were recorded.

Histopathological profiling

Biopsies of nasal polyps were obtained during surgery, fixed in 10% formaldehyde, and sent for histological evaluation by a single pathologist for consistency. H&E staining was performed and tissue were assessed by bright field light microscopy (Olympus

BX43) and reported in accordance to St Vincent Hospital's structured histopathological report⁽¹²⁾. The numbers of neutrophils, eosinophils, plasma cells, lymphocytes, and total inflammatory cells in the lamina propria were counted in 10 non-overlapping random fields at $\times 400$ magnification and recorded as the mean of 10 fields. Eosinophil count in tissue were reviewed and categorized based on numbers per high power field (HPF) and designated as <5, 5-10 or >10 per high power field (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. Eosinophilic disease was defined based on the cut off of >10 eosinophils per high power field in accordance to EPOS 2020 guidelines⁽⁶⁾.

Statistical analysis

Statistical analyses were performed using STATA v 16.0 (Stata-Corp LLC, College Station, TX, USA). Descriptive data were presented as percentages and means $\pm$ standard deviation (SD). For categorical data, Pearson's chi-square analysis was used for larger populations and Fisher's exact test was used for smaller populations (when a cell contained less than 5 patients). Student t test (2-tailed) was used for comparisons of parametric data. Mann-Whitney U Test (2-tailed) was used to compare nonparametric data. Pearson's correlation was used to describe relationship between two continuous variables. The significance level was set at a $\alpha = 0.05$.

Results

There were 66 patients who had undergone sinus surgery for chronic rhinosinusitis with nasal polyposis. One third of patients were undergoing revision surgery ($n=21$, 31.8%), with the highest number of previous surgeries recorded at 5. 54.6% had eosinophilic CRS and 45.4% had non-eosinophilic CRS. Demographic data for the 2 groups are compared in Table 1. There was no significant difference in terms of age, gender nor smoking status. However, there was a significantly higher prevalence of asthma in patients with eosinophilic disease compared to non-eosinophilic disease ($p = 0.003$). Diagnosis of asthma was based on clinician diagnosis listed in the electronic medical records. The proportion of patients with different ethnicities was commensurate with the distribution in our population, and there were no statistically significant differences when each ethnic group was considered separately. However, when the Chinese majority was compared against non-Chinese, there was a statistically significant higher proportion of non-eosinophilic disease within Chinese (56.8%) vs non-Chinese (22.7%) ($p=0.09$).

Blood parameters

There were no statistically significant differences in serum IgE levels between the group with eosinophilic CRS (295.5 ± 108.1 IU/mL) and non-eosinophilic CRS (295.9 ± 195.0 IU/mL) ($p = 0.99$).

Table 1. Demographic data.

		Eosinophilic	Non-eosinophilic	P value
Gender, n (%)	Female	17 (47.2)	12 (40.0)	0.56
	Male	19 (52.8)	18 (60.0)	
Age (years), mean (range)		50.9 (23-73) (	53.0 (22-81)	0.55
Ethnicity, n (%)	Chinese	19 (52.8)	25 (83.3)	0.07
	Indian	11 (30.6)	3 (10.0)	
	Malay	2 (5.6)	1 (3.3)	
	Caucasian	1 (2.78)	0 (0)	
	Sikh	1 (2.78)	1 (3.33)	
	Others	2 (5.56)	0 (0)	
Asthma, n (%)	Yes	17 (47.2)	4 (13.3)	0.003
	No	19 (52.8)	26 (86.7)	
Smoking, n (%)	Yes	7 (19.4)	5 (16.7)	0.77
	No	29 (80.6)	25 (83.3)	
NSAID Allergy, n (%)	Yes	8 (22.2)	4 (13.3)	0.35
	No	28 (77.8)	26 (86.7)	
Surgery, n (%)	Primary Surgery	23 (63.9)	22 (73.3)	0.41
	Revision Surgery	13 (36.1)	8 (26.7)	

However, only about half (n=35) of the study population had preoperative IgE levels measured as it is not uniformly performed in our practice.

There were significantly higher peripheral eosinophil levels in patients with eosinophilic CRS on tissue histology (mean absolute eosinophil count $0.59 \pm 0.18 \times 10^9$) compared with non-eosinophilic CRS (mean absolute eosinophil count $0.24 \pm 0.11 \times 10^9$) ($p = 0.00$). Positive predictive value of an elevated absolute eosinophil count above the upper limit of our laboratory's threshold (0.44×10^9) for elevated tissue eosinophilia was 61.1%, whereas a negative predictive value was 86.7%.

