The association of computed tomography findings with systemic eosinophilia in chronic rhinosinusitis with nasal polyps

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April 1, 2022

Abstract

S) score, posterior ethmoid sinus (PES) score, sphenoid sinus (SS) score, ethmoid sinus score/maxillary sinus score (ES/MS) ratio and posterior ethmoid sinus score/anterior ethmoid sinus score (PES/AES) ratio were significantly higher in the B-high subgroup. Logistic regression analyses disclosed that comparing with other sinus CT parameters, OC score was an independent predictor for systemic eosinophilia. There was a moderate correlation between OC score and the level of blood eosinophil (r=0.57, P<0.001). Conclusion: Olfactory cleft opacification shown in paranasal sinus CT may be a marker for the phenotype of CRSwNP with systemic eosinophilia, which appears to be closely related to olfactory dysfunction.

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Abstract

Objective: Systemic eosinophilia strongly linked to serious condition and poor prognosis in chronic rhinosinusitis with nasal polyps (CRSwNP). We aimed to explore the relationship between systemic eosinophilia and the features of paranasal sinus CT in CRSwNP.

Study design: Retrospective study.

Setting: A regional medical center in Guangzhou, China.

Participants: Patients suffered from CRSwNP under endoscopic sinus surgery from January 2015 to December 2017.

Main outcome measures: Patients in this cohort were classified into high blood eosinophils (B-high) and low blood eosinophils (B-low) subgroups with a cutpoint of 0.3×10^9/L. Clinical parameters, sinus Lund-Mackay (L-M) score and olfactory cleft (OC) scores were analyzed in both two subgroups.

Results: The treatment outcome was poorer in the B-high subgroup, and in which preoperative sinus L-M CT score and tissue eosinophil number were higher. B-Low subgroup showed lower concomitant rate of allergic rhinitis and asthma. What's more, OC score, ethmoid sinus (ES) score, posterior ethmoid sinus (PES) score, sphenoid sinus (SS) score, ethmoid sinus score/maxillary sinus score (ES/MS) ratio and posterior ethmoid sinus score/anterior ethmoid sinus score (PES/AES) ratio were significantly higher in the B-high subgroup. Logistic regression analyses disclosed that comparing with other sinus CT parameters, OC score was an independent predictor for systemic eosinophilia. There was a moderate correlation between OC score and the level of blood eosinophil (r=0.57,P <0.001).

Conclusion: Olfactory cleft opacification shown in paranasal sinus CT may be a marker for the phenotype of CRSwNP with systemic eosinophilia, which appears to be closely related to olfactory dysfunction.

Keywords: Nasal polyps; Systemic eosinophilia; Computed tomography; Olfactory cleft opacification; Association;

Key points

- Systemic eosinophilia strongly links to poor prognosis in nasal polyps.
- The percentage of patients at the uncontrolled status is significantly higher in the patients with blood eosinophilia.
- OC score, PES score, ES score, SS score, ES/MS ratio and PES/AES ratio are significantly higher in the B-high subgroup.
- Compared with other CT indicators, OC score is an independent predictor for systemic eosinophilia.
- Olfactory cleft opacification in paranasal sinus CT could be closely associated with the phenotype of CRSwNP with systemic eosinophilia.

1 Introduction

Chronic rhinosinusitis (CRS) is a heterogenous disease accompanied with persistent mucosal inflammation, which makes an impact on 3% to 6.4% of the whole population(1). CRS could be grouped into two phenotype based on the presence or absense of nasal polyps(2). Although the relative prevalence of CRSwNP phenotype is about 20%, CRSwNP shows more serious condition and a greater degree of impairment for quality of life(3, 4). Meanwhile, a few reports have shown that over thirty percentage of patients suffered from CRSwNP continue to be clinically uncontrolled after standard therapy(5, 6). Therefore, several biomarkers have been applied for predicting the prognosis and guiding the therapy and follow-up.

