

When rhinosinusitis is not just rhinosinusitis: clinical characteristics and phenotypes of patients with type 2 chronic rhinosinusitis with nasal polyps

Ignazio La Mantia¹, Giorgio Ciprandi², Attilio Varricchio³, Martina Ragusa¹, Federica Cipolla¹, Claudio Andaloro⁴

¹Otolaryngology Unit, Department of Medical Sciences, Surgical and Advanced Technologies, University of Catania, Catania, Italy; ²Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy; ³Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Campobasso, Italy; ⁴Department of Surgery, Otolaryngology Unit, Latisana-Palmanova Hospital, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Udine, Italy

Abstract. *Background and aim:* Chronic rhinosinusitis (CRS) is a chronic and recurrent disease that negatively affects patients' quality of life. CRS has two main phenotypes: CRS with nasal polyps (CRSwNP) and CRS without polyps (CRSsNP). Minimal research has been conducted to study the variability in patients' characteristics. Therefore, we conducted this study to examine these differences. *Methods:* A retrospective cohort study included patients with both CRSwNP and CRSsNP. Outcomes included symptom severity, radiographic severity, and number of sinus surgeries. Symptom severity was assessed using the Sino-nasal Outcome Test and the Lund-Mackay CT score was used to determine radiographic severity. Further subgroup analysis was done based on the presence or absence of comorbid asthma. *Results:* A total of 110 and 106 patients were included in the CRSwNP and CRSsNP groups, respectively. The mean age in the CRSwNP and CRSsNP groups was 50.2 and 48.7, and the proportion of female patients was 40.9% and 58.5%, respectively. No significant difference in symptom severity was noted between CRSwNP and CRSsNP group (68.1 ± 18.6 vs. 73.2 ± 21.27 ; $P=0.097$), while the Lund-Mackay score was significantly lower in the CRSsNP group (7.4 ± 2.3 vs. 11.9 ± 3.6 ; $P=0.016$). Also, the number of surgeries was significantly lower in the CRSsNP group as compared to the CRSwNP group ($P=0.023$). Subgroup analysis revealed statistically significant differences between those with and without asthma in patients with CRSwNP in terms of Lund-Mackay scores and number of surgeries ($P=0.038$ and 0.043), respectively. However, no significant differences were noted in the CRSsNP group ($P>0.05$). *Conclusions:* There is a clear variability in the characteristics of patients with CRSsNP and CRSwNP. A similar difference was noted in the CRSwNP group when patients were stratified based on the presence or absence of asthma. This warrants further investigation of potential correlation with the prognosis and optimum treatment strategies of this patient population (www.actabiomedica.it)

Key words: sinusitis, nasal polyps, paranasal sinuses

Introduction

Chronic rhinosinusitis (CRS) is a multifactorial disease, usually chronic and recurrent, characterized by an inflammatory process involving the nasal mucosa

and paranasal sinuses (1). CRS has been reported to affect around 5-15% of the European population, posing a significant yet detrimental impact on affected individual's performance and quality of life (QOL), which further increases the cost of associated care (2).

Generally, CRS can be categorized into two phenotypes depending on the presence/absence of nasal polyps into: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) (3). More recently, clinicians and scientist have proposed further subcategories for these two phenotypes into immune endotypes, which are hypothesized to have a beneficial prognostic value in predicting the course of the disease as well as the outcome depending on the provided therapeutic intervention (4).

Based on the recent recommendations of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS), the diagnosis of CRSwNP is based on the following criteria: 1 - the presence of symptoms suggestive of rhinosinusitis for a minimum of three months (i.e., nasal congestion, postnasal drip or anterior rhinorrhea, affected sense of smell, facial pain or headache), 2 - obstruction of paranasal sinus(es), and 3 - the presence of bilateral nasal polyps (NP) during endoscopy or evidence of sinus disease based on: (a) computed tomography (CT), (b) presence of type II inflammation which is characterized by the increase in immunoglobulin E (IgE) levels and high levels of cytokines (i.e., interleukin (IL)-4, 13, and 5). That being said, it is very common that cases with CRSwNP usually present with comorbid asthma, reflecting a systemic inflammatory disease rather than an isolated condition (5).

Extensive scientific evidence is accumulating that both entities are associated with type 2 inflammatory response, so the identification of underlying molecular pathways has a double benefit: for the understanding CRSwNP and asthma as a complex systemic process and for the development of specific treatment options with novel biologics targeting shared underlying type 2 inflammatory pathways (6).

Based on the aforementioned observations, we conducted this study to thoroughly understand the distinctive phenotypic characteristics as well as the disease outcome among patients with CRSwNP in comparison to CRSsNP patients. This hypothesis of potential differences in patients' characteristics and disease outcomes between both groups would be deemed highly valuable in properly understanding CRS and in providing novel therapeutic options.

