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LETTER

Nasal Cytology as a Complementary Cellular Window in Severe Asthma Phenotyping: Comments on the BRISA Study [Letter]

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Dear editor

We read with great interest the article by Domínguez-Ortega et al, "A Multi-Compartment Cytological Approach to Severe Asthma Phenotyping: The BRISA Study", recently published in the Journal of Asthma and Allergy.[1] The authors should be congratulated for addressing a clinically relevant and still unresolved issue, namely the need for more accurate inflammatory phenotyping in severe asthma through the integration of nasal cytology, induced sputum, peripheral blood, and circulating biomarkers.

The BRISA study is particularly valuable because it moves beyond the concept of a single biomarker and proposes a multi-compartment model of airway inflammation.[1] This approach is consistent with the current understanding of severe asthma as a heterogeneous disease, in which systemic biomarkers, lower airway inflammation, and upper airway involvement may not always overlap.[2,3] The finding that nasal cytology alone cannot replace induced sputum for inflammatory phenotyping is therefore important and clinically sound. However, we believe that this conclusion should not reduce the perceived value of nasal cytology, but rather help define its most appropriate role within a precision medicine framework.

Nasal cytology should be interpreted not as a surrogate of induced sputum, but as a complementary cellular window on the upper airways. Its main strength lies in the direct observation of the nasal mucosa, allowing the identification of inflammatory cells, including eosinophils, mast cells, neutrophils, lymphocytes, and epithelial alterations.[4] In this sense, nasal cytology does not merely provide a numerical count of inflammatory cells, but also offers morphological information regarding epithelial integrity, cellular activation, cytological phenotypes, mucus production, and possible mixed inflammatory patterns.

This distinction is clinically relevant. Severe asthma is frequently associated with allergic rhinitis, chronic rhinosinusitis, chronic rhinosinusitis with nasal polyps, and non-steroidal anti-inflammatory drug-exacerbated respiratory disease.[1,5] In the BRISA cohort, 72% of patients had allergic rhinitis, 50% had chronic rhinosinusitis with nasal polyps, and 27.3% had non-steroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD).[1] These comorbidities may contribute to disease burden, poor control, exacerbations, and therapeutic complexity. In patients with severe asthma, the nasal compartment may therefore represent not only an anatomical extension of lower airway disease, but also an independent inflammatory district with its own cellular features.

The incomplete agreement between nasal cytology and induced sputum observed in the BRISA study may thus reflect true biological heterogeneity between upper and lower airway compartments, rather than a limitation of nasal cytology itself.[1] Indeed, the authors reported poor concordance between induced sputum and nasal cytology inflammatory patterns, with a kappa index of −0.0862. They also observed that nasal cytology predominantly showed neutrophilic or mixed inflammatory patterns, whereas eosinophilic inflammation was more frequent in induced sputum.[1] From this perspective, the lack of full concordance between nasal and bronchial cytology should be considered informative.

A patient with eosinophilic sputum and non-eosinophilic nasal cytology, or conversely a patient with marked nasal eosinophilia, mast-cell inflammation, or mixed eosinophilic-mast-cell inflammation and non-eosinophilic sputum, may

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have different clinical implications, especially in the presence of rhinitis, chronic rhinosinusitis with nasal polyps, allergy, or N-ERD. These patterns could help identify patients in whom upper airway inflammation remains active despite control of lower airway inflammation, or patients in whom sinonasal disease may contribute to persistent symptoms and impaired quality of life.

Another relevant point concerns standardization. In the BRISA study, nasal cytology was performed by mucosal scraping from the middle third of the inferior turbinate, followed by May-Grünwald-Giemsa staining and light microscopy.[1] This procedure is consistent with the standard methodology widely used in nasal cytology.[4] Nevertheless, the authors correctly state that no standardized cut-off values have been established for differentiating nasal cellular patterns, partly because different sampling techniques, such as nasal lavage, scraping, and brushing, make comparisons difficult.[1]

This is precisely the point on which recent methodological developments should be considered. Nasal cytology has sometimes been regarded as a simple ancillary test, but it has progressively evolved into a reproducible method when performed according to standardized procedures.[4] This aspect has recently been strengthened by the expert-based Delphi consensus, which represents a structured standardization of nasal cytology methodology and interpretation.[6] In that consensus process, 100 members of the Italian Academy of Nasal Cytology participated in three iterative Delphi rounds and evaluated 30 statements covering sampling, staining, microscopic assessment, and clinical interpretation, with consensus defined as at least 70% agreement.[6] Therefore, nasal cytology should be increasingly considered a structured diagnostic method rather than a merely empirical or ancillary technique, with potential application in both clinical practice and research settings.

An additional methodological aspect concerns staining. May-Grünwald-Giemsa staining is not merely a routine laboratory procedure, but a key element of nasal cytology because it allows the simultaneous identification of epithelial cells, eosinophils, neutrophils, lymphocytes, bacteria, fungal elements, biofilm, and, importantly, mast cells.[4] This is clinically relevant because nasal inflammation cannot be reduced to eosinophilia alone. Mixed eosinophilic-mast-cell patterns may identify a more complex inflammatory phenotype, particularly in chronic rhinosinusitis with nasal polyps, N-ERD, and severe upper airway disease.[7] Therefore, in future studies on severe asthma, the systematic assessment of mast cells, together with eosinophils and epithelial alterations, could provide additional information beyond conventional eosinophil-based classification.

In addition, recent translational evidence has reinforced the role of nasal cytology as a cellular window into epithelial dysfunction and type 2 inflammation.[8] This perspective is particularly relevant in severe asthma, where epithelial barrier impairment, alarmin release, type 2 inflammation, and upper airway comorbidities may interact across compartments. Accordingly, nasal cytology may contribute not only to inflammatory cell profiling, but also to the interpretation of epithelial damage, goblet cell hyperplasia, squamous metaplasia, epithelial islets, mucus production, and mixed inflammatory patterns.

The BRISA study also raises an important methodological issue for future research. In severe asthma, the interpretation of nasal cytology may be strengthened if patients are stratified according to sinonasal comorbidities, including allergic rhinitis, chronic rhinosinusitis with nasal polyps, previous sinonasal surgery, local corticosteroid use, and biologic treatment history. These variables may strongly influence nasal cytological findings and could partly explain the observed dissociation between compartments. Similarly, the evaluation of mast cells, epithelial damage, squamous metaplasia, goblet cell hyperplasia, epithelial islets, mucus production, and mixed eosinophilic-mast-cell patterns may provide additional information beyond eosinophil counts alone.[1,7,8]

We therefore suggest that future multi-compartment studies in severe asthma should not aim to determine whether nasal cytology can replace induced sputum, but rather whether the integration of nasal cytology with sputum, blood eosinophils, FeNO, IgE, periostin, TSLP, DPP4, and other biomarkers can improve the recognition of clinically meaningful inflammatory profiles.[1,3] In this integrated model, nasal cytology could help characterize the upper airway component of severe asthma, identify relevant comorbid inflammatory phenotypes, and support a more personalized therapeutic strategy.

In conclusion, the BRISA study provides an important contribution by demonstrating both the feasibility and the limits of a multi-compartment cytological approach in severe asthma.[1] We believe that nasal cytology should be regarded as a complementary, non-invasive, repeatable, standardized, and clinically informative method, particularly when interpreted within the broader context of united airway disease. Rather than replacing induced sputum, nasal cytology may enrich severe

asthma phenotyping by adding a direct cellular assessment of the upper airways, an aspect that deserves further investigation in larger and specifically designed studies.

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