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Letter to the Editor

NEW INSIGHTS INTO THE IMPORTANCE OF ESTABLISHING HISTOMORPHOLOGICAL CRITERIA FOR CRSwNP

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To the Editor,

the advent of the newly developed monoclonal antibodies (mAbs) targeting type 2 (T2) inflammation has highlighted the importance of correctly typing patients with Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP), as a function of both the endotype and phenotype, in order to identify the different clinical and biological markers associated with a poor response to conventional treatments and with an increased risk of relapse[1]. In this perspective, several biomarkers have been progressively identified and associated with poor prognosis in CRSwNP patients, including Charcot-Leyden crystals (CLSs), which are slender bipyramidal hexagonal crystals (~ 100 µm in maximum length) composed of Galectin-10[2]. As a matter of fact, CLCs are nowadays specifically considered as hallmarks of eosinophil involvement in many diseases, such as asthma, allergic rhinitis, CRSwNP, and atopic dermatitis[3]. However, it is still unclear how crystalline CLCs found in nasal biopsies can be used to predict CRSwNP recurrence (**Fig. 1**). Recent studies have proposed the use of histomorphology methods to define a possible cut-off of CLC in nasal polyps biopsies, such as to establish the actual risk of CRSwNP recurrence, which in turn would also be affected by the different forms of CLC[4]. Indeed, not only there is no unanimous histopathological criterion regarding a cut-off point to define eosinophilia in nasal polyps, but also the eosinophil count could be excessively time-costing, as even more than 500 eosinophils per high power field could be detected. On the contrary, counting CLCs might be more easy-counting.

In addiction to CLCs count, we believe that histomorphology methods should aim at establishing a cut-off point for mast cells in nasal polyps' biopsies. Indeed, the great attention paid over the years

to the undoubtedly crucial role that eosinophils play in the pathogenesis of CRSwNP has led to underestimating the importance of other cells of immunophlogosis, such as mast cells, which are equally involved in the inflammatory mechanisms underlying the CRSwNP[5]. As a matter of fact, mast cells have been shown to be directly involved in the pathogenesis of CRSwNP, orchestrating type-2 cytokines and chemokines. Moreover, although CLCs have been traditionally considered a marker of eosinophilic inflammation, they have been shown to colocalize with both eosinophils and mast cells, thus being a marker of both cytotypes[6].

Interestingly, our preliminary studies have demonstrated that mast cells infiltrate the lamina propria of almost all nasal polyps and the epithelial layer of the most difficult to treat forms. Since the intraepithelial localization of mast cells is properly related to the severity of CRSwNP, a cut-off of intraepithelial mast cells could be established to identify the most severe endotypes of CRSwNP[7]. This would overcome a disadvantage of CLCs counting: hematoxylin-eosin staining is complicated and requires an optimal eosin pH value to visualize the smallest CLCs. As proof of this, CLCs are rarely detected during common histological investigations. On the contrary, intraepithelial mast cell counts could be performed using May-Grunwald Giemsa staining, which is already used for nasal cytology. This staining, unlike hematoxylin-eosin, would allow to visualize all the inflammatory cells that infiltrate the nasal polyps, including mast cells, without the risk of underestimating the count (**Fig. 2**).

In light of these evidence, establish standardized histomorphological criteria that define the different forms of CRSwNP is mandatory. We believe that the keystone could be represented by intraepithelial mast cells count. For this purpose, further studies are needed to define the cut-off of infiltrating intraepithelial cells associated with increased severity of CRSwNP.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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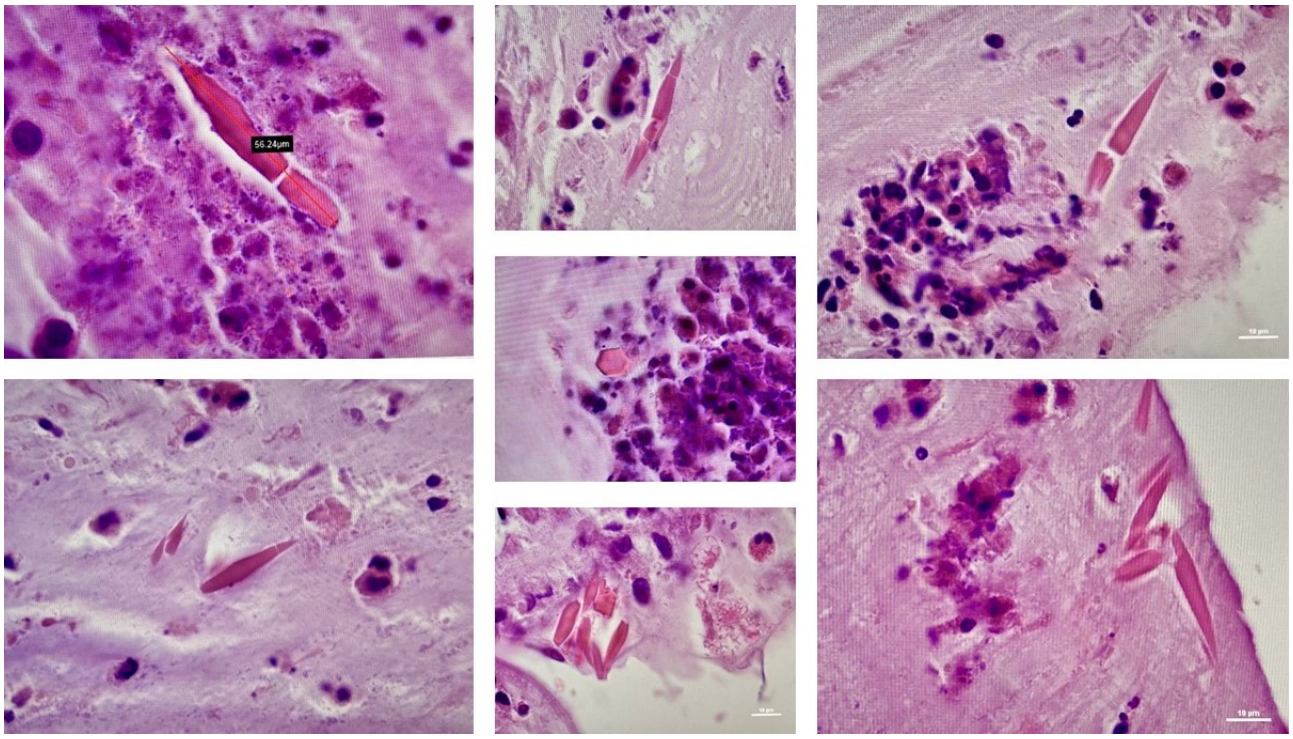