Materials and methods

This retrospective cohort study is based on the available medical records of patients with CRS with or without NPs who were treated at our outpatient academic center during the period from Feb, 2019 to May, 2020. The record review of available medical records yielded a total of 216 eligible patients (110 with CRSwNP and 106 patients with CRSsNP). The diagnosis of CRSwNP and CRSsNP was dependent on the rhinoscopic results as well as the findings from the pathology specimens.

We compared characteristics of patients in CRSwNP group with those of the CRSsNP group. Characteristics analyzed were age, sex, concomitant diseases (asthma, allergic rhinitis), smoking, sinusitis-related symptoms, disease severity (based on radiologic assessment), previous sinus surgeries, and results of peripheral blood eosinophil and IgE total mean. Prior to conducting this research, our study protocol was approved by the Institutional Review Board (IRB)- Ethics Committee of the University of Catania (n. 592/20). Written informed consent was retrieved from all participants upon recruitment. The study was performed in accordance with the ethical standards.

Allergic rhinitis was demonstrated by a positive skin prick test to common aeroallergens: house dust mites (*Dermatophagoides* and *Dermatophagoides pteronyssinus* flour), olive trees, dogs and cats' epithelial dander, timothy, a mixture of Composite, P. Judaica, cypresses and mould. Asthma diagnosis and severity were determined through the combination of symptom history, a positive test for bronchial hyper-responsiveness and FEV1% values

Sinusitis-related symptoms were investigated using the 22-item Sino-nasal Outcome Test (SNOT-22) right prior to the operation time. This questionnaire is made up of 22 questions, where each question can be rated from 0 (indicating no problem) to 5 (indicating a problem that is as bad as it can be), with an overall score ranging from 0-110. Important to say, higher scores reflect severe symptoms, whereas, lower scores reflect mild-to-no symptoms (7).

Sinus severity was identified based on radiological assessment through the interpretation of CT scan findings (i.e., the degree of sinus mucosal thickening).

Radiological assessments were carried out by clinical radiologists who were blinded to the participants and the outcomes of this research study. Furthermore, the Lund-Mackay CT score evaluating each sinus using a 0 to 2 scale (0 = normal; 2 = total opacification), and with a total score ranging from 0 to 24 (8).

Statistical analysis

The statistical analysis was performed using SPSS Statistics version 25 (IBM Corp., Armonk, NY). The data are expressed as the median and interquartile range. The differences between our populations of interest (CRSwNP and CRSsNP groups) were analyzed using the Chi-squared test for categorical variables. Meanwhile, we used the Mann-Whitney *U* test (2-tailed) to compare continuous outcomes between two groups. Of note, we further subcategorized the CRSwNP and CRSsNP groups into those with or without asthma. Eventually, the Kruskal-Wallis test was used to compare number of sinus surgeries and the mean Lund-Mackay CT score. A cut-off value of $P < 0.05$ was used to indicate statistical significance.

Results

A total 106 and 110 patients were included in the CRSsNP and CRSwNP groups. Baseline demographic and clinical characteristics of both patients are provided in Table 1. Patients in the CRSsNP group were significantly more likely to be females as compared to the CRSwNP group (58.5% vs. 40.9%; $P=0.042$), respectively. On the other hand, we found no statistically significant differences between both groups in terms of age and smoking status.

We noted that having comorbid conditions such as allergic rhinitis (43.6% vs. 19.8%; $P<0.05$) and asthma (48.2% vs. 15.1%; $P<0.05$) was significantly more frequent in the CRSwNP group as compared to the CRSsNP group, respectively. However, no statistically significant difference was noted between both groups regarding the severity of asthma (as measured by the FEV1 predicted percentage). That being said, we noted a difference in SNOT-22 score between CRSwNP and CRSsNP groups (68.1 ± 18.6 vs 73.2 ± 21.27 , respectively). However, this difference didn't reach statistical significance ($P=0.097$). In contrast,

Table 1. Baseline demographic and clinical characteristics of our study populations

