Chronic rhinossinusitis with nasal polyps (CRSwNP) biopsy – when, how and why?

Review Article

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Abstract

Objective: To assess the impact of nasal tissue neutrophilia on dupilumab response in severe, uncontrolled CRSwNP.
Methodology: Retrospective study, 23 CRSwNP patients on dupilumab assessed at baseline and 6 months. Systemic IgE and eosinophilia, tissue eosinophilia and neutrophilia were recorded. Evaluation of Sino-nasal Outcome Test (SNOT-22), Visual Analogue Scale (VAS) total symptoms, Nasal Polyp Score (SPN), Barcelona Smell Test 24 (BAST-24), Nasal Congestion Score (SCN), and Smell Loss Score (SPO).
Results: Mean tissue neutrophil count was 2±2.3, ranging from 0 to 8 per high-power field. Correlation was observed between tissue neutrophilia and SPO variation (r= 0.464, p = 0.034) and direct correlations between tecidual eosinophilia and neutrophilia (r=0.595, p=0.004) and between tecidual neutrophilia and sistemic IgE (r=0.548, p=0.010).
Conclusion: Higher neutrophil levels appear linked to resistance to dupilumab, with less improvement in SPO. Sample size limits data reliability, warranting further studies with larger samples.

Keywords: Nasal polyps, neutrophils, eosinophils, rhinossinusitis

Introduction

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is an inflammatory disease of the nasal mucosa and paranasal sinuses, characterized by the presence of nasal polyps. It is associated with persistent symptoms, such as nasal obstruction, rhinorrhea, and impaired olfaction, which substantially impact the patients' quality of life[1]. Despite advances in medical and surgical therapies, CRSwNP has a high recurrence rate.

The disease is classified into two types according to the predominant inflammatory profile. Type 1 inflammation is mediated by tumor necrosis factor α (TNF-α) and interferon-gamma, and is characterized by the predominance of neutrophils. Type 2 inflammation is observed

in over 80% of the Western population and is associated with eosinophilic infiltration in the sinonasal mucosa[1] and increased production of cytokines such as interleukin (IL)-4, IL-5, and IL-13[1]. Type 2 profile demonstrates the best response to dupilumab, an inhibitor of IL-4 and IL-13. In addition to these two profiles, mixed inflammatory patterns, characterized by the presence of both eosinophils and neutrophils in varying proportions have been described[1]. In such cases, the role of neutrophilic infiltration in the pathogenesis of CRSwNP is not fully understood. An emerging hypothesis suggests that neutrophilic infiltration may be associated with chronicity[2,3] and reduced responsiveness to biological therapeutic agents, such as dupilumab[4]. Considering the potential association between the presence of neutrophils and reduced treatment response to dupilumab, detailed characterization of the inflammatory infiltrate in CRSwNP is essential, particularly tissue neutrophilia. This study aimed to evaluate the effects of the tissue neutrophil count on resistance to dupilumab in patients with severe and uncontrolled CRSwNP, in addition to determining whether greater neutrophilic infiltration is associated with a poorer therapeutic response and higher resistance to dupilumab.

Materials and methods

This retrospective study included 23 patients over 18 years of age with severe, uncontrolled CRSwNP. Diagnosis was based on clinical criteria, including nasal obstruction, anterior and/or posterior rhinorrhea, and/or facial pressure lasting for more than 12 weeks, and either endoscopic evidence of nasal polyposis or imaging confirmation, according to the international guidelines.

All included patients presented with persistent symptoms despite prior medical and surgical treatment and met the formal indications for dupilumab therapy as defined by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) and European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) criteria. The criteria included at least three of the following: need for two or more corticosteroid courses in the past year, diagnosis of asthma requiring regular inhaled therapy, evidence of type 2 inflammation (systemic eosinophilia > 150 cells/μL or total systemic immunoglobulin E [IgE] > 100 IU/mL), significant olfactory impairment (hyposmia or anosmia), and substantial impact on the quality of life.

