

EDITORIAL

Clinical & Experimental Allergy

Profiling the immunological characteristics of exacerbation of chronic rhinosinusitis with nasal polyps

This editorial discusses the findings of the paper in this issue by Divekar et al. [6], pp. 767–778.

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Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the nasal and paranasal sinuses. It is a common health problem with significant medical cost and impact on general health. In the United States, CRS has been estimated to affect 12.5% of the total population or approximately 31 million patients [1], and in Europe, the overall prevalence is 10.9% [2]. Primarily based on the presence or absence of nasal polyps, CRS is classified into two clinical phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Approximately 20% of patients with CRS have nasal polyps [3], and CRSwNP is one of the most common indications for sinus surgery [1]. It is estimated that up to 20% of CRS patients are not well controlled even under guideline-based treatment, and particularly, a number of patients have experienced exacerbation and/or recurrence, reflecting the unmet need to improve the understanding of CRS [4].

Previous researches have mainly focused on characterizing CRS in its stable and persistent status in comparison with controls. Although those studies have provided valuable information regarding the clinical and immunopathological characteristics of CRS and expanded our insights into the pathophysiology of CRS, the aetiology of CRS, especially the initiating factors, remains unknown. Unlike asthma, the study of CRS exacerbation has received very little attention, despite that such stud-

ies may provide useful clues about the key processes involved in the CRS inception and progress. Multifactorial factors altering the host environment interaction such as bacteria, allergens, fungi, viruses or environmental toxins may trigger the inflammatory process. Allergen exposure and pathogen infection are the most important precipitants of asthma exacerbation, and both may also produce or worsen CRS [5].

In this issue of the Journal, Divekar et al. have profiled local and systemic immunological properties of CRSwNP patients during exacerbation by measuring a panel of growth factors and cytokines in nasal secretion and serum [6]. It is very interesting to find that CRSwNP patients demonstrate distinct immunological changes locally and systematically during acute exacerbation; in particular, vascular endothelial growth factor (VEGF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) levels in serum are uniquely increased in CRSwNP patients during exacerbation when compared with those in control subjects with exacerbation and CRS baseline without exacerbation. Thus, VEGF and GM-CSF in serum may serve as potential biomarkers for CRSwNP exacerbation. Up-regulated local production of VEGF and GM-CSF has been previously reported in polyp tissues [7, 8], whether the systemic VEGF and GM-CSF represent a 'spillover' from local production, and the function of these molecules in the exacerbation of CRSwNP remains to be defined.

In the study of Divekar et al. [6], they first investigated the changes in nasal secretions which are important for understanding the local immune response in CRSwNP patients. The levels of 10 cytokines and three granulocyte-derived proteins have been measured. They found that the levels of IL-6, IL-5 and major basic protein (MBP) were higher in CRSwNP than in controls during exacerbation. However, it should be noted that there was no significant difference between CRSwNP

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with and without exacerbation, which either underscores the need to confirm the role of IL-6, IL-5 and MBP in a larger cohort study or disfavours a role of these molecules in CRSwNP exacerbation.

Next, Divekar et al. [6] explored the changes in serum. CRS is mostly considered as a localized disease with profound immune disturbance at sinonasal mucosa; however, this does not preclude certain systemic presentations in CRS. For example, increased number of blood eosinophils has been documented in eosinophilic CRSwNP, which is correlated with mucosal eosinophils [9]. As blood samples are easily obtained with standardized non-invasive collection procedures, it is always attracting to dig out blood biomarkers for disease diagnosis, monitoring and outcome prediction. One great strength of this study is that Divekar et al. used network analysis and unsupervised agglomerative hierarchical clustering, which have been widely used in disease phenotype analysis in other complex diseases such as tumour and asthma in recent years [10], to investigate immunological changes of 39 markers during natural exacerbation of CRSwNP. Usually, conventional analyses measure the central tendency and are used for a limited number of variables. As it may compress the individual variations and potentially miss important information, it may not be suitable for the analysis of a large scale of variables. Fortunately, hypothesis-free methods such as latent class and cluster analysis allow the overview of a high number of variables without compromising information and thus lead to the discovery of associations and correlation without presumption [11]. The unsupervised statistical methods used in this article give us a novel insight into the research of CRS with an unbiased technique. By this method, VEGF and

GM-CSF were dug out that were uniquely increased in CRSwNP exacerbation.

Some limitations in the study of Divekar et al. [6] ask us to explain their data with caution. First, in their study, the sample size is small, which makes some conclusions hard to be reached and the subgroup analysis impossible. Authors also acknowledged in their paper that further confirmation with larger sample size is required. Second, in this study, CRSwNP was not defined clearly. CRSwNP was diagnosed based on the presence of symptoms, along with a sinus CT scan within the past 5 years, and nasal polyps documented within the past 3 years on physical exam. However, 7 (of 9) CRSwNP patients had previous surgery. It is reported that CRS with and without previous surgery may have different bacteria colonization and immune properties [12]. Whether there is a difference in exacerbation between CRS patients with and without previous surgery waits to be clarified. Third, the influence of coexisting asthma and allergy and medications was unable to be evaluated due to the limited sample size. It is hard to discriminate the real exacerbation of CRSwNP and those associated with worsening of coexisting allergic rhinitis.

Overall, Divekar et al., for the first time, have employed network analysis and unsupervised agglomerative hierarchical clustering to investigate immunological characteristic of CRSwNP exacerbation. This work has provided new insights into the pathophysiology of CRSwNP exacerbation. Although with small sample size and some confounding factors, it may serve as a good starting point for similar large-scale studies.

Conflict of interest: The authors declare no conflict of interest.

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