

Focus on the Involvement of the Nose and Paranasal Sinuses in Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome): Nasal Cytology Reveals Infiltration of Eosinophils as a Very Common Feature

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Keywords

Churg-Strauss syndrome · Eosinophilic granulomatosis · Polyangiitis · Nasal cytology · Nonallergic rhinitis

Abstract

Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a necrotizing vasculitis that predominantly affects small- to medium-sized vessels. It is characterized by a wide spectrum of extrapulmonary symptoms, including sinonasal and paranasal sinus abnormalities. These are the most common features of this disease, constituting diagnostic criteria for EGPA. However, the actual clinical features, cellular mechanisms and impact on patients' quality of life (QoL) are still a matter of study. **Methods:** Thirty-nine EGPA patients underwent multidimensional rhinological evaluations, including rhinofibroscopy, nasal cytology, and QoL questionnaires. This was coupled with respiratory and rheumatological assessments. **Results:** Twenty-eight patients were diagnosed with chronic rhinosinusitis (CRS). Of these, 18 had

nasal polyposis (NP). Chronic rhinitis was diagnosed in 10 patients. Of these, 3 had allergic rhinitis (AR) and seven had non-AR (NAR). Overall, only 1 patient (2.6%) was normal. Nasal cytology showed that hypereosinophilia was present in 17/28 patients with CRS, 4/7 patients with NAR and all patients with AR. SNOT-22 and SF-36 showed a severe impact of nasal symptoms on QoL. No differences in asthma control or rheumatological patterns for EGPA were observed among patients with or without NP. **Conclusions:** Even when the rheumatological assessment scored EGPA "under control" according to the Birmingham Vasculitis Activity Score and Vasculitis Damage Index, sinonasal diseases and related nasal inflammatory processes were not controlled. Therefore, there is a need for clinical monitoring and targeted treatment to control the inflammatory processes and improve the QoL of EGPA patients.

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a rare, systemic, necrotizing vasculitis affecting predominantly small- to medium-sized vessels. It is traditionally associated with antineutrophil cytoplasmic antibodies (ANCA) [1].

EGPA is characterized by a wide spectrum of extrapulmonary symptoms. Sinonasal symptoms represent one of the most common features of this disease. In fact, sinonasal involvement in EGPA is so frequent that it represents 1 of the 6 diagnostic criteria of this disease proposed by the American College of Rheumatology (ACR) [2]. Here, sinonasal involvement is indicated with the generic term “paranasal sinus abnormalities.” Although frequently encountered, the diagnosis of “paranasal sinus abnormalities” in EGPA has been based on a number of vague patient complaints and symptoms. This has made it difficult to assess the prevalence of this disease, the presentation pattern, and the clinical course of sinonasal involvement in EGPA.

Recently, diagnostic accuracy in the field of rhinology has significantly increased since the introduction of nasal cytology into clinical practice. However, this technique has never been applied to patients with systemic autoimmune diseases, including EGPA.

The purpose of this study is to better delineate the clinical features of the criterion “paranasal sinus abnormalities.” It also aims to describe the frequency of these abnormalities and their clinical presentation in one of the largest and most homogeneous groups of EGPA patients examined to date. We focused our analysis on the cytological examination of nasal smears from EGPA patients, which served as a tool to better diagnose sinonasal inflammatory diseases. We correlated these results to other assessment criteria of this disease. Furthermore, the impact of sinonasal symptoms on the quality of life (QoL) of EGPA patients was assessed and compared with other clinical and instrumental parameters. Furthermore, we examined the severity of asthma symptoms and extent of disease control in a group of asthmatic patients in order to determine whether chronic rhinosinusitis (CRS) affects asthma control.

Materials and Methods

This single-center, cross-sectional study included 39 consecutive EGPA patients who visited the University Hospital of Pisa from January 2010 to July 2014. The University Hospital of Pisa is a referral center for ANCA-associated systemic vasculitis in Italy.

The 39 EGPA patients were routinely evaluated by an interdisciplinary group of physicians, which included rheumatologists, otorhinolaryngologists, and pulmonologists.

Rheumatological Assessment

To be enrolled in this study, patients had to meet at least 4 of the 6 ACR disease classification criteria at the time of diagnosis [2]. At the time of our cross-sectional study, all patients had a confirmed diagnosis of EGPA. They were all receiving a therapy of oral steroids and/or disease-modifying drugs, including methotrexate, azathioprine, and mycophenolate mofetil. The disease was considered controlled by a rheumatologist according to the Birmingham Vasculitis Activity Score [3] and the Vasculitis Damage Index [4].

