

Biomarker Profile of Chronic Rhinosinusitis with Nasal Polyps Patients with a Mixed Inflammation Pattern



Barbosa EB^{1*}, Vieira GS², Toro MDC¹, Mariano FV² and Sakano E¹

¹Department of Ophthalmology and Otorhinolaryngology, University of Campinas, Brazil

²Department of Anatomical Pathology, University of Campinas, Brazil

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*Corresponding author: Elio Bittar Barbosa, Department of Ophthalmology and Otorhinolaryngology, University of Campinas, Campinas, São Paulo, Brazil

Abstract

Purpose: Chronic rhinosinusitis with nasal polyps (CRSwNP) present different endotypes. There is evidence that patients from Brazil may present with a different endotype than western countries, with a predominantly mixed pattern of inflammation. Biomarkers may be used to identify patients with poor prognosis. The objective of our study is to measure tissue and serum eosinophils in patients with CRSwNP and to evaluate the correlation of serum and tissue eosinophils, as well as the correlation of serum, tissue eosinophils and asthma with recurrence and time to recurrence (<12 months) of nasal polyps.

Methods: Overall, 143 patients with chronic rhinosinusitis with nasal polyps who were submitted to endoscopic sinus surgery between 2009 to 2019 were enrolled in this study. It was analyzed correlation between tissue and serum eosinophilia, concordance between both markers and analysis of nasal polyp recurrence.

Results: We observed a higher median in the tissue eosinophils infiltrate among our patients when compared to the literature. We also identified correlation between asthma ($p=0.027$) and eosinophilia ($p=0.003$) with early recurrence of nasal polyps. There was no correlation between tissue and serum eosinophilia.

Conclusion: The patients of our study presented with a higher eosinophil infiltrate; however, the results did not demonstrated concordance of the tissue eosinophils with serum eosinophils nor correlation with polyp relapse. Patients with asthma and high serum eosinophilia also presented a higher risk of short term (12 months) polyp relapse. They may be utilized as biomarkers of poor prognosis in a population with mixed inflammation pattern.

Keywords: Chronic rhinosinusitis; Nasal polyps; Biomarker; Type 2 inflammation

Abbreviations: CRSwNP: Chronic Rhinosinusitis With Nasal Polyps; CRS: Chronic Rhinosinusitis; IgE: immunoglobulin E; eCRS: Eosinophilic Chronic Rhinosinusitis

Introduction

Chronic rhinosinusitis (CRS) was initially divided into two phenotypes: CRSwNP and rhinosinusitis without nasal polyps (CRSSNP). This classification has long guided the treatment and prognosis of chronic rhinosinusitis. In 2006, Van Zele et al. [1] demonstrated that these phenotypes responded to distinct immunological patterns, with CRSwNP usually presenting a type 2 pattern. CRS with Th2 endotype presents eosinophilic infiltrate, increased interleukins IL-4, IL-5, IL-13, IL-33, IL-25, eotaxin, eosinophilic cationic protein, and immunoglobulin E (IgE) [2]. It represents up to 85% of western patients with chronic rhinosinusitis with polyps [3]. It seems relevant to emphasize that the

recurrence of polyps after surgical treatment can reach up to 60% over a period of 10 years [4], with up to 40% of patients presenting recurrence within a period of less than 12 months [5].

Fokkens et al. [6], in the most recent European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS, 2020), classified the diffuse chronic rhinosinusitis into eosinophilic chronic rhinosinusitis (eCRS) and non-eosinophilic chronic rhinosinusitis. Such definition is determined by the count of the number of eosinophils, as defined by the EPOS 2020 panel as ≥ 10 eosinophils in the high-power field (eos/HPF-400x). However, there is no consensus regarding the criteria for defining eCRS [7]. Furthermore, there is

evidence that patients from our country may present with a different endotype, with a predominantly mixed pattern of inflammation [8]. In the light of these recent findings, the objective of this study is to measure tissue and serum eosinophils in patients with CRSwNP and to evaluate the correlation of serum and tissue eosinophils, as well as the correlation of serum, tissue eosinophils and asthma with recurrence and time to recurrence (<12 months) of nasal polyps.

