

Clinical-Cytological-Grading and phenotyping in patients with chronic rhinosinusitis with nasal polyps: the relevance in clinical practice

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Abstract

Chronic rhinosinusitis (CRS) includes two main phenotypes: without nasal polyps (CRSsNP) and with nasal polyps (CRSwNP). CRSwNP may be associated with comorbidity, mainly concerning asthma, aspirin intolerance, and allergy. CRSwNP patients may also be evaluated by clinical-cytological grading (CCG). The current study investigated the prevalence and characteristics of the dif-

ferent CCG and phenotypes in CRSwNP outpatients examined in clinical practice. This retrospective cross-sectional study enrolled 791 consecutive CRSwNP outpatients (424 males, mean age 48.8 years). In the total population, asthma was a common comorbidity (30.8%) as well as aspirin intolerance (24.8%), and allergy (50.8%). As concerns CCG-grading, 210 (26.5%) outpatients had low-grade, 366 (46.3%) medium, and 215 (27.2%) high. As regards cytological phenotypes, 87 (11%) had neutrophilic type, 371 (46.3%) eosinophilic, 112 (14.2%) mast cell, and 221 (27.9%) mixed. High-grade CCG was significantly associated with more frequent asthma, aspirin intolerance, allergy, recurrent surgery, and mixed cytological phenotype. Low-grade CCG was characterized by fewer comorbidities and operations, and neutrophilic phenotype. Therefore, the present study confirmed that CCG is a useful tool in the management of outpatients with CRSwNP. CRSwNP is frequently associated with asthma, aspirin intolerance, and allergy comorbidity. High-grade CCG is frequently characterized by a mixed cytological phenotype, thus, by more severe progress. These real-world outcomes underline that CRSwNP deserves adequate attention for careful management and optimal identification of the best-tailored therapy; CCG and cytological phenotyping could be fruitful tools in clinical practice. Asthma and aspirin intolerance should be adequately investigated in all CRS patients.

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Introduction

Chronic rhinosinusitis (CRS) affects about 10-12% of the European population [1]. Based on the endoscopy and computed tomography (CT) findings, CRS may be classified into two main phenotypes: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP) [2]. CRSwNP is defined by the presence of nasal polyps and by signs and symptoms lasting longer than 8-12 weeks [2,3]. Nasal polyps are benign oedematous masses in the nasal cavities, paranasal cavities, or both. Their

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occurrence depends on an exaggerated inflammatory reaction. As nasal polyps occupy space into nasal cavities, they can cause nasal obstruction, rhinorrhoea, postnasal drip, and hypo/anosmia [4]. The CRSwNP overall prevalence has been approximately estimated to be 2% to 4% of the general population. It has been calculated that approximately 30% of patients suffering from CRSwNP also have asthma [1-3]. Patients with both diseases, *i.e.*, the CRSwNP-asthma phenotype, have a weak therapeutic response and a high recurrence rate, so the disease is more severe and challenging to treat [5]. CRSwNP-asthma phenotype also induces a severe impairment of quality of life (QoL) and causes a substantial financial burden for society [3]. Moreover, CRSwNP has frequently associated also with aspirin intolerance [6]. In particular, the coexistence of CRSwNP, asthma, and aspirin intolerance (the so-called aspirin triad or Widal's Syndrome or Samter's Syndrome) is a relevant adverse prognostic factor with a higher risk of postsurgical recurrences [6]. In this regard, CRSwNP may be, in turn, classified considering different phenotypes, including comorbidity, endoscopic outcomes, X-ray features, and cytological pattern [7]. In particular, a clinical-cytological grading (CCG) has been proposed for defining the best management strategy, to individuate a peculiar prognostic index of relapse, a personalized medical approach, and the association with olfactory dysfunction [8,9]. In this regard, recent technological advances, mainly in the fields of genetics and engineering, expanded the information concerning the phenotypes and the endotypes of chronic respiratory disorders, generally including the type of inflammation and immune response [10]. This information could enable more targeted, effective, and efficient Precision Medicine (PM). PM refers to the "ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology or prognosis of those diseases they may develop, or in their response to a specific treatment" [11]. Consequently, PM allows us to stratify patients into subgroups and to tailor treatment based on their peculiar pheno/endotypes [12]. This approach has been defined with the term Personalized Medicine [13]. Based on this background, we aimed to investigate a large group of Italian outpatients with CRSwNP, who were recruited in a real-world setting. The purpose was to define the prevalence and the characteristics of the different CCG and phenotypes in CRSwNP outpatients examined in clinical practice.