As far as patients' past medical history was concerned, the clinical and laboratory data of interest were retrieved using a standard form from the patients' clinical charts. Data collected in this form included demographic data and major anamnestic records. Based on a previous study [5], we subdivided our group using the patients' clinical subsets or phenotypes. One group included patients displaying ANCA-associated symptoms, i.e., mainly the features of small-vessel vasculitis (such as glomerulonephritis and mononeuritis multiplex). The other group included patients that displayed ANCA-negative symptoms related to eosinophilic tissue infiltration that leads predominantly to cardiopulmonary manifestations [6].

Rhinological Assessment

First, we collected all historical data relating to the first appearance of nasal symptoms for each patient, including the date of onset and the relationship between the development of asthma and the EGPA diagnosis. We recorded previous ear, nose, and throat ENT evaluations and surgery, as well as the therapy prescribed and its effect on the control of symptoms.

All patients underwent a fiberoptic nasal endoscopy using a nasolaryngoscope (Olympus ENF rhinolaryngo-fiberscope type GP; 33 cm in length, 3.4 mm in diameter; Olympus Medical System Corporation, Tokyo, Japan). Possible diagnoses included: (a) *normal* (in cases of no nasal symptoms and no sinonasal endoscopic alterations) and (b) *rhinitis*. Rhinitis was diagnosed as a chronic disease characterized by nasal congestion and rhinorrhea. It correlated variably with sneezing, hyposmia, and postnasal drip, which was associated with allergic rhinitis (AR) and its impact on asthma recommendations [7]. Rhinitis was considered to be AR if at least 1 skin test result was positive and there was a concordance with the chronological pattern of symptoms. If not, or in the case of a positive skin prick test not concordant with the chronological emergence of symptoms, rhinitis was defined as “nonallergic” (non-AR [NAR]) [8]. It was further examined using nasal cytology [9].

NAR was divided into different subtypes based on nasal cytology. These included: (1) NAR with neutrophils (which displayed a significant infiltration by neutrophils in the absence of bacteria, spores or biofilms), (2) NAR with eosinophils (NARES) (which had significant infiltration by eosinophils in the nasal mucosa, up to 50–70% of total inflammatory cells), (3) NAR with mast cells (in which mast cells were the most prevalent inflammatory population in the nasal mucosa), and (4) NARES with mast cells (in which both types of inflammatory cells are present concurrently with a portion of this population displaying a degranulated morphology). The duration and severity of both AR and NAR were classified ac-

cording to the recommendations by the ARIA (Allergic Rhinitis and its Impact on Asthma) taskforce [7], which included the following categories: (1) mild and moderately severe rhinitis; (2) intermittent and persistent rhinitis; and (c) chronic rhinosinusitis with (CRSwNP) and without nasal polyposis (CRSw/oNP) (i.e., nasal blockage, nasal drip, facial pain, and impaired reduction associated with endoscopic nasal signs of polyps, mucopurulent discharge, and/or mucosal edema in accordance with the European Position Paper on Rhinosinusitis and Nasal Polyps [10]). If nasal polyps were present, their severity was assessed by their size, which was measured by the clinical score established by Hox et al. [11] and Lund and MacKay [12]. Computed tomography scans were performed only in cases of CRSwNP with unclear symptoms or clinical presentation.

All patients underwent nasal cytology, which was performed according to recently validated criteria [9], and anterior rhinoscopy. Samples were collected by scraping the middle portion of the inferior turbinate using a Rhino-Probe (Arlington Scientific, Springville, UT, USA) [13]. The scraped material was transferred on a glass slide, air-dried, and stained by the May-Grünwald-Giemsa technique (Carlo Erba, Milan, Italy). The slides were visualized using a Nikon E600 light microscope (Nikon Canada Inc., Mississauga, ON, Canada). Fifty microscopic fields were examined at a magnification of $\times 1,000$ to quantify the numbers of different cell types (eosinophils, neutrophils, mast cells, and lymphocytes) and the ratio between epithelial ciliated cells and mucinous cells. Using recently validated criteria [9], nasal cytology was performed (if feasible) after an appropriate washout of topical and systemic drugs, such as steroids or antihistamines, for at least 1 week [13].

The 35-Item Short Form Health Survey (SF-36) was also used to assess individual patient's physical and mental status, in addition to QoL. Furthermore, we used a disease-specific QoL instrument, the 22-item SinoNasal Outcome Test (SNOT-22). The SNOT-22 is a widely adopted questionnaire with specific questions focused on nasal symptoms and their impact on psychological status, sleep, and ear and facial symptoms.

Respiratory Assessment

To assess respiratory involvement, all patients underwent pulmonary function tests (FEV_1 and FEV_1/SVC). Results were interpreted according to the European Respiratory Society criteria [14]. The methacholine challenge test was performed to estimate bronchial hyperreactivity according to standard procedures previously described [15]. Asthma severity was evaluated according to GINA guidelines, and the level of asthma control was assessed by a self-administered questionnaire, the Asthma Control Test (ACT) [16]. Airway eosinophilic inflammation was estimated by measuring exhaled nitric oxide [17]. Values >25 ppb were considered to be abnormal.