Recently, the clinical parameters such as blood eosinophil count and paranasal sinus compute tomography (CT) score have been proposed as markers for identifying phenotypes of CRSwNP and predicting disease severity(7-9). For example, the parameter about CT scores like the ES/MS ratio could be an predictor in diagnosis of eosinophilic CRS and prediction of CRSwNP recurrence(10). Ho, et al reported that blood eosinophil number can be used as a systemic predictor of eosinophilic CRS(11). In addition, paranasal sinus CT findings combined with eosinophilia in peripheral blood can be used for predicting the treatment outcome and the degree of disease severity of CRSwNP(12). Furthermore, our recent study showed that blood eosinophilia is an independent risk factor related to poor disease control in patients with CRSwNP(5). Together, these studies suggest that paranasal sinus CT and blood eosinophilia as useful markers may play important roles in prediction of phenotype and prognosis of CRS. However, few studies focus on the relationship between paranasal sinus CT and blood eosinophilia, and whether the imaging features of paranasal sinus CT could be closely related to the phenotype of nasal polyps with blood eosinophilia remains unknown.

Here, we hypothesized that the specific findings in paranasal sinus CT of CRSwNP patients may be associated with systemic eosinophilia. For the sake of confirming the hypothesis, we performed the retrospective study to determine the relationship between paranasal sinus CT features and blood eosinophilia in CRSwNP.

2 Materials and Methods

2.1 Ethical considerations

The project in the research was ratified by the XXX, and approval number was 2019[163]. This study was performed with the informed consent of participants.

2.2 Subjects and study design

The research workflow was summed up in Figure 1. CRSwNP patients who underwent endoscopic sinus surgery (ESS) were selected from the department of otolaryngology in the XXX from Jan 2015 to Dec 2017. CRSwNP was diagnosed in accordance with the European Position Paper on Rhinosinusitis and Nasal polyps (EPOS) 2012 guidelines (2). Excluding criteria: 1) patients with fungal sinusitis, cystic fibrosis, choanal

polyps and odontogenic sinusitis. 2) patients without blood routine examination and tissue specimens. 3) patients without preoperative sinus CT. 4) patients under 16 years old. 5) patients after treatment of systemic or intranasal glucocorticoid within four weeks before ESS. Patients accompanied by asthma was diagnosed according to the Global Initiative for asthma guidelines (GINA)2014(13). Patients with allergic rhinitis(AR) was confirmed base on the Allergic Rhinitis and its impact on Asthma (ARIA) 2010 guideline(14). Data for peripheral blood eosinophil counts were obtained according to routine blood test. On the strength of our previous study, systemic eosinophilia was defined as the eosinophil number in peripheral blood [?] $0.3\text{x}10^9$/L(5). Lund-Kennedy endoscopic (L-K) scores were assessed by two otolaryngologists who were unaware of disease condition in the retrospective study.

2.3 Assessment of treatment outcome

The level of clinical disease control and total nasal symptom score (TNSS) were included for the assessment of therapeutic effect in CRSwNP patients(2). Symptoms such as nasal congestion, rhinorrhea, postnasal drip and olfaction decline were incorporated in TNSS (Range of score: 0-12) , in which each symptom was assessed with zero indicating "None", one indicating "Mild", two indicating "Moderate" and three indicating "Severe". The status of disease control were assessed by two otolaryngologists according to classification criteria of EPOS 2012(2). In brief, the levels of disease control were divided into controlled, partly controlled, or uncontrolled. CRS under control was determined by nearly healthy or healthy mucosa, with no troublesome symptoms and unnecessary systemic medicine for controlling disease. Patients with partly controlled condition suffered from at least one as follow: continuous nasal obstruction, mucopurulent rhinorrhea/postnasal drip, decreased sense smell, facial pain, fatigue/sleep disorder, mucosal lesion examined by endoscope, and requirement with one course of systemic steroids/antibiotics nearly a month. CRS in uncontrolled state could be determined by no less than three items from the level of partly controlled.

2.4 Paranasal sinus computed tomography (CT) imaging

The examination of paranasal sinus CT(Toshiba Aquilion, Tokyo, Japan) was performed in each participant, and CT scoring was according to Lund-Mackay scoring system(15) and the olfactory cleft scoring protocol(16). The L-M CT scoring system contained scoring for the following sinuses: frontal sinus (FS), maxillary sinus (MS), anterior ethmoid sinus (AES), posterior ethmoid sinus (PES), sphenoid sinus (SS) and ostiomeatal complex score (OMC), in which every sinus was assessed with 0 indicating "Normal", 1 indicating "partly opacification" and 2 indicating "whole opacification", and OMC was assessed with 0 indicating "Normal" and 2 indicating "whole opacification". In addition, whole ethmoid sinus (ES) score, ES score/MS score ratio and PES score/AES score ratio were calculated. Similar to the above scoring system, each OC was evaluated by a similar scale of 0 indicating "no opacification", 1 indicating "partial opacification" and 2 indicating "total opacification". All of paranasal sinus CT scores were evaluated by two independent radiologists.