Characteristic	CRSwNP group (N = 110)	CRSsNP group (N = 106)	<i>p</i>
Age (years), mean \pm SD	50.2 \pm 8.7	48.7 \pm 9.8	0.347
Sex, n (%)			
Female	45 (40.9)	62 (58.5)	0.042
Current or Former Smoking, n (%)	34 (30.9)	38 (35.4)	0.233
Comorbid diseases, n (%)			
Allergic rhinitis	48 (43.6)	21 (19.8)	0.008
Asthma	53 (48.2)	16 (15.1)	0.005
FEV1 % Predicted, (mean \pm SD)	82.19 \pm 19.43	81.68 \pm 19.32	0.442
SNOT-22, mean \pm SD	68.1 \pm 18.6	73.2 \pm 21.27	0.097
Lund-Mackay score, mean \pm SD	11.9 \pm 3.6	7.4 \pm 2.3	0.016
Number of sinus surgeries, mean \pm SD	1.87 \pm 1.4	0.91 \pm 1.1	0.023
Peripheral eosinophil count ($\times 10^3/\mu\text{L}$), mean \pm SD	0.7 \pm 0.3	0.1 \pm 0.1	0.038
IgE total (UI/ml), mean \pm SD	315,2 \pm 301,6	221,2 \pm 205,3	0.021

CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; SD = standard deviation; FEV1 = forced expiratory volume in one second; SNOT-22 = 22-item Sino-Nasal Outcome Test.

there was a significant difference between both groups in terms of adverse effects on quality of life.

In terms of radiologically-assessed sinusitis severity, patients in the CRSwNP group had significantly higher Lund-Mackay score as compared to those in the CRSsNP group (11.9 ± 3.6 vs. 7.4 ± 2.3 ; $P=0.016$). The same was observed for the mean number of surgeries where the CRSwNP group had significantly higher mean number of sinus surgeries as compared to those in the CRSsNP group (1.87 ± 1.4 vs. 0.91 ± 1.1 ; $P=0.023$). This is consistent with laboratory indicators of sinusitis such as peripheral eosinophil count and IgE count. Patients in the CRSwNP group had significantly higher peripheral eosinophil count (0.7 ± 0.3 vs. 0.1 ± 0.1 ; $P=0.038$) and Ige levels (315.2 ± 301.6 vs. 221.2 ± 205.3 ; $P=0.021$) as compared to those in the CRSsNP group, respectively.

We further did subgroup analysis of both the CRSwNP and CRSsNP groups based on the presence or absence of asthma (Table 2). Surprisingly, in the CRSwNP group, those with asthma had significantly higher Lund-Mackay score (12.8 ± 3.2 vs. 9.7 ± 3.1 ; $P=0.038$) as well as higher number of sinus surgeries (2.34 ± 1.3 vs. 1.35 ± 0.8 ; $P=0.043$) as compared to those without asthma, respectively. However, in the CRSsNP group, no statistically significant differences were noted in those with or without asthma in terms of Lund-Mackay score or number of sinus surgeries.

Discussion

The relationship among clinically observable patient characteristics (phenotype), underlying cellular or molecular immunophlogosis patterns

(endotype), and heterogenic consequence, including response to treatment, are continually the aim of several studies (9,10). Although phenotypes are clinically meaningful and help in the classification of various groups within a disease population; however, no implications can be made from these phenotypes in guiding therapy. Therefore, novel approaches are recommended for this matter, including different CRS endotypes. By definition, endotypes are diseases subcategories with a distinguishable feature that is functionally and/or pathologically different from other categories secondary to the presence of a certain molecule or cell (11).

Different endotypes can be identified based on a particular laboratory marker, including but not limited to the level of eosinophils or neutrophils on T-helper cells or the level of IgE or other cytokines (i.e., IL-4, IL-5, or IL-13). In some western states (such as Europe and the United States), the most common endotype in CRSwNP is based on type 2 inflammatory pathway, characterized by a very high prevalence of eosinophils, mast cells and basophils, as well as high type 2 cytokines (IL -4, IL-5, IL-9, IL-13, IL-25 and IL-33) and Th2 cells.

Eosinophilia is induced by IL-5, IL-25 and IL-33, while IL-4 and IL-13 are responsible for the synthesis of IgE, which mostly happens in allergic cases (12, 13). On the other hand, in patients with CRSsNP, ciliary motility deficits and immune deficits are evident which are mainly due to the neutrophil-mediated immune response on the mucosa, which is mediated mainly by Th1/Th17 cells. In this particular patient population, it is unclear whether or not treatment with biological therapy would provide beneficial outcomes (14).