Statistical Analysis

Data were expressed as means $\pm$ SD for continuous variables and as absolute frequencies and percentages for nominal variables. The χ^2 test, McNemar test, ANOVA, and t tests were performed to determine if there were any associations between a patient's clinical symptoms and his/her serological parameters. Correlations between different variables were analyzed using linear regression and the Spearman coefficient ($p < 0.05$). Statistical analyses were carried out using SPSS 13 (SPSS Inc., Chicago IL, USA). This study was approved by the Ethics Committee of the University Hospital of Pisa.

Table 1. Demographics of the patients with eosinophilic granulomatosis and polyangiitis

Gender, <i>n</i>	
Female	19 (48.7%)
Male	20 (51.3%)
Atopy present, <i>n</i>	
Yes	
No	23 (59%)
Smokers, <i>n</i>	16 (41%)
Yes	3 (7.7%)
No	36 (92.3%)
Vasculitic pattern of EGPA, <i>n</i>	17 (43.4%)
Eosinophilic pattern of EGPA, <i>n</i>	22 (56.4%)
Age at study visit (mean $\pm$ SD), years	54.8 $\pm$ 13.8
Age at ENT onset (mean $\pm$ SD), years	29 $\pm$ 14.7
Age at asthma onset (mean $\pm$ SD), years	37.8 $\pm$ 13.9
Age at EGPA onset (mean $\pm$ SD), years	50.5 $\pm$ 14.6
FEV ₁ , % predicted (mean $\pm$ SD)	82 $\pm$ 21
BVAS (range 0–63), median (min–max)	0.0 (0–4)
VDI (range 0–64), median (min–max)	3 (0–11)

ENT onset, first appearance of nasal symptoms reported by the patient; BVAS, Birmingham Vasculitis Activity Score, version 3 (i.e., internationally validated tool for the assessment of disease activity); VDI, Vasculitis Damage Index (validated tool for the assessment of damage related to vasculitis or its treatment).

Results

Thirty-nine EGPA patients (19 females, 20 males) were enrolled in this cross-sectional study, and all patients gave written consent for their participation. The primary demographic and clinical characteristics of the patients are reported in Table 1.

As commonly happens in patients suffering from EGPA, nasal symptoms first appeared during adulthood (approximately at 29 years of age) and generally seemed to be a predictor for the subsequent development of asthma and EGPA of 10 and >20 years, respectively. At least 1 ENT evaluation was performed before the diagnosis of EGPA in 31/39 patients (79.5%); 25/39 patients (64.1%) underwent at least 1 surgical procedure before the diagnosis (a single procedure: 14/25; combined procedures: 9/25; inferior turbinoplasty: 1/25 [4%]; septoplasty: 6/25 [24%]; polypectomy: 5/25 [20%]; functional endoscopic sinus surgery: 14/25 patients [56%]). The majority of patients who underwent operations had CRSwNP ($n = 11$; 44%) or CRSw/oNP ($n = 8$; 32%). No statistical associations between the duration of the symptoms and the severity of the sinonasal disease were evident.

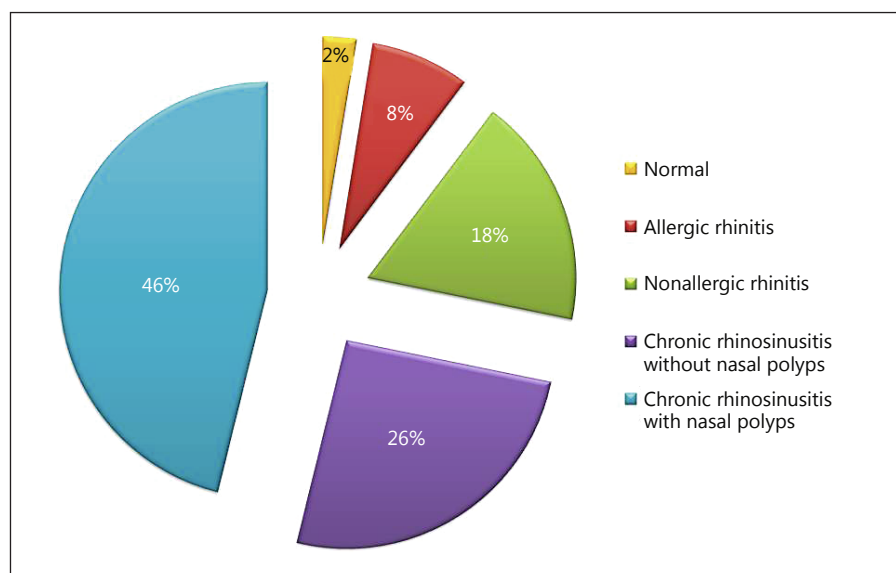


Fig. 1. Distribution of nasal and paranasal diseases in the 39 patients with eosinophilic granulomatosis and polyangiitis.

