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Histopathological parameters and immunoexpression of CD45RO (CLA) and CD68 in chronic rhinosinusitis with nasal polyps

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Abstract

Nasal polyps develop as a result of inflammation of the nasal and sinus mucosa. Allergies and nasal infections cause inflammation, and these are the main reasons why these symptoms appear in the first place. This study highlights the involvement of macrophages, as well as T- and B-lymphocytes, in the pathophysiology of nasal polyps. For the evaluation of lymphocyte activity, we analyzed the immunoexpression of cluster of differentiation 45RO [CD45RO; common leukocyte antigen (CLA)] and for macrophages we analyzed the immunoexpression of cluster of differentiation 68 (CD68). Our research, conducted on 110 sinonasal polyps harvested from chronic rhinosinusitis patients with nasal polyps, focused on analyzing both the epithelial and stromal compartments in relation to pre-established composite scores. Additionally, specific histopathological parameters were included in the study. We concluded that the inflammatory cells were more prevalent in the stromal compartment compared to the epithelial compartment. The statistical evaluation of CD45RO (CLA) and CD68 scores in the stromal compartment were also associated with high histological composite scores.

Keywords: nasal polyps, CD45RO, CD68, lymphocytes, macrophages.

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) represents an important clinical entity diagnosed by the presence of both subjective and objective evidence of chronic sinonasal inflammation [1]. Disruption or loss of the immune barrier of the nasal mucosa, often including increased permeability of mucosal epithelium and reduced production of important antimicrobial substances and responses, is a common feature of many forms of CRSwNP [2].

Although eosinophils play a key role, recent studies have shown the importance of other cells and molecules in the development of diseases like mastocytes, basophils, lymphocytes, platelets, neutrophils, macrophages, epithelial respiratory cells [3]. Macrophages seem to participate in creating the immune suppressive microenvironment and so help to sustain local inflammation [4]. The recent knowledge expansion into mechanisms underlying the pathogenesis of chronic rhinosinusitis is leading to a steadily increasing significance of precision medicine in the treatment of CRSwNP [5].

Aim

The objective of this study was to demonstrate the effectiveness of immunohistochemistry in analyzing histopathological (HP) alterations in nasal polyps. Further research into the mechanisms which trigger changes in nasal mucosa may produce a new approach for understanding the cause, prevention, prognosis, and treatment of CRSwNP.

Materials and Methods

The current study design was built upon our previous experience with utilizing biological material consisting of tissue samples obtained through biopsies (endoscopic guided polypectomies). Our study includes 334 patients who were admitted and operated on at the Ear, Nose and Throat (ENT) Department of the Emergency County Clinical Hospital of Craiova, Romania, between the years 2015–2023. The mucosal samples were fixed in 10% neutral buffered formalin and processed using the standard paraffin embedding technique (BioOptica automatic tissue processor), followed by sectioning at 3–5 μm and staining with Hematoxylin–Eosin (HE) using the BioOptica kit.

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Subsequently, we conducted a semi-quantitative evaluation of a series of HP parameters, assigning scores based on data from similar published studies [6–9] (Table 1).

Table 1 – *The scores given to the investigated histopathological parameters*

Parameters	Score			
	0	***1***	***2***	***3***
Basal membrane thickening	<9 µm	10–19 µm	20–29 µm	≥30 µm
Goblet cell hyperplasia	<3 cells	3–10 cells	11–20 cells	>20 cells
Epithelial infiltration with eosinophils	0 cells	1–2 cells	3–10 cells	≥11 cells
Basal layer hyperplasia	Absent	Focal	Zonal	Diffuse
Squamous metaplasia	Absent	Focal	Zonal	Diffuse
Stromal edema	Absent	Focal	Zonal	Diffuse
Epithelial alteration	Absent	Partial denudation	Complete denudation	–
Stromal infiltration with eosinophils	0 cells	1–3 cells	4–15 cells	>15 cells
Stromal infiltration with lymphocytes	<10 cells	11–30 cells	31–50 cells	>50 cells
Stromal infiltration with plasmocytes	<10 cells	11–30 cells	31–50 cells	>50 cells
Stromal infiltration with macrophages	0 cells	1–2 cells	3–9 cells	≥10 cells

For each case, we calculated the composite histological score (CHS) by summing the scores assigned to various parameters, with the resulting values ranging between 0 and 32. We classified a CHS below 11 as low, and a CHS above 11 as high.