Materials and Methods

Study population

A consecutive series of outpatients was visited at 26 Italian Rhinology Centers; after the initial screening, the outpatients were enrolled in this cross-sectional study conducted from June 2018 to June 2019.

The inclusion criteria were: i) age ≥ 18 yrs old, ii) documented diagnosis of CRSwNP, and iii) informed written consent.

The exclusion criteria were: i) severe anatomic defect of the nasal cavity and/or the nasal pyramid, and ii) concomitant diseases or treatments (including systemic corticosteroids) that could interfere with the interpretation of the results.

The Review Board of each clinical center approved the procedures used in this study.

Study design

All patients were evaluated by clinical history, objective examination, fiber-optic endoscopy, nasal cytology, and skin prick test.

The diagnosis of CRSwNP was performed according to validated criteria stated by European and International guidelines [3].

Outcome

The primary outcome of the current study was to stratify a large group of Italian outpatients with CRSwNP according to the 3 degrees of CCG, such as low (≤ 3), medium (4-6), and high (≥ 7), and the cytological phenotypes [13].

Variables

Clinical characteristics included age, gender, family predisposition to nasal polyps, asthma, and allergy. Age at onset was also evaluated as well as the number of surgery operations for NP. CRSwNP comorbidity included allergy, asthma, aspirin intolerance, and the aspirin triad, such as CRSwNP associated with asthma and aspirin intolerance. Satisfaction for surgery and medical treatment was assessed by the visual analog scale (VAS), where 0 means the lowest level of satisfaction and ten the maximal level.

Nasal endoscopy was carried out by a 3.4 mm diameter flexible fiberscope (Vision-Sciences[®] ENT-2000). Nasal polyp endoscopic 4-grade classification proposed by Meltzer was adopted [14].

Nasal cytology includes sampling, processing, and microscope reading. Sampling requires the collection of cells from the surface of the middle portion of the inferior turbinate by a sterile disposable curette. The procedure is performed under anterior rhinoscopy, with an appropriate light source, and it is painless. The sample obtained is immediately smeared on a glass slide, air-dried, and stained with May-Grünwald-Giemsa (MGG) for 30 min. The stained sample is read at optical microscopy, with a 1000x objective with oil immersion. Fifty fields are considered the minimum number to identify a sufficient number of cells. The count of each cell type was expressed by a semi-quantitative grading, as previously described [8]. The predominant type of inflammatory cell, present in the sample, was considered, such as neutrophilic, eosinophilic, mast cell infiltrates, and mixed cellularity (eosinophil and mast cell). In this way, four cytologic phenotypes were identified: neutrophilic, eosinophilic, mast cell, and mixed, according to validated methodology [14].

Skin prick test was performed, as stated by the European Academy of Allergy and Clinical Immunology [15]. The allergen panel consisted of the following: house-dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cats, dogs, grasses mix, *Compositae* mix, *P. Judaica*, birch, hazel trees, olive trees, cypress, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix. The concentration of allergen extracts was 100 immune reactivity/mL (Stallergenes-Greer Italia, Milan, Italy). A histamine solution in distilled water (10 mg/mL) was used as the positive control, and the glycerol-buffer diluent of the allergen preparations was used as the negative control. Each patient was skin tested on the volar surface of the forearm using 1-mm prick lancets. The skin reaction was recorded after 15 minutes by evaluating the skin response in comparison with the wheal given by the positive and the negative control. Wheel diameter of at least 3 mm was considered a positive reaction. Allergy was defined by the consistency between sensitization and symptom occurrence after the exposure to the sensitizing allergen [16].