Table 2. Nasal complaints and their impact on quality of life (QoL) according to SF-36 and SNOT-22

	n	ANCA, Y/N/ missing)	Allergy (SPT), Y/N/ missing	SNOT-22, M ± SD	ISF-36 M ± SD	ISM-36 M ± SD	Nasal symptoms				
							PND, Y/N	nasal obstruct., Y/N	anterior rhinor- rhea, Y/N	hypos- mia, Y/N	ACT, M ± SD
Total patients	39	11/25/3	23/16/0	31.6±21.2	41.6±10.4	47.1±11.6	32/7	27/12	25/14	23/16	21±4.33
Patients with nasal disease	38	10/25/3	23/15/0	31.8±21.5	41.8±10.5	47±11.7	32/6	27/11	25/13	23/15	21±4.37
AR	3	0/3/0	3/0/0	23.5±33.2	49.9±9.3	55.4±10.1	2/1	1/2	1/2	1/2	12.5±0.7
NAR	7	3/4/0	3/4/0	33.7±15.1	34.2±9.8	47.2±9.4	6/1	6/1	7/0	5/2	19.7±3.3
CRSw/oNP	10	2/6/2	4/6/0	26.3±25.4	42.2±11.7	47.6±14.4	10/0	5/5	5/5	3/7	22.8±4.3
CRSwNP	18	5/12/1	13/5/0	35±21.3	43.6±9.3	45.5±11.6	14/4	15/3	12/6	14/4	20±3.9
CRSw/oNP + CRSwNP	28	7/18/3	17/11/0	31.9±22.7	43.1±10	46.2±12.4	24/4	20/8	17/11	17/11	20.8±4.1

ACT, score of the Asthma Control Test.; ANCA, serologic presence of antimyeloperoxidase antineutrophil cytoplasmic antibodies; AR, allergic rhinitis; CRSw/oNP, chronic rhinosinusitis without nasal polyposis; ISF-36, physical index for SF-36; ISM-36, mental index for SF-36; M ± SD, mean ± SD; NAR, non-AR; PND, postnasal drip; SPT, skin prick test positivity; Y/N, present or absent.

ENT Evaluation

At the time of ENT evaluation, the most common complaints were persistent postnasal drip (32/39: 82%) followed by nasal obstruction (27/39: 69.2%), rhinorrhea (25/39: 64.1%), sneezing (25/39: 64.1%), and hyposmia (23/39: 59%) (Table 2). These symptoms positively correlated with additional diagnoses (Fig. 1). We detected CRS in 28 patients (71.8%). Of these, 18 patients had nasal polyps (CRSwNP: 46.2%), and 10 did not have polyps (CRSw/oNP: 25.6%). Among the 18 patients with CRSwNP, 12 (66.7%) had been treated surgically previ-

ously, and they displayed significant recurrence of polyps at the time of the ENT evaluation.

The other diagnoses included AR in 3 patients (7.7%). Of these, symptoms were mild and intermittent in 1 case, and severe and persistent in the other 2 cases. NAR was observed in 7 patients (17.9%). Of these, 5 were diagnosed with NARES, 2 displayed NAR with neutrophils, and only 1 of our 39 patients (2.6%) was considered normal. Although almost all of the patients (38/39: 97.4%) displayed active and persistent nasal symptoms, only 4 of them (10.5%) were under topical therapy at the time of the ENT