All participants underwent a comprehensive physical examination, including nasal endoscopy with biopsy of nasal polyps and the middle turbinate, which was performed at least one month after the last cycle of systemic corticosteroid therapy. Clinical and laboratory assessments were conducted at baseline and six months after the initiation of dupilumab therapy. The analyzed parameters included eosinophil count, neutrophil count, and total systemic IgE. Tissue parameters were eosinophil and neutrophil density quantified by High Power Field (HPF)[1] examination of the nasal polyp and middle turbinate biopsies, evaluated by a single pathologist to minimize interobserver variability. Additionally, validated subjective and objective instruments were used to assess the symptoms and olfactory function (Table 1).

Statistical analysis was conducted using Python (version 3.12.3) with the packages matplotlib (v3.10.0), openpyxl (v3.2.0), seaborn (v0.3.2), pandas (v2.2.3), and scipy (v1.15.0). A p-value < 0.05 was considered statistically significant.

Table 1
Objective and subjective instruments used to classify olfactory dysfunction

SNOT-22	Sino-Nasal Outcome Test
VASTS	Visual Analog Scale -Total Symptoms
NPS	Nasal Polyp Score
BAST-24	Barcelona Smell Test-24
NCS	Nasal Congestion Score
SLS	Smell Loss Score

Results

The study included 23 patients, with a median age of 57 years (range 32–79 years); 51% (n = 12) were men and 49% (n = 11) were women.

Histopathological analysis revealed a mean tissue neutrophil count of 2 ± 2.3 per HPF (range 0–8 neutrophils per HPF). The mean tissue eosinophil count was 29 ± 34.6 per HPF (range 0–100 eosinophils per HPF).

Correlation analysis demonstrated a statistically significant positive association between tissue neutrophilia and changes in the Smell Loss Score (SLS) over the follow-up period (r = 0.464, p = 0.034) (Figure 1).

Although not statistically significant, positive correlations were observed between tissue neutrophilia and changes in the Nasal Polyp Score (NPS) (r[19] = 0.100, p = 0.666) (Figure 2), Barcelona Smell Test - 24 (BAST-24) (r[19] = 0.116, p = 0.616) (Figure 3), and Visual Analog Scale-Total Symptoms (VASTS) (r = 0.293; p = 0.772) (Figure 4). Negative trends were observed between tissue neutrophilia and changes in the Sino-Nasal Outcome Test (SNOT-22) (r[19] = -0.241, p = 0.292) (Figure 5) and Nasal Congestion Score (NCS) (r[19] = -0.038; p = 0.870) (Figure 6), with no statistical significance.

A statistically significant positive correlation was also found between tissue eosinophilia and neutrophilia (r = 0.595, p = 0.004) (Figure 7), as well as between tissue neutrophilia and systemic total IgE (r = 0.548, p = 0.010) (Figure 8).

Figure 1
Relationship between tissue neutrophils and changes in the Smell Loss Score (SLS)

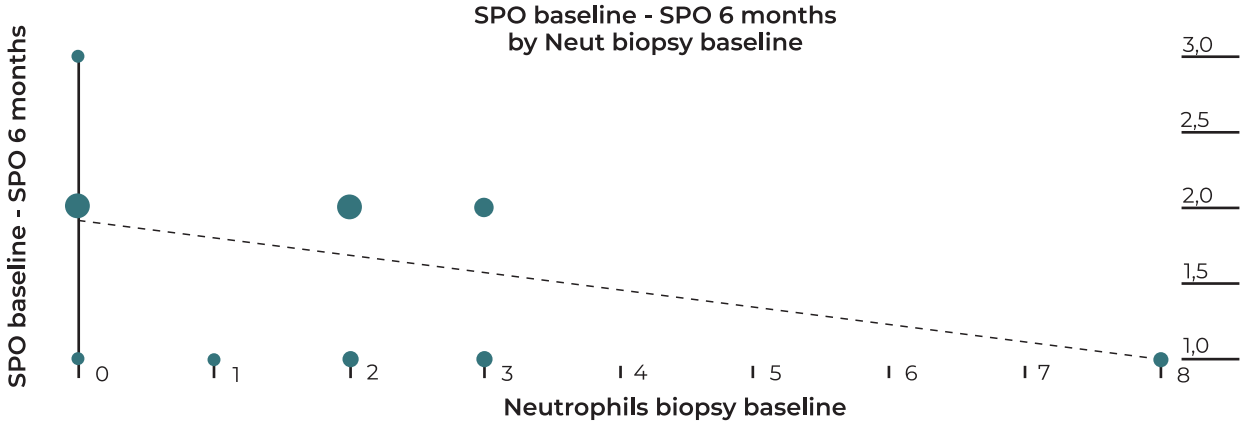


Figure 2
Relationship between tissue neutrophils and changes in the Nasal Polyp Score (NPS)