The immunohistochemical (IHC) study was conducted on 110 cases selected from the 334 histopathologically investigated cases. This study utilized enzymatic detection, specifically employing the Labelled Streptavidin–Biotin 2–Horseradish Peroxidase (LSAB2–HRP) System (Dako, code K0675). The results of the IHC reactions were visualized microscopically through the brown staining of the targeted antigens using 3,3'-Diaminobenzidine (DAB) chromogen (Dako, code 3467). Sections obtained from IHC processing were examined under a Panthera L binocular microscope equipped with a digital camera. For each antibody, both external positive and negative controls were performed using the same IHC technique. The antibodies used in the study, along with their clone and source, dilution, unmasking method, and tissue used for external control, are detailed in Table 2.

Table 2 – *Panel with antibodies used in the immuno-histochemical study*

Antibody	Clone / Manufacturer	Dilution	Antigen retrieval buffers	External control
CD45RO (CLA)	UCHL1/Dako	1:75	Citrate, pH 6	Tonsil
CD68	KP1/Dako	1:75	Tris-EDTA, pH 9	Lymph node

CD: Cluster of differentiation; CLA: Common leukocyte antigen; EDTA: Ethylenediaminetetraacetic acid.

For the semi-quantitative assessment of the analyzed markers, we employed a scoring system based on our previous research experience in immunohistochemistry [10–13] and earlier published scientific data from the same field of interest [14–17]. The data included focused on the number of immunolabeled cells:

• For cluster of differentiation 45RO [CD45RO; common leukocyte antigen (CLA)] lymphocytes: epithelial 0 (0 cells), 1 (1–2 cells), 2 (3–5 cells), 3 (>5 cells) and stromal 0 (0 cells), 1 (<10 cells), 2 (10–20 cells), 3 (>20 cells);

• For cluster of differentiation 68 (CD68) macrophages: epithelial 0 (0 cells), 1 (1–2 cells), 2 (3–5 cells), 3 (>5 cells) and stromal 0 (0 cells), 1 (1–2 cells), 2 (3–10 cells), 3 (>10 cells).

Results

We analyzed using IHC a number of 110 allergic sinonasal polyps obtaining 26 (23.6%) cases with high values (high CHS – HCHS) and 84 (76.4%) cases with low values (low CHS – LCHS).

Quantification of CD45RO (CLA)- and CD68-positive cells indicated different values of high and low CHS score specimens, both at the epithelial and stromal levels (Table 3).

Table 3 – *Distribution of the immunomarkers expression in relation to the CHS values*

Immunomarker / CHS		Epithelial				Stromal			
		0	***1***	***2***	***3***	***0***	***1***	***2***	***3***
CD45RO (CLA)	*LCHS*	73	11	0	0	7	46	31	0
	HCHS	7	15	2	2	4	7	11	4
CD68	*LCHS*	73	9	0	2	53	20	11	0
	HCHS	18	4	2	2	9	11	4	2

CD: Cluster of differentiation; CHS: Composite histological score; CLA: Common leukocyte antigen; HCHS: High CHS; LCHS: Low CHS.

CD45RO (CLA) immunoexpression

Analysis of CD45RO (CLA) immunoexpression in all 110 cases indicated cytoplasmic positivity at the epithelial level in 31 (28%) of these cases, while the marker was identified at the stromal level in 99 (90%) cases. For the entire analyzed batch, at the epithelial level the positive cases presented a number of 2–7 marked cells, with an average number of 2.5±1.5 and an average score of 1.2. At the epithelial level, positivity for CD45RO in cases with LCHS was identified in only 11 cases, with an average of two cells/×100 (no variation) (Figure 1A). For cases with HCHS, we found positivity for CD45RO in 20 cases, of which 15 cases with an average of two cells/×100 (without variations) and four cases with an average of six cells/×100 (with variation between 5–7 cells /×100) (Figure 1B).

In cases with stromal positivity, the number of labeled cells ranged from 4–45, with a mean number of 11.3±7.7 and a mean score of 1.5.

In the stromal compartment, in cases with LCHS, we observed positivity for CD45RO in 77 of the investigated cases, of which in 46 cases with an average of 6.8±1.6 cells/×100 (with variation between 1–9 cells/×100), in 31 cases with an average of 13.4±3.2 cells/×100 (with variation between 10–18 cells/×100) (Figure 1C).

For the cases with HCHS, we identified positivity in 22 of the analyzed cases, of which in seven cases with an average of 5.6±1.1 cells/×100 (with variation between 5–7 cells/×100), 11 cases with an average of 16.4±2.1 cells/×100 (with variation between 15–20 cells/×100) and in four cases with an average of 40 cells/×100 (with 35 and 45 cells/×100, respectively) (Figure 1D).