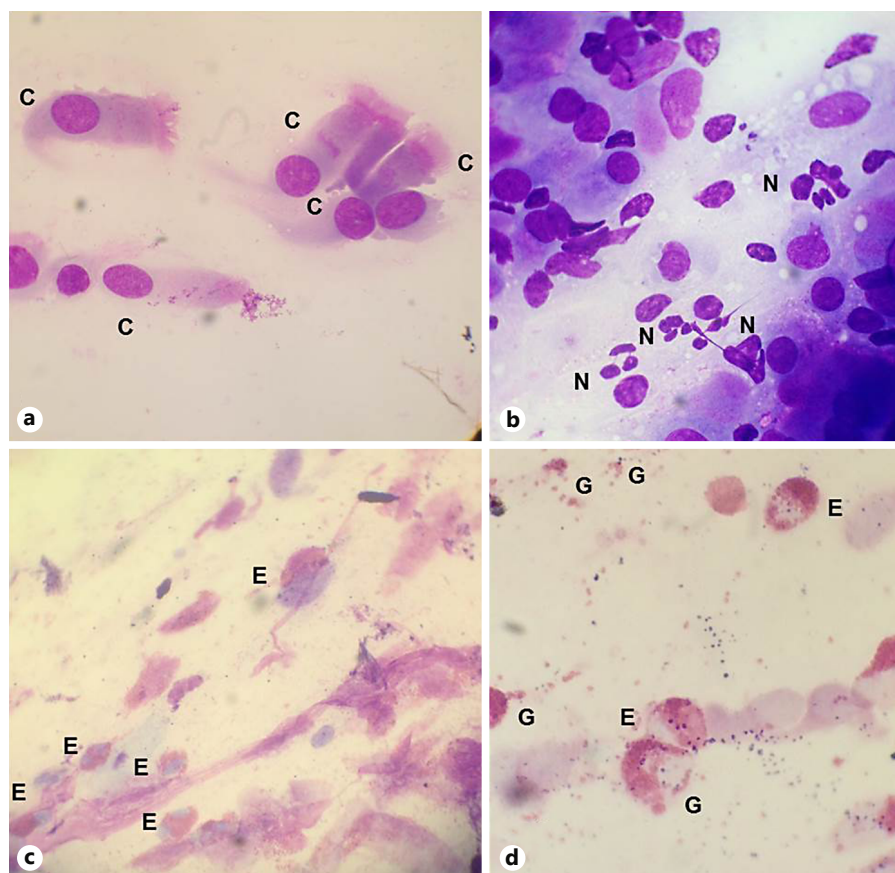


Fig. 2. Images of nasal cytology in patients with eosinophilic granulomatosis and polyangiitis. All samples were stained with May-Grünwald-Giemsa and examined using an optical microscope with a $\times 1,000$ objective with immersion oil. **a** Ciliated cells (C) without visible supranuclear hyperchromatic stria, a sign of unspecific cellular damage. **b** Neutrophils (N). **c** Numerous eosinophils (E). **d** Eosinophils (E) with extensive degranulation (G) and release of chemical mediators.

evaluation. (Specifically, nasal therapy consisted of mometasone furoate once a day.) None of the patients could interrupt oral steroid treatment because this was necessary for EGPA control. However, we asked for the suspension of nasal therapy for at least 7 days prior to the ENT evaluation.

Patients with CRSwNP often showed massive involvement of the nasal cavities characterized by a mean Hox score of 8.6 (range 4–17). Nine patients (50%) also displayed a Lund grade 3 polyposis, 7 patients a grade 2 polyposis (38.9%), and 2 patients a grade 1 polyposis (11.1%). Endoscopically, polyps had a typical grayish appearance without any distinctive features normally associated with “common” inflammatory polyps. Neither ulcerations nor crusting was observed in these patients. No statistically significant associations were found between the presence of a nasal disease and the pattern of EGPA presentation.

Cytological analyses were performed on all patients, even though the results could be affected by the concomitant steroid therapy in use in the majority of these individuals (37/39; 94.9%). Surprisingly, we noticed that a sig-

nificant number of inflammatory infiltrates were present in all samples except for 9 (23.1%). In these cases, the cytological analyses were normal. In a subgroup of 28 patients with CRSwNP and CRSw/oNP, the main feature we observed was intense eosinophilia in 17 cases (60.7%). In 1 case, mast cells were present, while eosinophilic degranulation was found in 4 other cases. Four nasal smears (14.3%) showed intense neutrophilia without eosinophils, and 6 others were normal. Some typical patterns of nasal cell inflammation detected in nasal cytology are depicted in Figure 2. In the group of patients diagnosed with rhinitis ($n = 10$; 25.6%), the cytological analyses confirmed that eosinophils were the predominant inflammatory cell population. Specifically, eosinophils were present in 3 AR patients (100%) as expected. They were also found in 5/7 NAR patients (71.4%). However, no statistically significant correlation was found between nasal and peripheral hypereosinophilia ($p = 0.168$).

Sinonasal diseases greatly affected the QoL of our EGPA patients. The average SNOT-22 score of the nasally affected EGPA patients (38/39) was 31.8 ± 21.5 ,