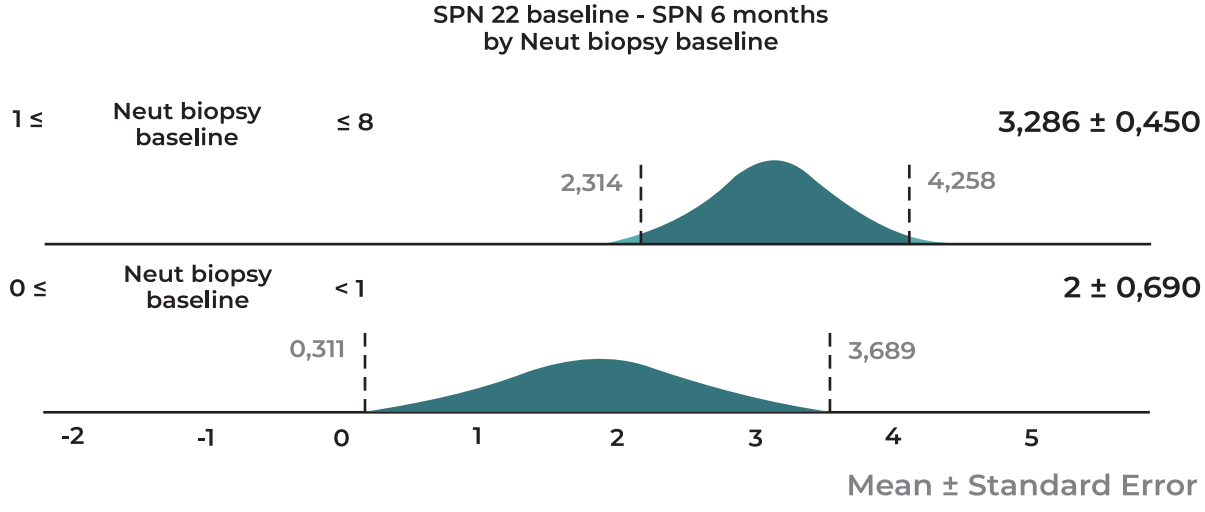


Figure 3
Relationship between tissue neutrophils and changes in the Barcelona Smell Test -24 (BAST-24)