Statistical analysis of CD45RO immunoexpression

indicated the presence of increased scores of the marker at the epithelial level with high values of SHC, although the differences were not statistically significant (χ^2 test, p=0.523) (Figure 1E). Regarding the statistical analysis of CD45RO scores at the stromal level, we found that high values were associated with HCHS, while for LCHS cases, low CD45RO scores predominated, aspects that were statistically significant (χ^2 test, p=0.014) (Figure 1F).

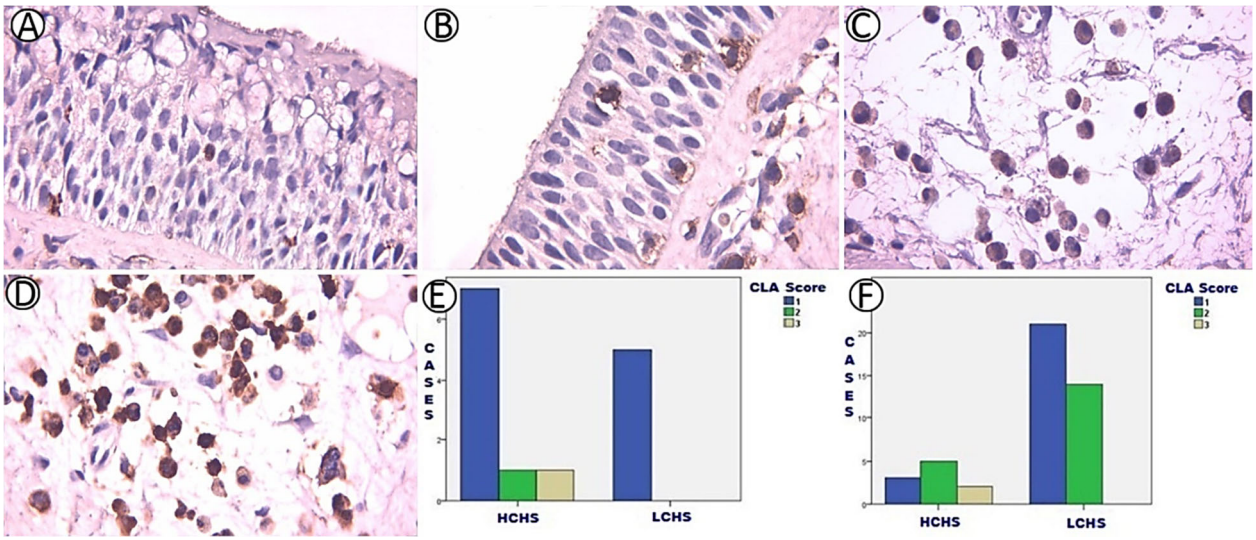

Figure 1 – ***(A) LCHS polyp; (B) HCHS polyp; (C) LCHS polyp; (D) HCHS polyp; (E) Distribution of cases in relation to CD45RO and CHSs in epithelial compartment; (F) Distribution of cases in relation to CD45RO and CHSs in stromal compartment. CD45RO epithelial immunoexpression: (A and B) ×100. CD45RO stromal immunoexpression: (C and D) ×100. CD45RO: Cluster of differentiation 45RO; CHS: Composite histological score; CLA: Common leukocyte antigen; HCHS: High CHS; LCHS: Low CHS.***

CD68 immunoexpression

Analysis of CD68 immunoexpression indicated cytoplasmic positivity at the epithelial level in 20 (18%) cases and at the stromal level in 48 (44%) cases.

In the epithelial compartment, for the entire group, the number of CD68-positive cells was between 1 and 7, with a mean value of 3±2.5 and a mean score of 1.5. We found that, at the epithelial level, CD68 positivity for cases with LCHS was present in 11 of the investigated cases, nine cases with an average of 1.2±0.5 cells/×100 (with variation between 1–2 cells/×100) and two cases with seven cells/×100 (Figure 2A). For cases with HCHS, we found CD68 positivity in nine cases, of which four cases averaged 1.5 cells/×400 (with variation between 1–2 cells/×100), two cases with five cells/×400 and two cases with seven cells/×400 (Figure 2B).

The number of stromal CD68-positive cells for the analyzed cases ranged from 1–12, with a mean value of 3±2.5 and a mean score of 1.4.