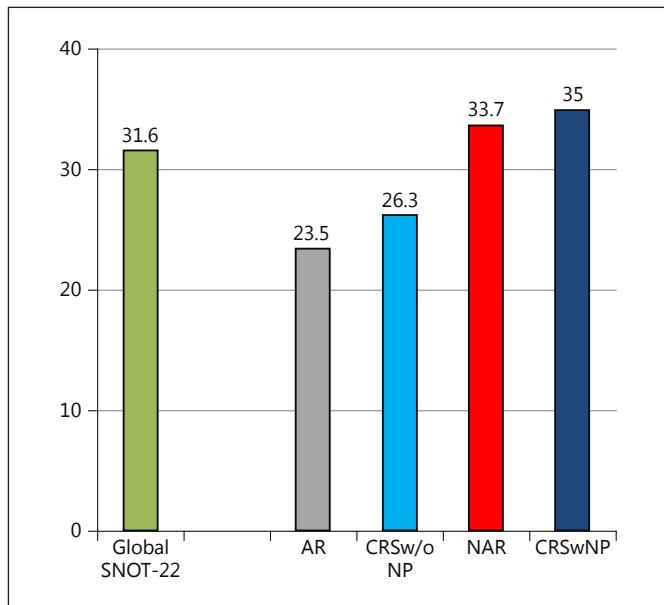


Fig. 3. SinoNasal Outcome Test-22 (SNOT-22) results in patients with eosinophilic granulomatosis and polyangiitis and allergic rhinitis (AR), non-AR (NAR), and chronic rhinosinusitis with (CRSwNP) and without nasal polyposis (CRSw/oNP).

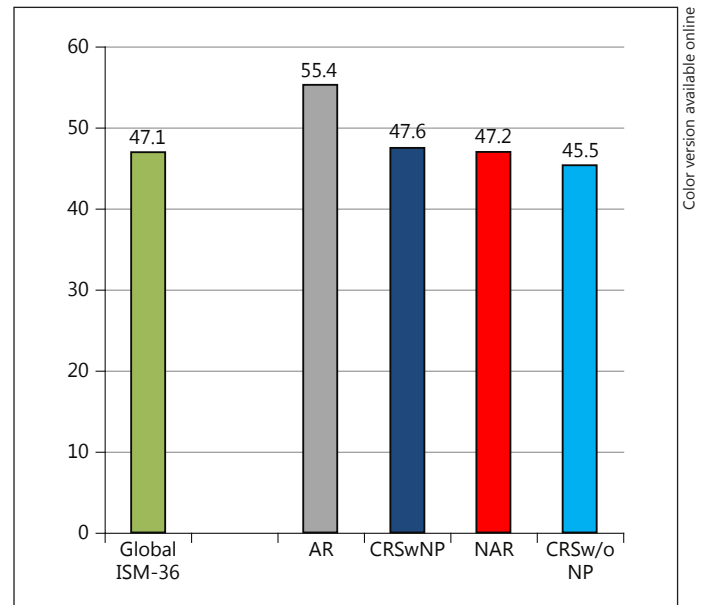


Fig. 4. Mental scores (ISM-36) in the 36-Item Short Form Health Survey (SF-36) in patients with eosinophilic granulomatosis and polyangiitis and allergic rhinitis (AR), non-AR (NAR), and chronic rhinosinusitis with (CRSwNP) and without nasal polyposis (CRSw/oNP).

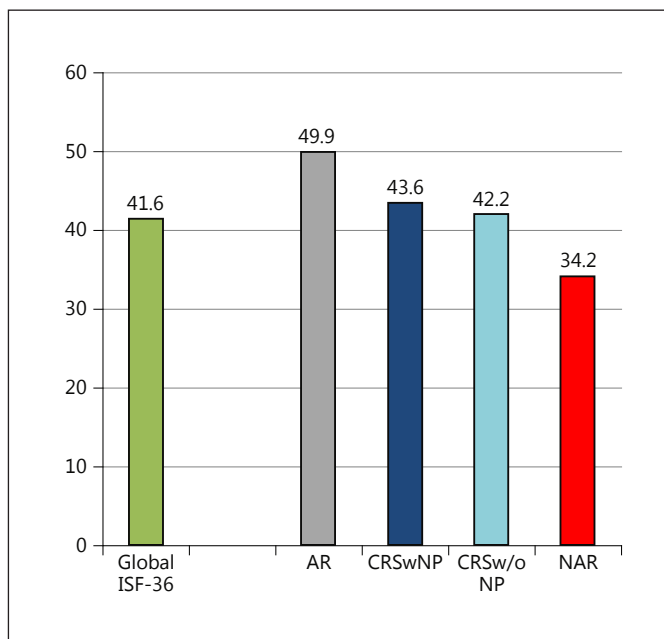


Fig. 5. Physical scores (ISF-36) in the 36-Item Short Form Health Survey (SF-36) in patients with eosinophilic granulomatosis and polyangiitis and allergic rhinitis (AR), Non-AR (NAR), and chronic rhinosinusitis with (CRSwNP) and without nasal polyposis (CRSw/oNP).

which was significantly higher than that of controls patients (9.5 ± 1.8). Certain subgroups of patients, such as patients with NAR and CRSwNP, had worse outcomes (Table 2; Fig. 3). However, statistical analysis using a univariate ANOVA did not reveal any statistically significant differences amongst these groups.

As demonstrated by the SF-36, patients in the EGPA group had lower mental (ISM-36) and physical (ISF-36) scores compared to healthy sex- and age-matched individuals in the general population (normal value: 49 ± 10) (Table 2; Fig. 4, 5). Similar to the SNOT-22 results, CRS and NAR patients had lower QoL scores compared to the remaining patient categories, even though statistical significance was not reached. However, SF-36 and SNOT-22 had a mutual correspondence, which was demonstrated by their significant statistical correlation ($p < 0.000$ and $p < 0.001$ for ISM-36 and ISF-36, respectively).