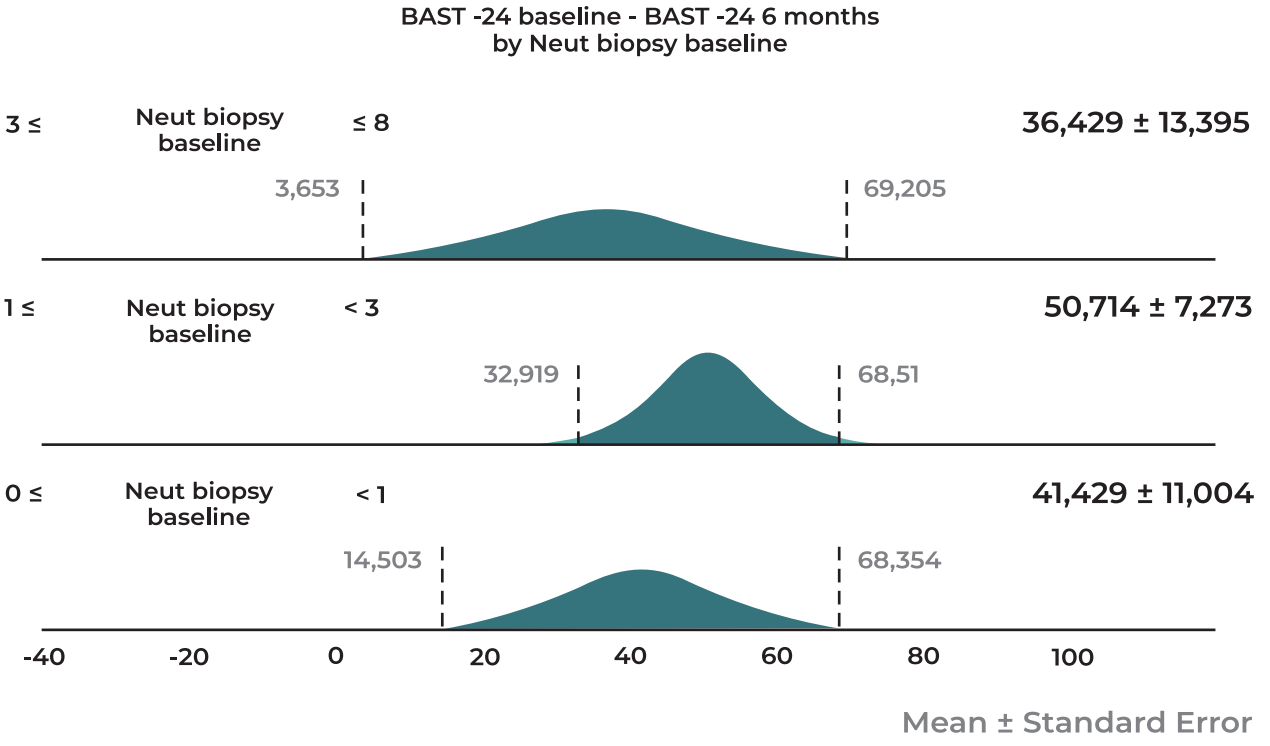


Figure 4
Relationship between tissue neutrophils and changes in the Visual Analog Scale -Total Symptoms (VASTS)

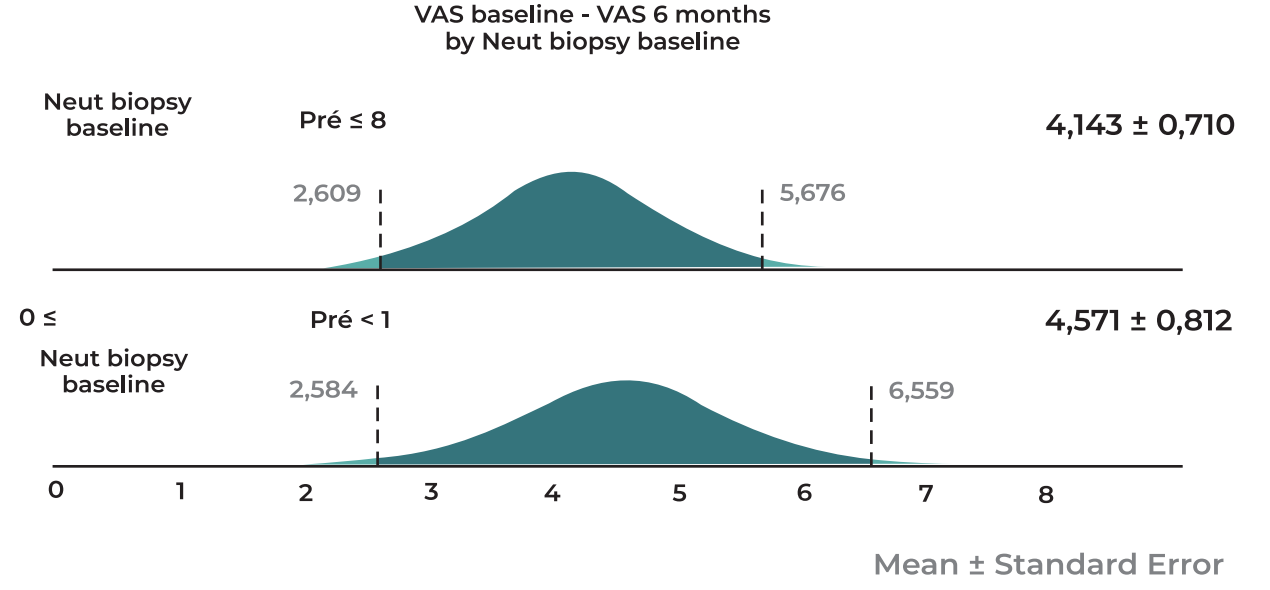


Figure 5
Relationship between tissue neutrophils and changes in the Sino-Nasal Outcome Test (SNOT-22)

