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Chronic rhinosinusitis with nasal polyps: 64 pheno-endotypes for personalized therapy. Time to change the paradigm

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Dear Editor,

Chronic rhinosinusitis with nasal polyps (CRSwNP) is still often considered, both in clinical practice and in the literature, as a homogeneous entity. Yet, nasal polyposis is not all the same — in fact, one might say these are not “polyps” in the strict pathological sense [1-3].

Using the Clinical-Cytological Grading (CCG) approach [1], which crosses 4 clinical phenotypes (ASA sensitivity, asthma, allergy, ASA+asthma) with 4 cytological endotypes (neutrophilic, mast cell, eosinophilic, eosinophilic-mast cell), 64 different pheno-endotypes emerge, each with its own recurrence prognostic index. Naturally, adding molecular and clinical parameters could reveal even more [4]. This compels a radical shift in paradigm: there is not one disease, but many forms, each with a distinct biological and clinical narrative.

In this context, nasal cytology is a fundamental diagnostic tool [1,5]. It allows for the identification of mast cell cytotypes, often associated with more severe, refractory forms, which traditional pathology frequently misses. Routine hematoxylin-eosin staining does not highlight mast cells, leading to systematic underestimation. Nasal cytology has unveiled an entire “hidden world” of nasal inflammation — and is now even awakening the interest of pathologists, in close cooperation with cytologists, as shown in a recent study [2].

From a terminology standpoint, it is time for clarity. The EPOS guidelines, from the early versions to the 2023 update [6], have progressively renamed the condition as “chronic rhinosinusitis with nasal polyps” — a longer but not necessarily more precise label. It might have been better to go in the opposite direction: to abandon the word 'polyposis', now inaccurate, and instead use a term that reflects its real pathophysiology: Chronic Hyperplastic Rhinosinusitis [7].

This is not mere semantics: it is rooted in the general pathology we all studied in our first years of medical school. True polyps, by definition, have a fibrovascular axis and, once removed, do not recur. These nasal formations, wrongly called “polyps,” do recur — because they are the manifestation of chronic hyperplastic mucosal inflammation, now more precisely defined immunologically as “Type 2 inflammation” [3,5]. A condition dominated by eosinophils, mast cells, and interleukins IL-4, IL-5, and IL-13, paving the way to new nosology and therapeutic strategies.

This terminological confusion dates back to Hippocrates, who — let me joke — hadn’t yet taken his general pathology exam [7], and misnamed these mucosal growths. We, on the other hand, have passed that exam, and should finally name things properly, guided by modern science.

The future of CRSwNP lies in personalized therapy — not just guided by molecular markers but also by clinical and cytological profiling. A truly multidisciplinary approach that involves ENT

specialists, allergists, pulmonologists, immunologists — and finally gives this condition the nosological dignity it deserves.

Moreover, improper stratification of the disease leads to inappropriate treatments and significant economic burden for the healthcare system. The use of expensive biologics should follow objective, stratified criteria — otherwise we risk both under- and overtreatment [4]. Only with precise phenotyping can we ensure therapeutic appropriateness, economic sustainability, and real clinical benefit for the patient.

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