In the stromal compartment, in the cases with LCHS, we observed positivity in 31 of the investigated cases, of which in 20 cases, with an average of 1.5±0.5 cells/×100 (with variation between 1–2 cells/×100) and in 11 cases with an average of 4.8±0.8 cells/×100 (with variation between 4–6 cells/×100) (Figure 2C). For the cases with HCHS, we found positivity in 18 analyzed cases, of which in 11 cases with an average of 1.6±0.5 cells/×100 (with variation between 1–2 cells/×100), four cases with an average of 4.5 cells/×100 (with variation between 4–5 cells/×100) and two cases single case with 12 cells/×100 (Figure 2D).

Analysis of CD68 scores at the epithelial compartment indicated insignificant differences in relation to CHS values (χ^2 test, p=0.455) (Figure 2E).

The aspect was also observed at the stromal compartment, where although high scores (score 2 and 3) predominated in HCHS, low CD68 scores were common for both types of CHS (χ^2 test, p=0.380) (Figure 2F).

Discussions

The pathophysiology of CRSwNP is not fully understood and this delays the development of targeted drugs. It is believed that the formation of polyps is initiated by an epithelial injury, which occurs within the context of chronic local inflammation that may sustain itself indefinitely. Various local and systemic factors may contribute to this inflammatory process [18]. The current therapeutic approaches for managing CRSwNP are still being debated and are not curative [19]. When attempting to elucidate the pathogenesis of nasal polyposis, it is important to recognize that this area is continuously evolving. Currently, there is no well-defined pathway that fully explains the progression from initial lesion to tissue transformation. Present understanding revolves around identifying and clarifying the different inflammatory mediators and pathways involved. CRSwNP involves a complex interplay of various immune cells beyond lymphocytes, contributing significantly to the self-sustaining inflammatory process. Understanding these cellular dynamics is crucial for developing targeted therapies. Eosinophils are traditionally viewed as central to CRSwNP, but recent studies suggest their role may be less critical than previously understood. Eosinophil depletion did not significantly reduce polyp size or improve clinical outcomes, indicating a potential shift in focus towards other immune cells [20]. There is emerging evidence that points to B-lymphocytes as significant players in CRSwNP. Their dysfunction may contribute to disease pathogenesis, and targeting B-cells could offer new therapeutic strategies [21, 22]. Mastocytes and basophils are

activated by type 2 cytokines [interleukin (IL)-4, IL-13] and contribute to the inflammatory habitat, promoting mucus hyperproduction and tissue remodeling [22, 23]. Lastly, increased numbers of goblet cells lead to mucus overproduction, exacerbating nasal obstruction and inflammation [22]. In summary, while lymphocytes are crucial, eosinophils, B-cells, mastocytes, and goblet cells also play vital roles in the inflammatory landscape of CRSwNP, suggesting a multifaceted approach to treatment may be necessary.