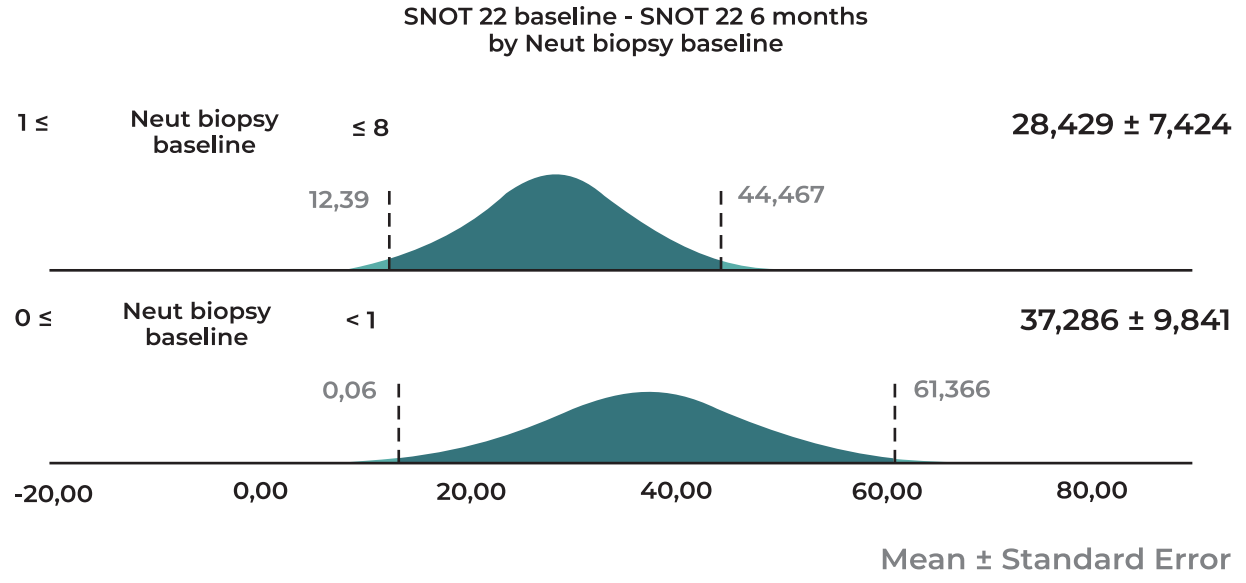


Figure 6
Relationship between tissue neutrophils and changes in the Nasal Congestion Score (NCS)