Clinical-Cytological Grading has been previously described in detail elsewhere [8,9]. Briefly, CCG is a score based on both nasal cytology findings and some co-morbidities, including asthma, allergy, and aspirin intolerance. To each variable a score value was assigned: neutrophilic infiltrate was scored as 1, mast cell infiltrate was scored 1, eosinophilic infiltrate was scored 2, eosinophilic +

mast cell was scored 4; similarly, aspirin intolerance was scored 1, asthma 2, allergy 2, aspirin intolerance + asthma 3. The CCG was composed as the sum of these individual scores. A global score between 1-3 is considered low grade, 4-6 is medium, and ≥ 7 is high [8,9].

Statistical analysis

Continuous variables were given as means with standard deviations or medians and interquartile ranges (IQR), and categorical variables as the number of subjects and percentage values. The three classes of CCG (low, medium, and high) were considered as the primary outcome. Any statistically significant difference in the mean values among patients with different CCG scores was evaluated by ANOVA followed by Bonferroni *post-hoc* test.

Statistical significance was set at $p < 0.05$, and the analyses were performed using GraphPad Prism software, GraphPad Software Inc, CA, USA and Epi-Info statistical software (Centers for Disease Control and Prevention, Atlanta, GA, USA) were used.

Results

This study included 791 outpatients, mean age 45.88 ± 16.26 years, 424 males, and 367 females. Demographic and clinical characteristics are reported in Table 1. There was a slight preponderance of males: 53.6% *versus* 46.4%. Family predisposition to nasal polyps was present in 205 (25.9%) outpatients, to asthma in 242 (30.6%), and allergy in 305 (38.6%). The mean age at onset was

Table 1. Demographic and clinical characteristics of the outpatients with CRSwNP.

Total outpatients (n=791)	
Age (years) Mean \pm SD	45.88 \pm 16.26
Males N (%)	424 (53.6)
Females	367 (46.4)
Family predisposition to nasal polyps N (%)	205 (25.9)
Family predisposition to asthma N (%)	242 (30.6)
Family predisposition to allergy N (%)	305 (38.6)
Age at onset (years) Mean \pm SD	39.86 \pm 14.42
Asthma comorbidity N (%)	244 (30.8)
Aspirin intolerance N (%)	196 (24.8)
Aspirin triad N (%)	165 (20.9)
Allergy N (%)	402 (50.8)
Operations median (IQR)	1 (0-1)
Satisfaction for surgery (VAS) Median (IQR)	7 (5-8)
Satisfaction for medical treatment (VAS) Median (IQR)	7 (6-8)
CCG N (%)	
Low	210 (26.5)
Medium	366 (46.3)
High	215 (27.2)
Cytological phenotypes N (%)	
Neutrophilic	87 (11.0)
Eosinophilic	371 (46.9)
Mast cell	112 (14.2)
Mixed (eosinophils + mast cells)	221 (27.9)

39.86 ± 14.42 years. Therefore, the mean duration of the disease was about six years. Asthma comorbidity was found in 244 (30.8%) outpatients, aspirin intolerance in 196 (24.8%), the aspirin triad in 165 (20.9%), and allergy in 402 (50.8%). Findings concerning operations, and satisfaction grades are reported in Table 1.

The CCG grade was low in 210 (26.5%) outpatients, medium in 366 (46.3%), and high in 215 (27.2%). Neutrophilic phenotype was identified in 87 (11%) outpatients, eosinophilic phenotype in 371 (46.9%), mast cell phenotype in 112 (14.2%), and mixed (eosinophils and mast cells) phenotype in 221 (27.9%).

The comparison among CCG grades is reported in Table 2. The age was significantly higher in outpatients with the low CCG grade. There was a preponderance of the male gender in the low CCG grade. Outpatients with high CCG grade had greater family predisposition to allergy, lower age at onset, more prevalent asthma comorbidity, more frequent aspirin intolerance, allergy, and aspirin triad.

