Rom J Morphol Embryol 2026, 67(2):317–319 ISSN (print) 1220–0522, ISSN (online) 2066–8279 doi: 10.47162/RJME.67.2.13

LETTER TO THE EDITOR

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Integrating histological, cytological and clinical assessment in CRSwNP: a complementary perspective on CHS and CCG

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To the Editor,

We read with great interest the article by Enache *et al.* on histopathological parameters and cluster of differentiation (CD)45RO and CD68 immunoexpression in chronic rhinosinusitis with nasal polyps (CRSwNP) [1]. The study provides a detailed tissue-based assessment of inflammatory and remodeling features and applies a composite histological score (CHS) derived from basal membrane thickening, goblet cell hyperplasia, epithelial and stromal eosinophilic infiltration, basal layer hyperplasia, squamous metaplasia, stromal edema, epithelial alteration, and stromal infiltration by lymphocytes, plasmacytes and macrophages. The purpose of this Letter is not to propose an alternative to histological assessment, but to discuss whether tissue inflammatory findings could be strengthened by integration with nasal cytology and clinical phenotype, and to suggest comparative validation of CHS and the clinical-cytological grading (CCG) system.

The two approaches interrogate related but not identical dimensions of CRSwNP. CHS is tissue-based and captures structural remodeling and inflammatory cell distribution within epithelial and stromal compartments. In the study by Enache *et al.*, higher stromal CD45RO scores were associated with high CHS, whereas CD68 showed a less consistent relationship with CHS [1]. Histology and immunohistochemistry (IHC) therefore provide spatial information that cannot be reproduced by surface sampling, including compartment-specific inflammatory localization and remodeling. Conversely, the CCG combines the inflammatory cellular pattern detected by nasal cytology with selected clinical comorbidities, originally including asthma, allergy and acetylsalicylic acid sensitivity, to obtain a clinical-cytological severity score [2, 3]. Thus, CHS emphasizes tissue architecture and compartmental pathology, whereas CCG adds a longitudinally accessible mucosal cellular profile and clinical phenotype.

Available evidence supports associations between CCG and selected clinical or inflammatory features, but these associations should not be interpreted as proof that CCG is a formally validated stand-alone prognostic model or a guideline-defined criterion for biological treatment. The original longitudinal experience linked combinations of cytological patterns and clinical comorbidities with postsurgical recurrence risk [2], while subsequent work explored CCG-guided non-surgical management [3]. Histological correlations have also been reported: Galectin-10 expression was associated with CCG [4], and intraepithelial tryptase-positive/CD117-positive mast cells (MCs) increased with greater CRSwNP severity and showed concordance with cytological detection [5]. These findings suggest biological coherence between cytological phenotyping and tissue inflammation; however, whether CCG improves prediction beyond established clinical measures or histological scores remains to be demonstrated.

The distinction between nasal cytology and histopathology is methodologically important. Nasal cytology samples the superficial mucosal compartment and can quantify eosinophils, MCs, neutrophils and other cell populations repeatedly in the outpatient setting. Tissue examination, by contrast, evaluates epithelial and stromal compartments, remodeling, edema and deeper inflammatory infiltrates. MC distribution illustrates this difference particularly well: glandular and stromal MC phenotypes have been described histologically [6], whereas intraepithelial MCs may be detected by both cytology and IHC [5]. Cytological findings may also vary with sampling site, disease activity and recent anti-inflammatory treatment, and they cannot substitute for biopsy when tissue architecture, spatial heterogeneity or immunophenotyping is required. Accordingly, cytology and histology should be considered complementary rather than interchangeable techniques.

Independent evidence also supports the use of nasal cytology as a dynamic monitoring tool. In a prospective study of patients receiving Dupilumab, Danisman *et al.* found a significant reduction in nasal eosinophils during treatment, although baseline cytology did not reliably predict clinical response [7]. This distinction is relevant: a biomarker may be useful for describing local inflammatory activity or monitoring change without being sufficiently validated for therapeutic selection. Similarly, broader biomarker studies indicate associations between inflammatory markers and disease control, but no single tissue or cytological marker currently captures the full clinical complexity of CRSwNP [8].