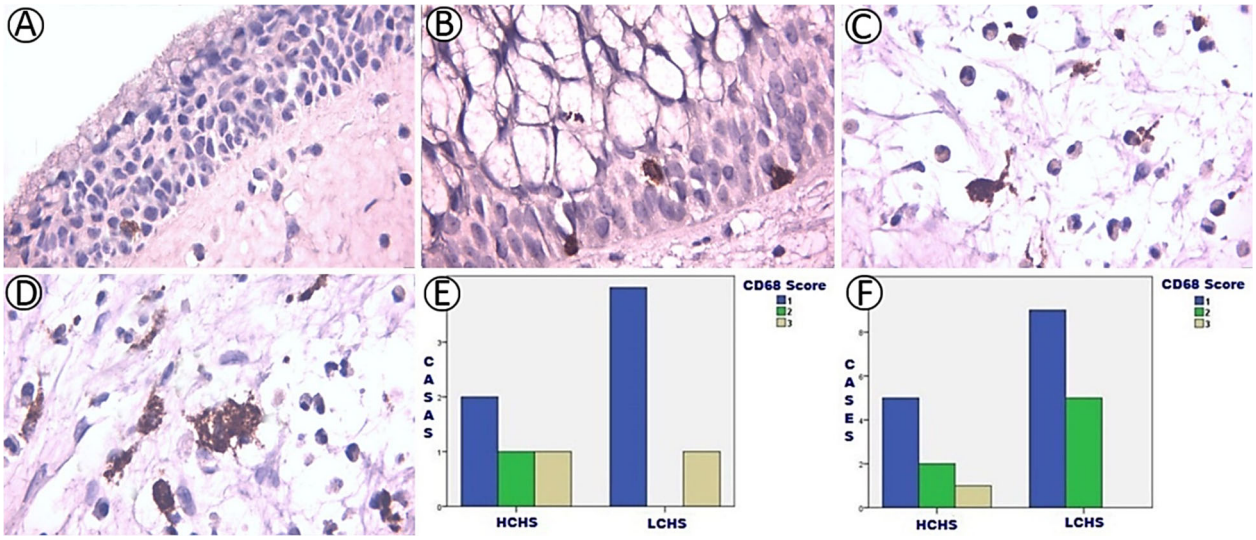

Figure 2 – ***(A) LCHS polyp; (B) HCHS polyp; (C) LCHS polyp; (D) HCHS polyp; (E) Distribution of cases in relation to CD68 and CHSs in epithelial compartment; (F) Distribution of cases in relation to CD68 and CHSs in stromal compartment. CD68 epithelial immunoexpression: (A and B) ×100. CD68 stromal immunoexpression: (C and D) ×100. CD68: Cluster of differentiation 68; CHS: Composite histological score; HCHS: High CHS; LCHS: Low CHS.***

Lymphocytes are a major component of the cellular population found in nasal polyps, which suggests their potential involvement in the chronic inflammation associated with lesions. While several IHC studies [24, 25] have examined the inflammatory cell population within nasal polyps, a comprehensive analysis of the lymphocytic infiltrate has yet to be conducted. The correlation between HP findings and clinical symptoms was explored, and it was concluded that specific HP parameters in CRSwNP are associated with certain symptoms. Particular HP and immune changes like the 'superantigen response' determined by the interaction of bacterial enterotoxins and B-cells can predict the persistence of symptoms even after endoscopic sinus surgery [26].

The correlation between CD45RO (CLA) and CD68 immunoexpression levels with disease severity in CRSwNP is an emerging area of research [27]. Several studies have explored various biomarkers and their relationship with disease severity, providing insights into the inflammatory processes involved. While specific studies on CD45RO and CD68 were not highlighted, the general trend indicates that inflammatory markers, including IL-5 and calprotectin, are significantly elevated in patients with uncontrolled CRSwNP, suggesting a link to disease severity [26, 27]. Research indicates that levels of leukotrienes and prostaglandins in nasal secretions correlate with nasal polyp severity, which may indirectly relate to CD68 expression as a marker of macrophage activity in inflammation [28]. The identification of various biomarkers, including IL-5 and eosinophils, has been shown to differentiate between CRSwNP phenotypes, suggesting that CD45RO and CD68 could serve similar roles in assessing disease severity [29]. In this way, these two immunomarkers may prove linked to disease severity.

In our study, we observed cytoplasmic immunoexpression of CD45RO (CLA). CD45RO immunolabeling enabled the quantification of T- and B-lymphocytes, revealing their presence at both the epithelial (28%) and stromal (90%) levels. High CD45RO scores were significantly associated with HCHS values, particularly at the stromal level.

The presence of a high number of CD68+ histiocytic macrophages, primarily located in the deep layers of the *lamina propria*, may be responsible for the phagocytosis of eosinophils within polyp tissue. Consequently, it may be inferred that the increased macrophages in nasal polyps do not stimulate the growth of polyps. Instead, they may contribute to reducing eosinophil numbers in already-formed nasal polyps [30].

Nasal polyps are characterized not only by eosinophilia but also by a predominance of lymphocytes, particularly those expressing CD45RO and CD68. CD68 may be a stem cell marker for nasal polyps. CD68+ cells were more prominently expressed in nasal polyps with eosinophil predominance compared to those dominated by neutrophils [31]. The macrophage mannose receptor (MMR), an innate pattern-recognizing receptor capable of phagocytosing invaders and mediating signal transduction for proinflammatory mechanisms, might play a crucial role in immune interactions in chronic sinus disease [32].

In our study, we observed cytoplasmic CD68 immunoexpression in both epithelial (18%) and stromal (44%) compartments. However, we did not find significant correlations between CHS and CD68 scores, though high CD68 scores were more common in cases of HCHS at the stromal level.

Although an increased accumulation of M2 macrophages has been noted in CRSwNP, especially in the eosinophilic type, their functional significance in CRSwNP remains

poorly understood. The total number of macrophages is reduced in eosinophilic polyps, despite the upregulation of M2 macrophages in these types of polyps [33].