Materials and Methods

Our retrospective study included patients with chronic rhinosinusitis with polyps, who underwent surgery between 2009 and 2019 at our institution. The participating patients were initially treated clinically and when there was no clinical response, they were referred for surgical treatment according to EPOS guidelines. Patients presenting eosinophilic granulomatosis with polyangiitis, primary ciliary dyskinesia, cystic fibrosis, immunodeficiency or neoplasia, and patients who had less than 1 month of postoperative follow-up were excluded. Clinical data such as gender, age, presence of asthma, presence of sensitivity to non-steroidal anti-inflammatory drugs, presence of recurrence, time to recurrence after surgery, and serum eosinophilia were obtained. Biopsies were performed in the office setting with a washout period from corticosteroids (oral and topical) of four weeks. Standard techniques were used to prepare all samples. The microscopic review was performed by two independent observers using a binocular microscope (Leica DM4000B LED, Switzerland). The observers were blinded to the clinical data and characteristics of the patients. Initially, the areas with the greatest subepithelial infiltrate were identified and, subsequently, examined in the high-power field (HPF-400x). The three fields with the highest infiltration were selected and photographic documentation was carried out.

Five photos of the area were taken in a standardized way for all patients in the sample, which determined an area compatible with the HPF area of the microscope used (0,333mm²). Afterwards, the eosinophils were counted and the average of the 3 areas was obtained. Patients were treated postoperatively with nasal irrigation with saline solution and topical nasal corticosteroids (budesonide or mometasone). Follow-ups were carried out with clinical evaluation and nasal endoscopy. The study was approved by the local ethical committee of the Campinas University Hospital (53910621.5.0000.5404) and an informed consent was obtained from every patient.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) software (IBM SPSS Statistics for Macintosh, Version 28.0.). In the event of missing data, the characteristics of patients who had less than 40% missing data were inserted in the database using the XLSTAT Statistical Software for

Excel. For qualitative (categorical) data, the missing data were estimated using the NIPALS (Nonlinear Iterative Partial Least Squares) algorithm, while for quantitative (numerical) data, missing data were estimated using the MCMC (Markov Chain Monte Carlo) multiple imputation algorithm. The Spearman correlation test was used in the comparison between groups and the significance level was set at $\alpha = 0,05$.

Results

One hundred and forty-three patients were included in the study, most of them were men (59.4%) and their average age was 50 years. Other relevant data found included the fact that the prevalence of asthma among participants was 39.1% and patients with aspirin exacerbated respiratory disease represented 11.9% of those included in the study (Table 1). The serum eosinophilia median was 360 eosinophils/mm³ (eos/mm³) and the tissue eosinophils median count was 234 eos/HPF (Table 2). Considering the cutoff point proposed in the latest EPOS, we observed that 90% of the population might be considered to have chronic sinusitis with eosinophilic predominance. Sixty-nine patients (48.5%) presented recurrence and, out of them, thirty-five (50%) developed it before 12 months of follow-up. The mean time for nasal polyp relapse was 18.6 months. No variable was correlated with polyp recurrence. However, the Spearman test showed that patients with asthma ($p < 0.027$) and serum eosinophilia > 300 eos/mm³ ($p < 0.003$) presented greater chances of recurrence before 12 months of follow-up (Table 3 & Table 4).

Table 1: Descriptive analysis of markers with categorical distribution and that were evaluated in this study.

Marker	Groups	Distribution [N (%)]
Gender	Male	85 (59.4%)
	Female	58 (40.6%)
Asthma	Yes	56 (39.1%)
	No	87 (60.9%)
Aspirin exacerbated respiratory disease (AERD)	Yes	17 (11.9%)
	No	126 (89.80%)
Recurrence	Present	69 (48.25%)
	Absent	74 (51.75%)
Time to recurrence	< 12 months	35 (50.7%)
	>12 months	34 (49.3%)

Table 2: Descriptive analysis of markers with numerical distribution and that were evaluated in this study.

Marker	Median Distribution and Confidence Interval 95%
Serum eosinophils (eos/mm ³)	360 (325 to 401)
Tissue eosinophils (eos/HPF)	234 (169 to 231)

Eos, eosinophils; HFP, high-power field.

Table 3: Spearman correlation between serum eosinophil count and tissue count in patients subjected to surgical procedure.

Comparison	P-value*	Correlation Coefficient	95% CI
Serum eosinophil vs. tissue eosinophil count	0.075	0.15	-0.020 to 0.311

95% CI, 95% confidence interval.

Table 4: Association between recurrence and the time to recurrence with categorization of tissue and serum eosinophils, and in the presence of asthma in patients subjected to surgery.

Marker	Groups	Time to Recurrence			P-value
		≤12 months	>12 months	Total	
Tissue eosinophil count	<10 (eos/HPF)	3 (60.0%)	2 (40.0%)	5	1.000***
	≥10 (eos/HPF)	32 (50.0%)	32 (50.0%)	64	
Tissue eosinophil	< 43 (eos/HPF)	5 (45,5%)	6 (54,5%)	11	0.708**
	≥43 (eos/HPF)	30 (51,7%)	28 (48,3%)		
Serum eosinophil count	<150(eos/mm ³)	4 (30.8%)	9 (69.2%)	13	0.113**
	≥150 (eos/mm ³)	31 (55,4%)	25 (44.6%)	56	
Serum eosinophil count	<300 (eos/mm ³)	8 (28.6%)	20 (71.4%)	41	0.003**
	≥300 (eos/mm ³)	27 (65.9%)	14 (34.1%)	41	
Asthma	Presence	19 (67.9%)	9 (32.1%)	28	0.027**
	Absence	16 (39.0%)	25 (61.0%)	41	

Eos, eosinophils; HFP, high-power field.