Imaging

We used the radiologic Lund-Mackay score as a surrogate for disease severity. Scores were similar for both groups, with the mean score for the eosinophilic group being 15.5, 95% CI (13.6, 17.4), and that of non-eosinophilic disease being 14.1, 95% CI (11.9, 16.3), $p = 0.32$. The Lund-Mackay score did not show significant correlation with asthma ($p = 0.29$), NSAID allergy ($p = 0.70$) nor serum eosinophils ($r = -0.038$, $p = 0.77$) and serum IgE levels ($r = -0.182$, $p = 0.30$).

Histopathological data

Comparison of histopathological characteristics between eosinophilic and non-eosinophilic groups was performed (Figure 1). There was overall more severe inflammation amongst the eosinophilic group ($p = 0.02$). There were also more eosinophil aggregates (defined as a minimum of two distinct aggregates

of at least 10 cells each/HPF within the mucin) amongst those with eosinophilic disease ($p = 0.04$). Patients with eosinophil aggregates also had higher prevalence of asthma ($p = 0.03$), but not NSAID allergy ($p = 0.46$).

Nasal polyp tissue from patients with eosinophilic CRS had more basement membrane thickening, mucosal ulceration, and Charcot-Leyden crystals, whereas the non-eosinophilic group tended to have more neutrophilia, squamous metaplasia as well as hyperplastic/papillary change, though these did not reach statistical significance.

Discussion

The prevalence of chronic rhinosinusitis in Asian populations has been reported to be from 2.5-8.4%⁽¹³⁾. There is increasing awareness in the region of the mindshift from phenotypes to inflammatory endotypes in the classification of chronic rhinosinusitis. In a recent survey of Asia-Pacific otorhinolaryngologists, 71.4% reported consideration of type 2 versus non-type 2 endotypes in their management of patients with CRSwNP⁽¹⁴⁾. The importance of endotyping CRSwNP lies not just in increasing our understanding of the underlying disease process, but also helps to direct medical care and prognosticate disease. This is reflected in the latest EPOS guidelines, which emphasized the new classification of CRS into inflammatory endotypes and provided guidance on the use of biologicals in treating nasal polyposis. Significantly, the guidelines also commented that one of the major challenges was finding reliable biomarkers to define type 2 inflammation and predict response to medication⁽⁶⁾.



Figure 1. Comparison of histopathological characteristics between eosinophilic and non-eosinophilic groups.

We sought to study the variation in inflammatory endotypes in our multi-ethnic population and found that overall, there was a slight preponderance toward eosinophilic disease (54.6%). When analysed by ethnicity, Chinese were found to have a statistically significant higher proportion of non-eosinophilic disease (56.8%). This is congruent with studies conducted in other parts of Asia. Zhang et al showed that cytokines from TH1/TH17 pathways, namely IFN- γ , IL-1 β , IL-6, and IL-17 protein levels were significantly upregulated in southern Chinese compared to their Belgian counterparts⁽¹⁵⁾.

However, this non-eosinophilic predominance represents just a snapshot in time, as the distribution of eosinophilic and non-eosinophilic disease has been shown to evolve with time. Katotomichelakis et al. compared 47 nasal polyp tissue samples from 1999 with 42 equivalent samples from 2011 and found an increase in the absolute number of eosinophils samples, from 5 to 35⁽¹⁶⁾. Shin et al. proposed that this increase in eosinophilic polyps in Asian populations is due to concomitant factors such as bronchial asthma, aspirin intolerance, chronic local infections, atopy, allergies, and environmental pollutants⁽¹⁷⁾. With increasing globalisation, there may also be increased blending of both genetic and environmental exposures, hence it may be increasingly perplexing to define disease by geographical location. Another challenge in classifying CRSwNP is the lack of consensus as to what constitutes eosinophilic chronic rhinosinusitis. Toro et al. performed a systematic review of cut off points for eosinophilic CRS, and identified the following parameters that have been used as reference: standard deviation of controls, immunohistochemistry, asthma and allergy, quality of life (QoL) scores, polyp recurrence and combined parameters in cluster analysis⁽¹⁸⁾. Other studies have used eosinophil counts in serum⁽¹⁹⁾, mucin⁽²⁰⁾ and tissue⁽²¹⁾ to define eosinophilic disease. Cut off values for tissue eosinophilia have ranged from 5-350 eosinophils per high power field⁽²¹⁻²⁴⁾. Wang et al. utilised the ratio of tissue Eosinophilic Cationic Protein (ECP) versus Myeloperoxidase (MPO), with a ratio of greater than 1 being eosinophilic and a ratio of less than 1 being non-eosinophilic/neutrophilic disease⁽⁸⁾. Chitsuthipakorn et al. highlighted the importance of definition in affecting perceptions of inflammatory endotypes in different populations. They performed a systematic review and re-analysis of the raw data of existing papers studying CRS endotypes across different ancestry populations. Pooled data in the original papers reported 59% of Asian patients as non-eosinophilic CRS. However after applying a consistent criteria of >10 cells per high power field, the reverse was true, with 62.31% of Asians reclassified as eosinophilic disease⁽²⁶⁾.