To sum up, while direct evidence linking CD45RO and CD68 to CRSwNP severity is limited, the broader context of inflammatory biomarkers suggests a potential correlation that warrants further investigation. The goal of research in this particular area is to perfect existing medications which show promise in modulating the immunoexpression of CD45RO and CD68 in CRSwNP [34, 35]. These medications target specific inflammatory pathways, potentially altering the expression of these immune markers. The therapeutic implications of these findings suggest a shift towards more personalized treatment strategies for CRSwNP, especially in patients who do not respond to conventional therapies.

Conclusions

While eosinophils have traditionally been considered the primary culprits in the onset of the disease, our study demonstrates, using HP and IHC techniques, that other cells such as lymphocytes and macrophages also play a significant role in the pathology of nasal polyposis.

HP findings underscore the severity of this condition, while IHC provides further insight into the underlying pathophysiological mechanisms. We observed a higher concentration of inflammatory cells in the stromal compartment compared to the epithelial compartment.

Statistical analysis revealed that higher scores for CD45RO (CLA) and CD68 in the stromal compartment were correlated with elevated CHS. The application of IHC can aid in the development of targeted therapeutic protocols for CRSwNP, a condition that profoundly impacts both physical and mental health, especially given the recurrent nature of nasal polyps. Patients with CRSwNP are currently screened for relapse of mucosal degeneration and polyp formation, and, by utilizing this technique, it becomes possible to anticipate the progression of the disease, even in patients currently undergoing treatment.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol Pract, 2016, 4(4): 565–572. https://doi.org/10.1016/j.jaip.2016.04.012 PMID: 27393770 PMCID: PMC4939220

[2] Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. Annu Rev Pathol, 2017, 12:331–357. https://doi.org/10.1146/annurev-pathol-052016-100401 PMID: 27959637 PMCID: PMC5514544

[3] Rodríguez-Jiménez JC, Moreno-Paz FJ, Terán LM, Guaní-Guerra E. Aspirin exacerbated respiratory disease: current topics and trends. Respir Med, 2018, 135:62–75. https://doi.org/10.1016/j.rmed.2018.01.002 PMID: 29414455

[4] Dutsch-Wicherek M, Tomaszewska R, Lazar A, Strek P, Wicherek Ł, Piekutowski K, Jóźwicki W. The evaluation of metallothionein expression in nasal polyps with respect to immune cell presence and activity. BMC Immunol, 2010, 11:10. https://doi.org/10.1186/1471-2172-11-10 PMID: 20214821 PMCID: PMC2848203

[5] Czerwaty K, Piszczatowska K, Brzost J, Ludwig N, Szczepański MJ, Dżaman K. Immunological aspects of chronic rhinosinusitis. Diagnostics (Basel), 2022, 12(10):2361. https://doi.org/10.3390/diagnostics12102361 PMID: 36292050 PMCID: PMC9600442

[6] Ardehali MM, Amali A, Bakhshaee M, Madani Z, Amiri M. The comparison of histopathological characteristics of polyps in asthmatic and nonasthmatic patients. Otolaryngol Head Neck Surg, 2009, 140(5):748–751. https://doi.org/10.1016/j.otohns.2009.01.027 PMID: 19393423

[7] Dhong HJ, Kim HY, Cho DY. Histopathologic characteristics of chronic sinusitis with bronchial asthma. Acta Otolaryngol, 2005, 125(2):169–176. https://doi.org/10.1080/00016480410015767 PMID: 15880948

[8] Altın Kule Z, Deveci HS, Kule M, Erden Habeşoğlu T, Somay A, Gürsel AO. The correlation of clinical measures with the histopathological findings in nasal polyposis. ENT Updates, 2015, 5(1):1–8. https://doi.org/10.2399/jmu.2015001002

[9] Takabayashi T, Kato A, Peters AT, Suh LA, Carter R, Norton J, Grammer LC, Tan BK, Chandra RK, Conley DB, Kern RC, Fujieda S, Schleimer RP. Glandular mast cells with distinct phenotype are highly elevated in chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol, 2012, 130(2):410–420.e5. https://doi.org/10.1016/j.jaci.2012.02.046 PMID: 22534535 PMCID: PMC3408832

[10] Mîndrilă I, Osman A, Mîndrilă B, Predoi MC, Mihaiescu DE, Buteică SA. Phenotypic switching of B16F10 melanoma cells as a stress adaptation response to Fe_3O_4/salicylic acid nanoparticle therapy. Pharmaceuticals (Basel), 2021, 14(10):1007. https://doi.org/10.3390/ph14101007 PMID: 34681232 PMCID: PMC8537856