Fig. 1 Charcot-Leyden Crystals (CLCs) in nasal polyps samples stained with hematoxylin-eosin.

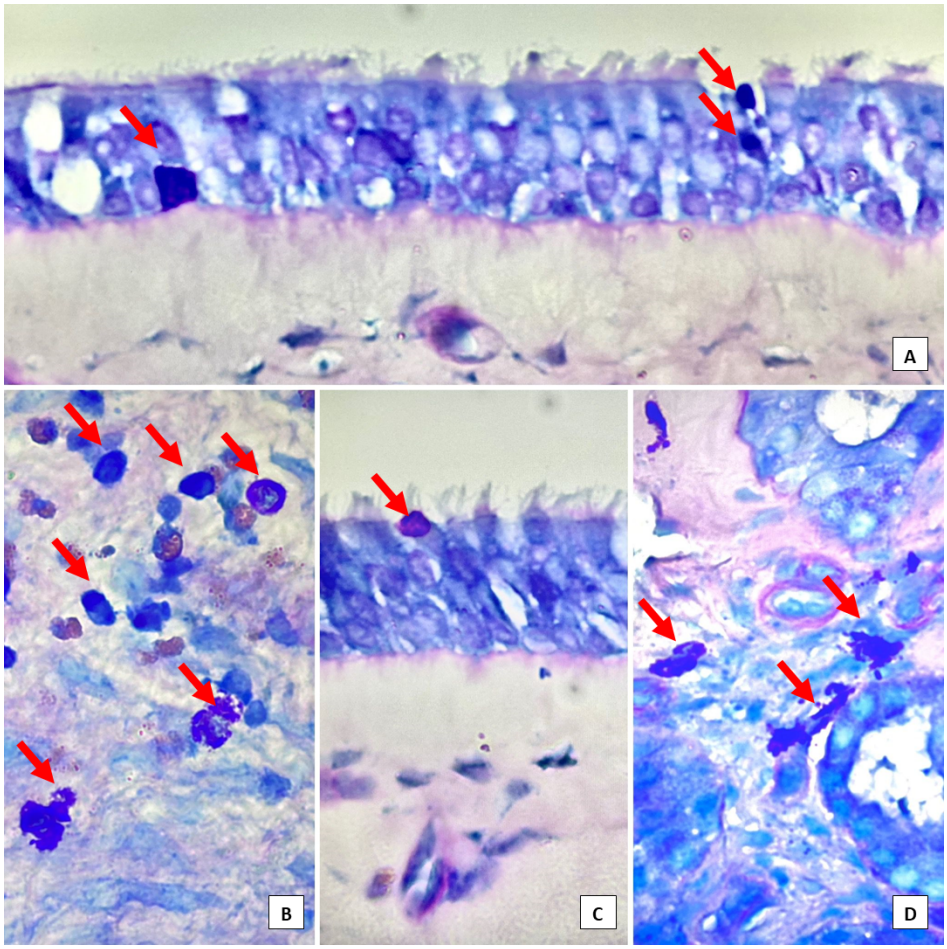

Fig. 2 Nasal polyp biopsies stained with May-Grunwald Giemsa (MGG). The arrows indicate mast cells, located in the epithelial layer (**A-C**) and in the lamina propria (**B-D**) of nasal polyps.

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