Further stratification into type 2 versus non type 2 disease is even more contentious. Bo et al. used clustered cytokines to define inflammatory phenotypes: 1) IL-5, ECP, IgE, and SE-IgE (type-2 inflammation); 2) MPO, IL-8, and IL-6; 3) TNF- α and IFN- γ ; and 4) IL-17. Recently, Nakayama even performed RNA sequen-

cing for endotype stratification, and identified prominent type 2 inflammatory transcript expression: C-C motif chemokine ligand 13 (CCL13) and CCL18 in M2 macrophages, as well as cystatin SN (CST1) and CCL26 in basal, suprabasal, and secretory epithelial cells⁽²⁵⁾. This myriad of investigations underscores the difficulty in establishing an international guideline to define inflammatory endotypes in CRS. This partially accounts for the wide variation and sometimes even conflicting data on the distribution of endotypes in different centres. In fact, Stevens et al. have shown that patients can have mixed endotypes exhibiting certain phenotypes, for instance the T1 and T2 mixed endotype shows the highest asthma comorbidity in CRSwNP but not in CRSsNP⁽²⁷⁾. Therefore, the community needs to work towards using parameters that are accessible, reproducible, and consistent for more accurate classification and understanding of disease.

In further analysis of the structured histopathological reporting, we found a significant correlation between serum and tissue eosinophilia with an 86.7% negative predictive value. This is consistent with results reported by Asghari et al., which showed that the mean percentage of eosinophils in blood and tissue increased significantly with increasing CT scan score of patients⁽²⁸⁾. We found significant correlations between tissue eosinophilia and degree of inflammation as well as presence of eosinophil aggregates in mucin. This was consistent with findings in literature^(12,29), in which eosinophil activation is associated with histopathological presence of mucin with eosinophilic aggregates and Charcot-Leyden crystals. Clinically the implications are that of more severe upper airway remodeling, manifesting as more severe clinical disease. Brescia et al. found significant correlations of tissue eosinophil count and subepithelial edema, goblet cell hyperplasia and basement membrane thickness. They postulated that this is due to the release of eosinophilic pro-inflammatory factors that prompt subepithelial edema as a first response then goblet cell hyperplasia and increasing fibrosis in the basement membrane as a sign of late response to inflammation⁽³⁰⁾.

Our study involves patients managed by only one surgeon operating in a tertiary hospital, who routinely sends nasal polyp biopsies for structured reporting. Due to the single-surgeon study design, pre-operative treatment is standardized across patients, and no oral corticosteroids are given immediately pre-operatively, which may suppress inflammation and affect tissue histology reporting. Our tissue samples were read by a single pathologist and were rigorously evaluated using a structured format, which ensured consistency across reporting.

Limitations to our study include small sample size, as well as incomplete IgE results for all patients. One of the challenges faced in the study design and data analysis was deciding how to classify nasal polyps as eosinophilic or non-eosinophilic, due to the variety of classification methods used in literature. Comparing final patient outcomes after ESS with pre-operative and

intra-operative biomarkers may provide the most meaningful results, as the intent of classifying inflammatory polyp endotypes is to help prognosticate disease course and assist in therapeutic decision making. These are definitely areas for further research.

Conclusions

Our multiracial population provides a unique opportunity to study the inflammatory patterns for Asian patients with CRS. We found that Chinese tended toward non-eosinophilic disease, whereas the population as a whole had a slight predominance of eosinophilic disease. Future studies with a larger sample size of each ethnicity, as well as prospective data with outcome measures would allow even more understanding of this relationship. We also found that an elevated serum eosinophilia and presence of asthma can be potentially used as predictors of type 2 inflammation in our population. Further international collaborative efforts will be required to define biomarkers that define each endotype to provide more clarity on suitability of targeted therapy.

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Authorship contribution

XSH analysed and interpreted the data and wrote the manuscript. MV collected data. JH performed the histopathological analyses. NT and CTC provided feedback and amendments on the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was obtained from the SingHealth Centralised Institutional Review Board.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Conflict of interest

The authors declare that they have no competing interests.

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