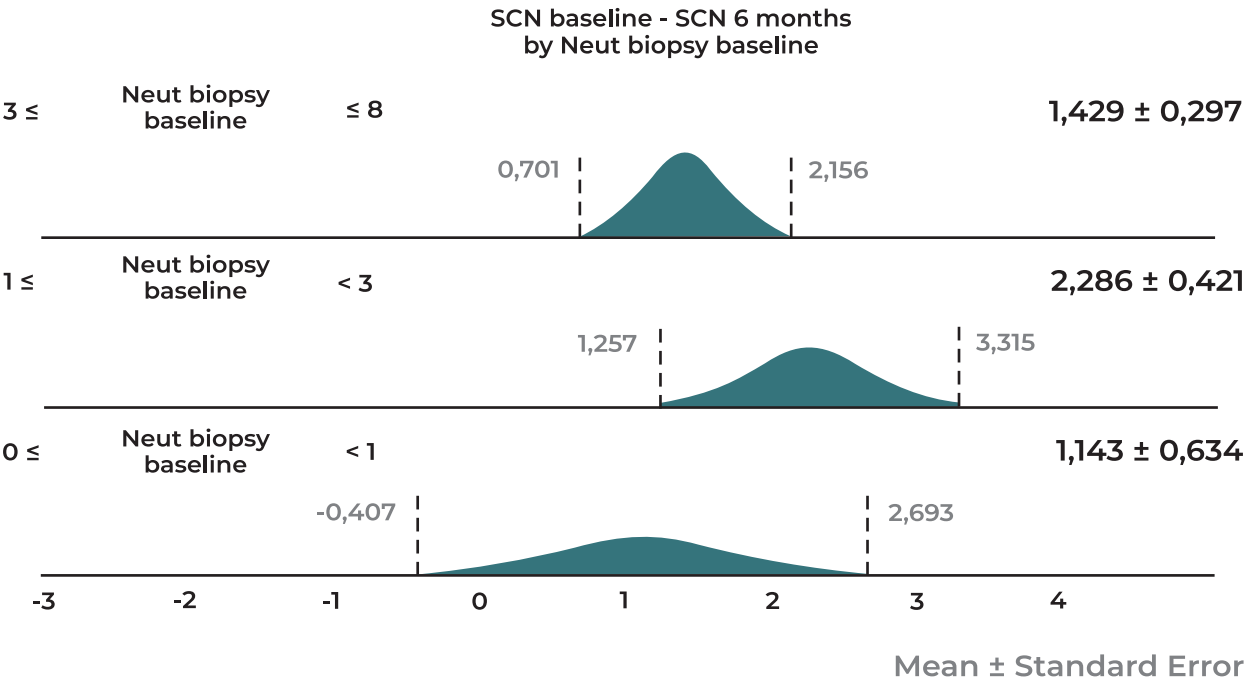


Figure 7
Relationship between tissue neutrophils and eosinophils

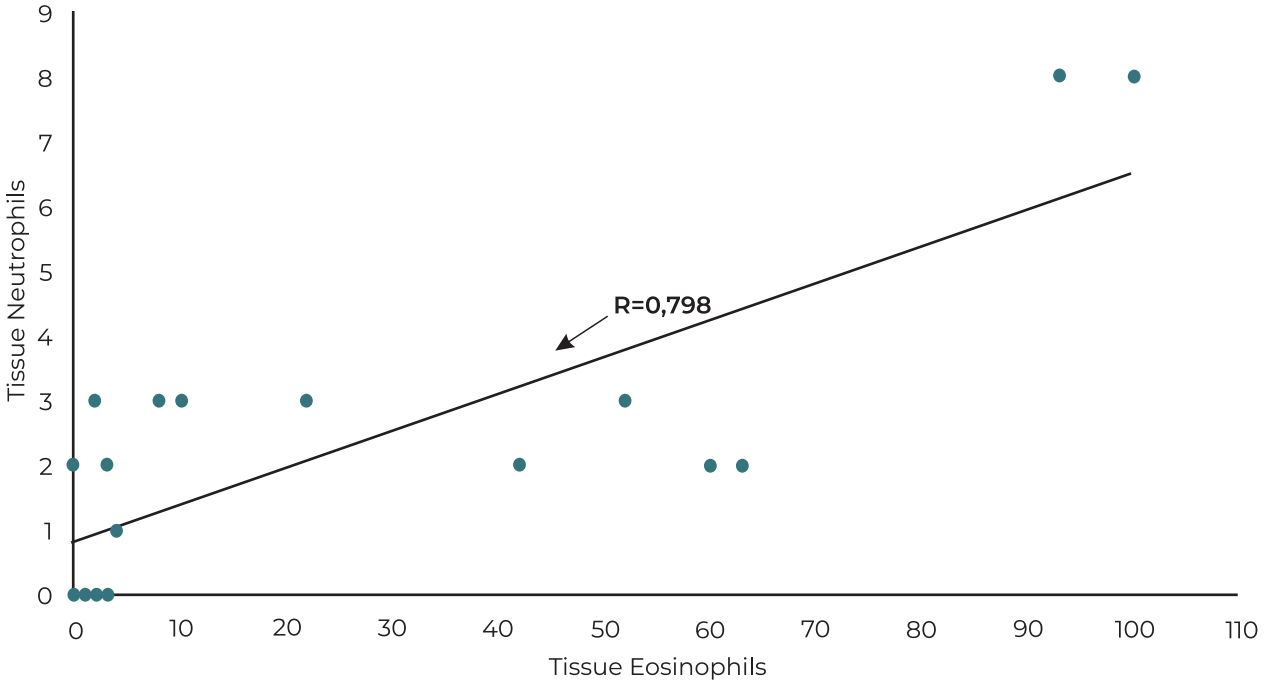
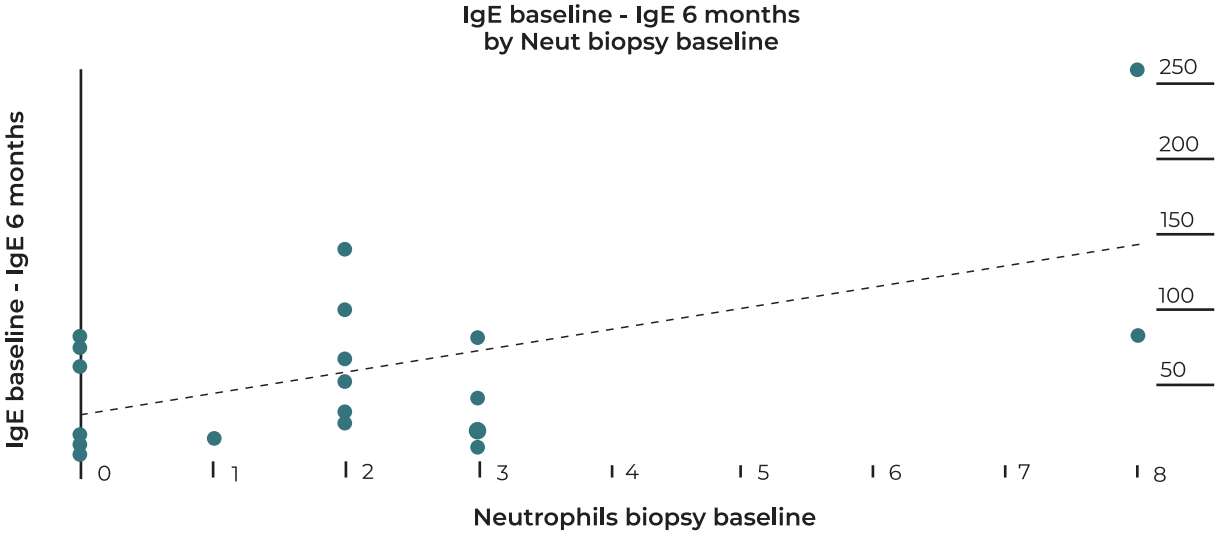