For the respiratory evaluation, lower airway symptoms usually appeared after nasal symptoms, displaying a mean latency period of 7.8 years (Table 1). Similar to the observed nasal symptoms, the respiratory evaluation demonstrated that many patients had a poorly controlled disease even though they were considered “controlled” by a rheumatologist. Specifically, the majority of patients

showed persistent bronchial obstruction (FEV_1/SVC : $79 \pm 13\%$ of predicted; FEV_1 : $82 \pm 21\%$ of predicted) and moderate-to-severe asthma, which was often partially or poorly controlled (ACT, mean $\pm$ DS: 20 ± 4). The level of eosinophilic inflammation was moderately high, as assessed by the level of exhaled nitric oxide (FeNO median: 36.5, range: 8–177 ppb).

We did not observe any difference in the ACT test. The extent of eosinophilic inflammation (blood eosinophil count and FeNO) and lung function in patients with CRSwNP appeared similar to those of patients with CRw/oNP. The control of asthma determined by the ACT test strongly correlated with FEV_1 ($p < 0.001$) and FeNO ($p < 0.003$). On the other hand, no correlation was found between ACT and SF-36, suggesting that the physical status is significantly influenced by nasal symptoms and not by the extent of asthma control in this group of patients.

Discussion

Sinonasal involvement is a common feature in patients with EGPA, and “paranasal sinuses abnormalities” was included as 1 of the 6 diagnostic criteria for EGPA in the 1990 ACR publication [2]. The concept of “paranasal sinuses abnormalities” is, however, vague and imprecise from a diagnostic and lexical perspective. In fact, it is unclear if it should be determined based upon symptomatic, clinical, or radiological criteria.

Therefore, we provide an updated clinical definition of the sinonasal involvement in EGPA, a rare disease that has important clinical implications. Our study demonstrates that sinonasal involvement is frequent and severe, and it significantly reduces a patient’s QoL. This condition is mediated mainly by eosinophils, which we detected in the nasal smears, and clinically it is represented mostly by the clinical picture of CRS, both with and without polyps. Even though systemic therapy is capable of controlling the disease, nasal involvement seems to have an independent behavior requiring targeted assessment and therapy.

The main limitation of previous studies focused on EGPA relates to the rarity of this disease, which only affects 10–15 people in 1 million in Europe [18], resulting in an annual incidence of 0.9 per million in the population [19]. However, the number of patients in our study is substantial. Our 39 EGPA patients, who underwent a uniform diagnostic protocol and care management over a relatively short period of time, represent one of the largest cohorts studied in a single European institution.

Studies of ENT involvement in EGPA have been scarce over the last 35 years. The global incidence of sinonasal diseases in EGPA patients has been found to fluctuate from 69% [20] to 75% [21] or 87.5% [22]. Furthermore, the distribution of subdiagnoses varies significantly from one study to another. For example, AR afflicted 42.8% of the EGPA patients in a study by Bacciu [21], 53.5% of those patients in a study by Lane et al. [23] and 62.5% in a study by Solans et al. [22]. Additionally, CRSwNP was found to be uncommon (25% incidence) by Solans et al. [22], common (50% incidence) in a study by Olsen et al. [20], and the most typical symptom (76.1% incidence) in the study by Bacciu et al. [21]. Nasal crusting is also very common and may range from an incidence of 36.3% [20] to 75% [24].

Our group obtained different incidence rates which differed from the aforementioned studies. This may be a direct consequence of the setting of this study, which focused on the nasal symptoms of EGPA patients. In our group, the global incidence of sinonasal diseases was 97.4% ($n = 38/39$). This is the highest incidence reported so far. We observed no nasal crusting or ulcerations. Using nasal cytology, it was possible to classify NAR in EGPA patients for the first time, making it possible to study NAR and its relationship to autoimmune diseases.

Nasal cytology confirmed that in the noses and other anatomical locations of EGPA patients, eosinophils promote this disease independently of the allergic pattern of the patients. Nasal eosinophils, which lead to the development of NAR and NARES, are the main inflammatory cell population responsible for nasal symptoms in EGPA patients. This may cause the low QoL observed in this subgroup of patients, and it may be responsible for the development of more complicated and serious nasal diseases, such as nasal polyposis, if not treated [25]. These symptoms are found in our EGPA patients, too. More interestingly, nasal cytology showed that eosinophils were persistently present in the nasal smears of EGPA patients even during long-term immunosuppressive systemic steroid therapy. Therefore, steroid therapy should be considered by rheumatologists to be effective in controlling EGPA in accordance with the Birmingham Vasculitis Activity Score and Vasculitis Damage Index questionnaires. However, it is insufficient for reducing local nasal inflammation, which is indicated by the persistence of eosinophils in nasal smears. This should be taken into consideration when dealing with EGPA patients especially because peripheral hypereosinophilia does not correlate with nasal hypereosinophilia in these patients.