[11] Enache I, Ioniţă E, Anghelina F, Mogoantă CA, Ciolofan MS, Căpitănescu AN, Vîlcea AM, Florescu AM, Simionescu CE. Involvement of inflammatory cells in chronic rhinosinusitis with nasal polyps. Rom J Morphol Embryol, 2020, 61(3):871–877. https://doi.org/10.47162/RJME.61.3.25 PMID: 33817728 PMCID: PMC8112756

[12] Ciolofan MS, Ioniţă E, Ioniţă I, Mogoantă CA, Anghelina F, Enescu AŞ, Ciobîrcă DM, Osman A, Foarfă MC, Mateescu GO. Chondrosarcoma of the hyoid bone: a case report. Rom J Morphol Embryol, 2015, 56(2 Suppl):811–816. PMID: 26429177

[13] Enache I, Ioniţă E, Mitroi M, Anghelina F, Mogoantă C, Ciolofan S, Căpitănescu A, Stepan A, Simionescu C. Histopathological features of chronic rhinosinusitis with nasal allergic polyps. Curr Health Sci J, 2020, 46(1):66–71. https://doi.org/10.12865/CHSJ.46.01.09 PMID: 32637167 PMCID: PMC7323723

[14] Zhu H, Sun N, Wang Y, Zhu H, Cai X, Li X. Inflammatory infiltration and tissue remodeling in nasal polyps and adjacent mucosa of unaffected sinus. Int J Clin Exp Pathol, 2018, 11(5):2707–2713. PMID: 31938386 PMCID: PMC6958245

[15] Schraven SP, Wehrmann M, Wagner W, Blumenstock G, Koitschev A. Prevalence and histopathology of chronic polypoid sinusitis in pediatric patients with cystic fibrosis. J Cyst Fibros, 2011, 10(3):181–186. https://doi.org/10.1016/j.jcf.2011.01.003 PMID: 21296035

[16] Putu Lusy Indrawati L, Arfiana Nurul Fatimah V, Sianipar O. Conference Paper: Representation of lymphocytes in sinonasal tissue of chronic rhinosinusitis patients. The UGM Annual Scientific Conference Life Sciences 2016, KnE Life Sci, 2019, 4(11):109–121. https://doi.org/10.18502/kls.v4i11.3857

[17] Hulse KE, Stevens WW, Tan BK, Schleimer RP. Pathogenesis of nasal polyposis. Clin Exp Allergy, 2015, 45(2):328–346. https://doi.org/10.1111/cea.12472 PMID: 25482020 PMCID: PMC4422388

[18] Bartier S, Coste A, Bequignon E. Stratégies de prise en charge de la polypose naso-sinusienne primitive de l'adulte [Management strategies for chronic rhinosinusitis with nasal polyps in adults]. Rev Mal Respir, 2021, 38(2):183–198. https://doi.org/10.1016/j.rmr.2020.10.004 PMID: 33541753

[19] Ta NH. Will we ever cure nasal polyps? Ann R Coll Surg Engl, 2019, 101(1):35–39. https://doi.org/10.1308/rcsann.2018.0149 PMID: 30286644 PMCID: PMC6303820

[20] Kariyawasam HH, James LK. Chronic rhinosinusitis with nasal polyps: eosinophils *versus* B lymphocytes in disease pathogenesis. Curr Opin Allergy Clin Immunol, 2024, 24(1): 15–24. https://doi.org/10.1097/ACI.0000000000000959 PMID: 38018818

[21] Xu Z, Huang Y, Meese T, Van Nevel S, Holtappels G, Vanhee S, Bröker BM, Li Z, de Meester E, De Ruyck N, Van Zele T, Gevaert P, Van Nieuwerburgh F, Zhang L, Shamji MH, Wen W, Zhang N, Bachert C. The multi-omics single-cell landscape of sinus mucosa in uncontrolled severe chronic rhinosinusitis with nasal polyps. Clin Immunol, 2023, 256:109791. https://doi.org/10.1016/j.clim.2023.109791 PMID: 37769787