Figure 8
Relationship between tissue neutrophils and changes in total systemic IgE



Discussion

The characterization of inflammatory infiltrates in CRSwNP is increasingly being recognized as a critical factor for guiding individualized treatment strategies. Recent studies have suggested that neutrophilic infiltration may be associated with poor symptom improvement, suboptimal outcomes, and reduced responsiveness to dupilumab therapy. Therefore, this study examined the relationship between tissue neutrophilic and eosinophilic infiltration and the treatment response.

Our findings indicate that neutrophilic infiltration may influence the treatment response. A significantly positive correlation was found between tissue neutrophilia and eosinophilia ($r = 0.595$, $p = 0.004$), supporting

the notion that inflammation in CRSwNP often presents as a mixed pattern, with concomitant neutrophilic and eosinophilic inflammation challenging the traditional dichotomy of type 1 (neutrophilic) versus type 2 (eosinophilic) inflammation. Moreover, the significantly positive association between tissue neutrophilia total systemic IgE ($r = 0.548$, $p = 0.010$) reinforces the hypothesis that multiple immune mediators may contribute to CRSwNP beyond the typical eosinophilic response. Clinically, tissue neutrophilia was significantly associated with variation in SLS ($r = 0.464$, $p = 0.034$), suggesting that patients with higher neutrophilic infiltration may experience less recovery of olfaction after six months of dupilumab therapy. The underlying pathophysiology may reflect a more resistant neutrophil-driven inflammation involved in olfactory neuroepithelium regeneration, particularly driven by the presence of TNF-α, as already suggested in another study[7].