Our study confirms that sinonasal diseases affect the health-related QoL in patients with EGPA. This impact can be underestimated by general practitioners, who are more prone to think that patients under chronic systemic steroid therapy are somehow “covered” with respect to sinonasal symptoms. This may justify the use of low doses of nasal corticosteroids, which are the primary therapy for AR and CRSwNP among our patients (10.5%) and in the EGPA literature (32%) [24]. Independently of the reason that may justify this insufficient therapy, patients seem to disagree and feel the problem as significant in their life, which is evidenced by their high SNOT-22 and SF-36 scores. In our analysis, the lowest scores were reported by NAR and CRS patients, and these data confirm those of the existing literature [25]. In particular, existing evidence shows that NAR is more frequently associated with impaired sleep, excessive daytime sleepiness, concentration problems, and increased irritability when compared to AR [26]. Furthermore, all health-related scores are significantly worse in patients with NARES [27]. Health-related QoL is significantly lower in patients with CRS plus EGPA, which was demonstrated by Srouji et al. [24]. The impact on patients’ QoL is similar to that of patients suffering from other common chronic conditions, such as diabetes mellitus or rheumatoid arthritis. When the clinical symptoms of CRS are not controlled (particularly in case of CRSwNP), new biological drugs, such as omalizumab [28], have been used in EGPA patients with very promising results (withdrawal of oral steroids, good asthma control).

We aimed to find correlations between sinonasal and cytological profiles of the disease and rheumatological ones. We tried to compare this to ANCA status, peripheral eosinophilia, and clinical manifestations of the disease [5]. We failed to show any significant statistical associations, which was different from what seen in the literature [20, 29]. ENT symptoms are present in ANCA-positive patients, whereas cardiac manifestations associated with poor survival are more frequent in ANCA-negative patients. Conversely, Sinico et al. [5] hypothesized that ANCA-positive patients are less likely to have nasal polyps. We did not find any methodological or selection biases to justify this lack of correspondence.

Our EGPA patients had chronic asthma with persistent bronchial obstruction despite systemic treatment with oral corticosteroids, immunosuppressive drugs, inhaled corticosteroids, and long-acting β_2 -agonists, which was in agreement with other authors [30]. In the literature, the relationship between sinonasal disease and poor

asthma control has been widely described [31]. Nevertheless, we did not observe differences in asthma control between our patients with or without nasal polyps. The most important parameters that seem to influence asthma control are lung function and bronchial eosinophilic inflammation [32].

Considering that our patients were “controlled” with respect to systemic involvement according to existing requirements, such as the Birmingham Vasculitis Activity Score and the Vasculitis Damage Index [33], it is evident that sinonasal diseases and related nasal inflammatory processes are not. Currently, specific tools that may be applied to evaluate the sinonasal contribution to EGPA are lacking. In the future, the control of sinonasal eosinophilic inflammatory processes should be considered in a multidisciplinary approach to treat EGPA patients. Given the central role of eosinophilic inflammation in EGPA, we believe that monitoring of these patients cannot be separated by a periodic reevaluation of the nasal status. Currently, it remains difficult to establish how much and how long patients who are considered to be in remission for the systemic disease should be treated with glucocorticoids and immunosuppressive drugs. It is a delicate balance between risk of systemic disease exacerbations and side effects from treatment. We believe that monitoring of systemic biomarkers of eosinophilic inflammation and nasal cytology could provide an important tool to support treatment decisions regarding local and systemic therapy.

Our study demonstrates that EGPA is a heterogeneous and complex disease. It requires multidisciplinary management, not only during the diagnostic phase but also during clinical and therapeutic follow-up. Current standardized therapies are able to control the systemic symptoms of EGPA, but they are not sufficient to control the nose and sinonasal phenotypes. Therefore, sinonasal diseases require specific clinical and functional monitoring in addition to targeted treatment. This is necessary not only to control the inflammatory processes but also to improve the health-related QoL of these patients.

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Disclosure Statement

The authors declare that they have no conflict of interest.

Author Contributions

We state that all authors have contributed to, read, and approved this paper. In particular, V. Seccia, C. Baldini, M. Latorre, L. Cristofani-Mencacci, E. Bacci, and M.L. Bartoli substantially contributed to the conception and design of the article, and acquisition of data; P. Paggiaro, S. Sellari-Franceschini, M. Gelardi, and I. Dallan were involved in drafting the article and revising it critically for important intellectual content and corrected the final version of this article.

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