The number of operations was significantly different among CCG grades. There was a significant ($p=0.002$) difference in the level of satisfaction for medical treatments: more evident between the medium and high-grade CCG. There was a significant difference in the cytological phenotypes among CCG grades (Figure 1). A most common neutrophilic phenotype characterized the low-grade CCG in comparison with the medium-grade and the high-grade; no subject had the mixed phenotype in this group. The medium-grade CCG had the highest prevalence of eosinophilic phenotype in comparison with the low-grade and the high-grade. The high-grade CCG had the highest prevalence of the mixed phenotype in comparison with the low grade and the medium-grade; no outpatient had the neutrophilic phenotype, and only six subjects had the mast cell phenotype.

Discussion

The current study, conducted in real-world settings and scattered across Italy, provided some outcomes that could have clinical relevance in daily practice.

Asthma comorbidity was rather common as about 30% of outpatients were asthmatic as well as about half of them were allergic. These findings are consistent with the concept of united airway

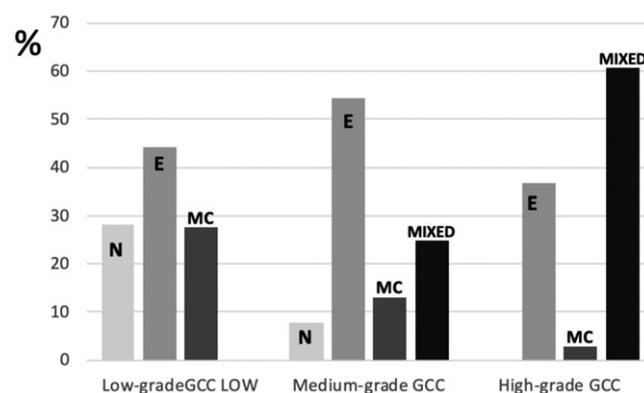


Figure 1. Frequency distribution among CCG grades considering the different cytological phenotypes: N, neutrophilic; E, eosinophilic; MC, mast cell; Mixed, eosinophilic+mast cell.

diseases, such as rhinitis, rhinosinusitis, and asthma, which are frequently coexisting [17,18]. In particular, the CRSwNP-asthma phenotype, mainly if associated with aspirin intolerance, is particularly severe and needs careful management [7].

The distribution of the outpatients according to the CCG grading showed that the most frequent grade was the medium (about half), whereas the other grades were similar (about ¼ each one). The nasal cytology assessment allowed us to identify four cytological phenotypes: eosinophilic, the most common as affected about the half of the sample, mixed (27.9%), mast cell (14.2%), and neutrophilic (11%). Knowing these characteristics is very important in the light of Precision Medicine. Pheno/endotyping-driven is crucial in clinical practice to tailor the best treatment for every patient [19]. However, the bulk of the evidence on this topic derives from studies or trials, recruiting selected patients whose results have limited applicability as do not reflect what is commonly observed in clinical practice [20]. Indeed, high-level evidence deriving from very selected subjects could not concern all patients. There is consequently the need to recruit a CRSwNP population in a real-world setting.

The primary outcome showed that CCG was able to detect significant differences among the grades that could be translated into clinical practice. Outpatients with high-grade CCG had more frequent asthma and aspirin intolerance comorbidity as well as associated allergy. These associations were also consistent with the family predispositions to have asthma and/or allergy. These findings underline the relevance of type 2 inflammation in the pathogenesis of upper and lower airways diseases [21-23]. Moreover, outpatients with high-grade CCG had more operations and consequently greater dissatisfaction with surgery. More interestingly, the cytological phenotyping underlined the relevance of CCG. Indeed, high-grade CCG very frequently was associated with a mixed phenotype. Usually, patients with mixed nasal infiltrate present severe

airway disorder characterized by more intense symptoms and reduced responsiveness to standard treatments [1]. On the other hand, no high-grade CCG outpatient had the neutrophilic phenotype, as well as no low-grade CCG outpatient, had mixed phenotype. This finding suggests a severity gradient of CRSwNP from the lower grade to the higher one. Consistently high-grade CCG was associated with a series of adverse prognostic factors that could predict an unfavorable outcome, characterized by refractory to both medical and surgery standard options. In this regard, the potential use of biologics could pave the way to new therapeutic strategy [24-28]. Therefore, a thorough workup is mandatory to individuate the better treatment. An adequate pheno/endotyping could identify individual therapy.