Although other correlations did not reach statistical significance, the observed trends may have clinical relevance. Positive associations of tissue neutrophilia with NPS and BAST-24 may be related to reduced polyp regression and limited improvement of olfactory function. Negative associations with SNOT-22 and NCS raise the hypothesis of a less favorable symptomatic response in patients with higher neutrophilic infiltration. These trends should be interpreted cautiously, as they may become significant in future studies with larger cohorts and greater statistical power.

Conclusion

Nasal biopsy plays an increasingly important role in the evaluation of CRSwNP, as detailed characterization of the inflammatory infiltrate, particularly the distinction between eosinophilic, neutrophilic, and mixed patterns, has become essential due to the advances in biological therapies. This differentiation enables a more personalized therapeutic approach, ultimately improving patient outcomes.

Our findings indicate that tissue neutrophilia may be associated with a reduced response to dupilumab, particularly in terms of olfactory recovery. While dupilumab effectively modulates type 2 inflammation, neutrophilic inflammation could represent a mechanism of therapeutic resistance. Accordingly, detailed characterization of the inflammatory infiltrate in nasal polyps and mucosa may be valuable for predicting the treatment response and identifying patient subgroups that could benefit from alternative or combined therapeutic strategies, thereby facilitating individualized targeted care.

This study has some limitations. Nasal biopsy provides only a localized tissue sample and may not fully capture the heterogeneity of the inflammatory infiltrate across the entire sinonasal mucosa. Additionally, the small sample size limits the generalizability and statistical power of the findings. Prospective studies with larger cohorts are needed to clarify the role of neutrophilia in modulating dupilumab responsiveness and to determine alternative therapeutic approaches. Such efforts may facilitate the identification of predictors of treatment response in patients with mixed or predominantly neutrophilic inflammation, and contribute to the development of more personalized treatment strategies.

Conflict of Interests

The authors declare that they have no conflict of interest regarding this article.

Data Confidentiality

The authors declare that they followed the protocols of their work in publishing patient data.

Human and animal protection

The authors declare that the procedures followed are in accordance with the regulations established by the directors of the Commission for Clinical Research and Ethics and in accordance with the Declaration of Helsinki of the World Medical Association.

Privacy policy, informed consent and Ethics committee authorization

The authors declare that they have obtained signed consent from the participants and that they have local ethical approval to carry out this work.

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Scientific data availability

There are no publicly available datasets related to this work.

References

1. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S. et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600.
2. Xie X, Wang P, Jin M, Wang Y, Qi L, Wu C. et al. IL-1β-induced epithelial cell and fibroblast transdifferentiation promotes neutrophil recruitment in chronic rhinosinusitis with nasal polyps. Nat Commun. 2024 Oct 22;15(1):9101. doi: 10.1038/s41467-024-53307-0.
3. Lin YT, Tsai MH, Su YY, Huang SC. Comparison of cytokine expression and disease severity between plasma cell-dominant and eosinophil-dominant patients in chronic rhinosinusitis with nasal polyps. Allergy Asthma Clin Immunol. 2024 May 21;20(1):34. doi: 10.1186/s13223-024-00896-6.
4. Habenbacher M, Moser U, Abaira A, Kiss P, Holzmeister C, Pock J. et al. Investigation of blood count-based inflammatory biomarkers as predictors of response to dupilumab treatment in patients with chronic rhinosinusitis with nasal polyps. Pharmaceutics. 2024 Oct 25;16(11):1370. doi: 10.3390/pharmaceutics16111370.
5. Delemarre T, Holtappels G, De Ruyck N, Zhang N, Nauwynck H, Bachert C. et al. A substantial neutrophilic inflammation as regular part of severe type 2 chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2021 Jan;147(1):179-188.e2. doi: 10.1016/j.jaci.2020.08.036.
6. Delemarre T, Bachert C. Neutrophilic inflammation in chronic rhinosinusitis. Curr Opin Allergy Clin Immunol. 2023 Feb 1;23(1):14-21. doi: 10.1097/ACI.0000000000000868.
7. Lane AP, Turner J, May L, Reed R. A genetic model of chronic rhinosinusitis-associated olfactory inflammation reveals reversible functional impairment and dramatic neuroepithelial reorganization. J Neurosci. 2010 Feb 10;30(6):2324-9. doi: 10.1523/JNEUROSCI.4507-09.2010.