[22] Bachert C, Hicks A, Gane S, Peters AT, Gevaert P, Nash S, Horowitz JE, Sacks H, Jacob-Nara JA. The interleukin-4/interleukin-13 pathway in type 2 inflammation in chronic rhinosinusitis with nasal polyps. Front Immunol, 2024, 15: 1356298. https://doi.org/10.3389/fimmu.2024.1356298 PMID: 38690264 PMCID: PMC11059040
[23] Wynne M, Atkinson C, Schlosser RJ, Mulligan JK. Contribution of epithelial cell dysfunction to the pathogenesis of chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy, 2019, 33(6):782–790. https://doi.org/10.1177/1945892419868588 PMID: 31382760 PMCID: PMC6843741
[24] Linder A, Karlsson-Parra A, Hirvelä C, Jonsson L, Köling A, Sjöberg O. Immunocompetent cells in human nasal polyps and normal mucosa. Rhinology, 1993, 31(3):125–129. PMID: 8256081
[25] Liu CM, Shun CT, Hsu MM. Lymphocyte subsets and antigen-specific IgE antibody in nasal polyps. Ann Allergy, 1994, 72(1): 19–24. PMID: 8291744
[26] Van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: inflammation. J Allergy Clin Immunol, 2011, 128(4):728–732. https://doi.org/10.1016/j.jaci.2011.07.049 PMID: 21868076
[27] De Corso E, Baroni S, Settimi S, Onori ME, di Cesare T, Mastrapasqua RF, Sarlo F, Penazzi D, D'Agostino G, D'Auria LM, De Maio G, Fetoni AR, Galli J. Correlation between inflammatory biomarkers and disease control in chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol, 2024, 14(7):1195–1205. https://doi.org/10.1002/alr.23319 PMID: 38266634
[28] Gelardi M, Bocciolini C, Notargiacomo M, Schiavetti I, Lingua C, Pecoraro P, Iannuzzi L, Quaranta VA, Giancaspro R, Ronca G, Cassano M, Ciprandi G; Italian Study Group on Nasal Polyps. Chronic rhinosinusitis with nasal polyps: how to identify eligible patients for biologics in clinical practice. Acta Otorhinolaryngol Ital, 2022, 42(1):75–81. https://doi.org/10.14639/0392-100X-N1699 PMID: 35292789 PMCID: PMC9058935
[29] Gokani SA, Espehana A, Pratas AC, Luke L, Sharma E, Mattock J, Gavrilovic J, Clark A, Wileman T, Philpott CM. Systematic review of protein biomarkers in adult patients with chronic rhinosinusitis. Am J Rhinol Allergy, 2023, 37(6):705–729. https://doi.org/10.1177/19458924231190568 PMID: 37491901 PMCID: PMC10548774
[30] Bayar Muluk N, Arikan OK, Atasoy P, Kiliç R, Tuna Yalçinozan E. The role of CD68 (+) histiocytic macrophages in nasal polyp development. J Neurol Surg B Skull Base, 2020, 82(6):700–708. https://doi.org/10.1055/s-0040-1715593 PMID: 34745840 PMCID: PMC8563265
[31] Wu X, Wang LF, Zang YH. [Expression of CD68 CD45RO CD20 and proliferating cell nuclear antigen in nasal polyps]. Zhonghua Er Bi Yan Hou Ke Za Zhi, 2003, 38(3):187–190. PMID: 14515776
[32] Claeys S, De Belder T, Holtappels G, Gevaert P, Verhasselt B, Van Cauwenberge P, Bachert C. Macrophage mannose receptor in chronic sinus disease. Allergy, 2004, 59(6):606–612. https://doi.org/10.1111/j.1398-9995.2004.00471.x PMID: 15147445
[33] Wang ZC, Yao Y, Wang N, Liu JX, Ma J, Chen CL, Deng YK, Wang MC, Liu Y, Zhang XH, Liu Z. Deficiency in interleukin-10 production by M2 macrophages in eosinophilic chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol, 2018, 8(11):1323–1333. https://doi.org/10.1002/alr.22218 PMID: 30281939
[34] Bequignon E, Mangin D, Bécaud J, Pasquier J, Angely C, Bottier M, Escudier E, Isabey D, Filoche M, Louis B, Papon JF, Coste A. Pathogenesis of chronic rhinosinusitis with nasal polyps: role of IL-6 in airway epithelial cell dysfunction. J Transl Med, 2020, 18(1):136. https://doi.org/10.1186/s12967-020-02309-9 PMID: 32209102 PMCID: PMC7092549
[35] Shishodia S, Haloob N, Hopkins C. Antibody-based therapeutics for chronic rhinosinusitis with nasal polyps. Expert Opin Biol Ther, 2024, 24(6):491–502. https://doi.org/10.1080/14712598.2024.2370397 PMID: 38900023

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