The present study has some limitations, including the cross-sectional design, the lack of mediators' assessment, and the absence of imaging documentation. On the other hand, the current study was performed in a real-world setting. The real-world studies as they may provide information more adherent to the daily practice that randomized controlled trial that involves selected patient populations that rarely mirror the real situation [29,30]. Finally, the sample was large and well-distributed across Italy.

Conclusions

The present study confirmed that CCG is a useful tool in the management of outpatients with CRSwNP. CRSwNP is frequently associated with asthma, aspirin intolerance, and allergy comorbidity. High-grade CCG is frequently characterized by a mixed cytological phenotype, thus, by severe progress. These outcomes underline that CRSwNP deserves adequate attention to careful management and optimal identification of the best-tailored thera-

Table 2. Stratification of the outpatients with CRSwNP based on the CCG grade.

Variables	CCG low N=210 (26.5%)	CCG medium N=366 (46.3%)	CCG high N=214 (27.2%)	p
Age (years), mean ± SD	48.46 ± 16.89* °	43.96 ± 16.30	46.60 ± 15.20	0.004
Males, N (%)	128 (61.0)** °	178 (48.6)	118 (54.9)	0.016
Family predisposition to NP, N (%)	43 (20.5)	102 (27.9)	60 (27.9)	0.110
Family predisposition to asthma, N (%)	54 (15.7)	116 (31.7)	72 (33.5)	0.182
Family predisposition to allergy, N (%)	59 (28.1)** § *** °	143 (39.1)* ^	103 (47.9)	0.000
Age at onset (years) mean (SD)	42.59 ± 15.28* ° *** §	39.01 ± 14.60	38.63 ± 12.88	0.006
Asthma comorbidity, N (%) mean (SD)	29 (13.8)*** § ** °	86 (23.5)** ^	129 (60.0)	0.000
Aspirin intolerance, N (%) mean (SD)	38 (18.1)*** ° *** §	82 (22.4)	76 (35.3)	0.000
Aspirin triad, N (%) mean (SD)	25 (11.9)*** ° *** §	75 (20.5)	65 (30.2)	0.000
Allergy, N (%) mean (SD)	2 (1)*** ° *** §	212 (57.9)***	188 (87.4)	0.000
Operations median (IQR)	1 [0-1]* ° *** §	1 [0-1]	1 [1-1]	0.000
Satisfaction for surgery, median (IQR)	7 [7-9]	6 [7-9]	7 [5-9]	0.388
Satisfaction for medical treatment, median (IQR)	7 [6-7]* °	7 [6-8.25]	7 [5-8]	0.002
Cytological phenotypes N (%) mean (SD)				0.000
neutrophilic	59 (28.1)** ° *** §	28 (7.7)** ^	0 (0)	
eosinophilic	93 (44.3)** ° * §	199 (54.4)* ^	79 (36.7)	
mast cell	58 (27.6)*** §	48 (13.1)** ^	6 (2.8)	
mixed	0 (0)*** ° *** §	91 (24.9)* ^	130 (60.6)	

NP, nasal polyps. At *post-hoc* analysis: °CCG low vs medium; §CCG low vs high; ^CCG medium vs high; *p<0.05; **p<0.001; ***p<0.0001.

py, and, in this regard, CCG could be a fruitful tool. In particular, considering the estimated prevalence of CRSwNP and the current findings, it could be reasonably expected that about 600.000 Italians have CRSwNP with high-grade CCG. Therefore, intercepting the most severe patients and launching an early and tailored treatment, including the new biologics, could positively modify the natural history and improve the quality of life. In this regard, asthma and aspirin intolerance should be adequately investigated in all CRS patients.

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