Discussion

CRS is an illness that affects between 5% and 12% of the global population [6]. Despite great advances in the understanding of immunological pathways [1-3], chronic rhinosinusitis is still a complex disease, with several endotypes and heterogeneous clinical results. In a recent study, Calus [9] reported that up to 80% of the patients might present polyp recurrence in the long term, and around 36% of them might require revision surgery. This data confirms the results obtained by van der Veen et al. [10], which demonstrated that 40% of the patients did not have control of their disease based on the EPOS control guidelines. Classically, tissue eosinophils count has been used as the type 2 inflammation biomarker CRS. However, lack of consensus about the cutoff point [7] hampers the comparison of data from different regions or institutions. Our study demonstrated a population with type 2 inflammation like that found in the literature [9], representing 90% of the sample. However, the median tissue eosinophils (234 eos/HPF) of our sample were much higher than that of other similar studies developed with western populations [11,12].

Other authors [13] had previously suggested that the cutoff point widely used (≥10 eos/HPF) might not represent properly the eCRS. In fact, great heterogeneity is found in the studies [7], most did not describe how many researchers carried out the histopathological analysis and about half of them did not mention the number of high-power fields used in the count of their area. Also, the area of the HPF reviewed and the use of graduated reticle mounted within the eyepiece objectives are not standardized in the literature. Other aspect to be explored in the difference of the

tissue eosinophil count is geographical and ethnic differences in the CRS endotypes [14]. Our population presents a distinct ethnic conformation due to its diversity. Recently, Romano et al. [8] reported that in a multi-institutional study from Brazil most of the patients with CRSwNP presented with a mixed inflammation pattern demonstrated with a high concentration of cytokines from type 1,2 and 3 pattern. There was no difference in cytokines concentration when utilized the EPOS cut-off point (>10 eos/HPF) in the patients of the study. Therefore, it was proposed a cutoff point (≥43 eos/HPF) according to the cluster analysis of the patients based on the cytokines concentration.

The interest in serum eosinophil as a type 2 marker in chronic rhinosinusitis was recently renewed [15,16], mainly for its use in the indication of immunobiological drugs such as it is used in asthma. Previously, Tokunaga et al. [17] and Sakuma et al. [18] had already proposed the inclusion of serum eosinophilia and asthma in their models for the eCRS definition. However, the correlation between serum and tissue eosinophils remains unclear, and conflicting results are found in the literature [19,20]. Our results pointed out that there was no correlation between serum and tissue eosinophils in the patients of the sample. This may indicate that different endotypes could have different correlations between serum and tissue eosinophils due to different patterns of inflammation. The use of polyp recurrence is one of the main markers of severity and the presence of the type 2 inflammation in CRS.

The literature has recently demonstrated that asthma patients [21] and increased serum eosinophilia [16] tend to present

a worse prognosis with increased risk of polyp recurrence and reoperation. Our results agree with these conclusions, with serum eosinophilia ≥ 300 (eos/mm³) ($p < 0.003$) and the presence of asthma ($p < 0.027$) indicating early recurrence (< 12 months of follow-up). Moreover, they also indicate that tissue eosinophil count from our population might be closer to the reported by Asian authors [17,22] than to those presented by western authors [23,24]. However, there was no correlation between recurrence of nasal polyps with the eosinophil infiltrate. This study has some limitations such as the inclusion of a convenience sample from a referral university hospital, which might prevent the generalization of the results obtained in relation to other research centers. The sample size was relevant considering other studies published, however, limited in relation to statistical power. Moreover, since this is a retrospective study, the postoperative follow-up showed some chronological variation. Thus, conclusions based on the findings must be considered with caution.

Conclusion

The chronic rhinosinusitis is a challenging disease with multiple endotypes and high percentage of recurrence and reoperation. The patients of our study presented with a higher eosinophil infiltrate; however, the results did not demonstrated concordance of the tissue eosinophils with serum eosinophils nor correlation with polyp relapse. Patients with asthma and high serum eosinophilia also presented a higher risk of short term (12 months) polyp relapse. They may be utilized as biomarkers of poor prognosis in a population with mixed inflammation pattern.

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