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This is particularly important in the era of biologics. Current *European Position Paper on Rhinosinusitis and Nasal Polyps* (EPOS)/*European Forum for Research and Education in Allergy and Airway Diseases* (EUFOREA) recommendations define eligibility and response using clinical parameters, type 2 inflammation and disease burden; CCG itself is not a formal criterion for initiating biological therapy [9]. Likewise, international consensus on disease control emphasizes symptoms, systemic corticosteroid requirements and patient-reported control, with endoscopy and olfaction among additional relevant domains [10]. We therefore view CCG as a proposed clinical-cytological stratification tool that may complement, rather than replace, guideline-based assessment.

A practical integrated framework could include four layers: (*i*) clinical phenotype and disease burden; (*ii*) repeatable nasal cytology to characterize superficial inflammatory patterns; (*iii*) tissue histology and IHC, when tissue is available, to define remodeling, spatial distribution and molecular/cellular markers; and (*iv*) an integrated multidimensional assessment for research stratification and longitudinal follow-up (Figure 1). Such a framework should remain hypothesis-generating until prospectively validated.

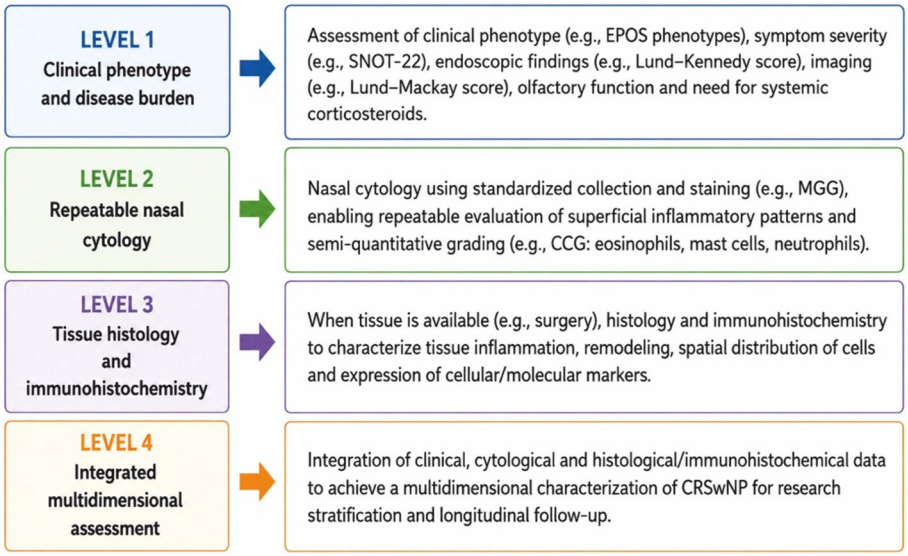

Figure 1 – ***Conceptual framework for the complementary integration of clinical phenotype and disease burden, repeatable nasal cytology, and tissue histology/immunohistochemistry in CRSwNP. The four-level model illustrates a multidimensional approach combining clinical, cytological, and tissue-based information for research stratification and longitudinal disease assessment. This framework is hypothesis-generating and requires prospective comparative validation before clinical implementation. CCG: Clinical-cytological grading; CRSwNP: Chronic rhinosinusitis with nasal polyps; EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps; MGG: May-Grünwald–Giemsa; SNOT-22: Sino-Nasal Outcome Test-22.***

The next necessary step is therefore direct comparative validation. Studies including patients undergoing surgery could obtain nasal cytology before tissue sampling and calculate both CCG and CHS in the same individuals. Analyses should assess correlation between scores, interobserver reproducibility, associations with objective disease severity, postoperative recurrence, need for systemic corticosteroids or revision surgery, and response to biological therapy. Most importantly, predictive performance should be compared for CHS alone, CCG alone and a combined model, with appropriate internal and external validation. Only such studies can establish whether integration provides incremental clinical value.

In conclusion, the work of Enache *et al.* highlights the value of detailed tissue-based inflammatory assessment in CRSwNP. Nasal cytology and CCG add a different, repeatable and clinically contextualized perspective, but their role should be framed according to the strength of current evidence. Rather than advocating replacement of one method by another, we propose that histology, cytology and clinical assessment be studied as complementary dimensions of a multidimensional CRSwNP phenotype.

Conflict of interests

The authors declare no conflict of interests.

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Received: April 23, 2025

Accepted: August 31, 2026