In phenotyping of CRS, the cornerstone is the presence (CRSwNP) or absence (CRSsNP) of polyps, evaluated by endoscopic examination and radiological

Table 2. Subgroup analysis of CRSwNP and CRSsNP groups based on the presence of comorbid asthma

Characteristic	CRSwNP group with comorbid asthma (n = 53)	CRSwNP group without comorbid asthma (n = 57)	<i>p</i>	CRSsNP group with comorbid asthma (n = 16)	CRSsNP group without comorbid asthma (n = 90)	<i>p</i>
Lund-Mackay score, mean \pm SD	12.8 ± 3.2	9.7 ± 3.1	0.038	7.8 ± 2.4	6.9 ± 1.9	0.294
Number of sinus surgeries, mean \pm SD	2.34 ± 1.3	1.35 ± 0.8	0.043	0.94 ± 0.4	0.86 ± 0.3	0.188

CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; SD = standard deviation

imaging. CRS with respiratory disease exacerbated by aspirin (15), allergic fungal rhinosinusitis (16), infectious CRS, CRS in patients with cystic fibrosis (17) and other rare associations such as CRS with primary cilia dyskinesia constitute other phenotypes. According to recent findings, central compartment atopic disease (CCAD) has been reported in a specific subgroup of cases with centrally located nasal inflammatory condition along with NPs due to inhalant-associated allergy (18). We conducted a comprehensive phenotypic characterization study to determine the clinical features of patients with CRSwNP, comparing them with CRSsNP patients in order to highlight any discrepancy between both groups in terms of patients' characteristics and disease outcomes, which will further have a huge impact on developing proper management regimens for these particular subsets of patients.

Based on previous reports, CRSwNP patients are more likely to be males than females, and this is consistent with our findings (19).

The prevalence of asthma among patients with CRSwNP in our study was 48.2%, which is consistent with published cohorts in the literature. For instance, Stevens et. al. conducted a study among a surgical cohort and it was noted that asthma was present in 53.6% of patients with CRSwNP (19). Similarly, Promsopa et. al. found a very similar rate of asthma comorbidity of 48.3% among patients with CRSwNP based on their otolaryngology clinic records (20).

Interestingly, in our study, we noted that patients with CRSwNP and asthma had significantly higher lung function as compared to their peers. Similarly, patients within this endotype had significantly worse QOL and more severe asthma symptoms (21). This is of high clinical importance because these differences were not observed in the CRSsNP group. Therefore, we hypothesize that this finding would be of great value in guiding clinical decisions and not only for pathological relevance.

In our study a diagnosis of comorbid asthma strictly affects radiologic disease severity in CRSwNP patients, so they had significantly higher Lund-Mackay scores than those without asthma. Previously published data has similar findings, where it was highly evident that there is a positive correlation between the severity of asthma and the severity of radiologically-assessed sinusitis (20,22). Of note, one of the factors

we have noticed in our work is the remarkable link between high peripheral EOS levels and the CRSwNP as compared to those in the CRSsNP group.

In the literature, many studies hypothesize that the inflammation of nasal mucosa, which is mediated through neutrophils, is the basis of the development of NP. Moreover, this factor has a negative impact on prognosis and therapeutic failure (23-26).

Also, eosinophilic inflammation has been shown to correlate with sinusitis severity. A recent study conducted among Indian patients with CRS revealed that patients with eosinophilic CRSwNP had worse outcomes due to the increased severity of symptoms (27). This goes in line with our observations. This finding would be of great value in tailoring the best individualized treatment approach for CRSwNP patients. The probability of onset of the CRSwNP phenotype within cases of allergic rhinitis is higher than in cases without allergic rhinitis (28).

Allergic rhinitis may play a different part in CRSwNP: it may be a disease-modifying factor in the inflammatory process, or it can only be one of the comorbidities, thus increasing the burden of symptoms. Constant exposure to allergens may result in a chronic inflammatory response that may cause the progression of allergic rhinitis towards low airway disease, like asthma, following the concept of allergic march (29,30).

Actually, the loss of smell, evaluable with SNOT 22 score or with cognitive neuro-olfactometry, could be useful in clinical practice to phenotype CRSwNP patients, identify the best treatment, and avoid under or overtreatment (31).

However, our study had several limitations, the most important of which is the small number of cases within each sub-group, which would have affected the power to detect any statistically significant differences especially in those with CRSsNP (either with or without asthma). Furthermore, specific biomarkers should be implemented and better defined, especially because of the advent of biological drugs.

Conclusion

There is clear and distinctive variability between both CRSwNP and CRSsNP patients in terms of

clinical presentation, which implicates a potential prognostic value worthy of examination. Similarly, there is heterogeneity within patients with CRSwNP based on the presence of asthma or not. This highlights the importance of further investigating the discrepancy in clinical presentation of different endotypes of CRS. More studies are still warranted to confirm our observations in a prospective cohort setting with a larger sample size.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

Ethics approval and consent to participate: This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki as revised in 2001. The patients received a thorough explanation of this study and gave their written informed consent to be included in this analysis.

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Correspondence:

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Ignazio La Mantia, MD

Otolaryngology Unit, Department of Medical Sciences,

Surgical and Advanced Technologies, University of Catania,

Catania, Italy

Via S. Sofia, 78

Catania, 95123, Italy

Phone: +39095694519532

E-mail: igolama@gmail.com