2.5 Histological evaluation

Samples of nasal polyps were obtained from each participant during surgery, and which were treated with fixation and embedded in paraffin. Then, all of samples were sliced up sections and stained with hematoxylin and eosin, which were evaluated by two independent observers under the light microscope (Leica DM4B, Wetzlar, Germany). Five fields with densest inflammatory cells infiltration in the subepithelial layer were chosen at 100xmagnificantion in each sample. Afterwards the whole inflammatory cells and eosinophils were observed at 400xmagnificantion (high power field, HPF), and counted in the focal area. The amount of eosinophils and whole inflammatory cells were recorded in every focal area under HPF, and the proportion of eosinophils accounted for the whole inflammatory cells was calculated.

2.6 Statistic analysis

The analyses of data were carried out by statistical software, SPSS 26.0 (IBM, Inc., Chicago, Illinois). Categorical variables like asthma comorbidity were performed with χ^2 test. T-test for two independent samples was applied to analyze continuous variables conforming to normal distribution, and which were

described as mean ± SD. with abnormal distribution, continuous variables were described as median and interquartile range, which were analyzed by Mann-Whitney U test. Correlation analysis was performed to analyze between sinus CT features and the level of eosinophil in peripheral circulation. The predictive factors for systemic eosinophilia was estimated by multiple logistic regression model. If the$P$ value was less than 0.05, and the difference was determined to be statistically significant.

3 Results

3.1 General information

135 patients (90 males and 45 females) were included in the retrospective study (shown in Figure 1). The average follow-up period was 119.3 weeks, and the average age was 38.7 years old. 10.3% of patients suffered from allergic rhinitis, and 11.9% of patients were diagnosed as asthma. About 9.6% of patients were current smokers, and 46 out of 135 patients underwent endoscopic sinus surgery more than once.

3.2 Demographic and clinical characteristics of the retrospective cohort

To characterize the patients with systemic eosinophilia, the subjects were divided into B-high subgroup and B-low subgroup. There were 54 patients (40%) in the B-high subgroup and 81 patients (60%) in the B-low subgroup. The clinical features of two subgroups were shown in the Table 1. Patients in the B-low subgroup were younger than B-high subgroup (P =0.026). Moreover, compared with B-low subgroup, B-high subgroup showed higher percentage of AR (P =0.002) and asthma (P =0.012), higher preoperative L-M CT scores (P =0.014), higher blood and tissue eosinophil counts (Both$P$ <0.001). Moreover, there was significantly different in the clinical disease control status between two subgroups (P =0.022). Compared to the B-low subgroup, the percentage of patients at the uncontrolled status was significantly higher in the B-high subgroup (P =0.026).

3.3 L-M CT score and OC score between subgroups of CRSwNP

Compared with B-low subgroup, the OC score was significantly higher in B-high subgroup(P <0.001). For sinus L-M CT scoring, the PES score, ES score, SS score, ES/MS ratio and PES/AES ratio were remarkably higher in B-high subgroup than which in B-low subgroup (P <0.001, =0.002, =0.011, <0.001 and <0.001, respectively) (shown in Figure 2). No significant difference of MS score, AES score, FS score and OMC score between both subgroups was found(P >0.05) (shown in Table E1).

3.4 Correlation analysis and multiple logistic regression analysis between sinus CT imaging findings and systemic eosinophilia

A positive and weak correlation was found between blood eosinophil count and PES score, ES score, SS score, ES/MS ratio and PES/AES ratio, but there was a moderate and positive correlation between OC score and the level of blood eosinophil count (r=0.57, P <0.001) (shown in Figure 3). We further determined the independent effects of PES score, ES score, SS score, ES/MS ratio, PES/AES ratio and OC score in predicting systemic eosinophilia by logistic regression model, the above mentioned factors were adjusted for clinical parameters, such as prior ESS, gender, AR, age and asthma (shown in Table 2). Only OC score was significantly associated with blood eosinophilia (P <0.001).

4 Discussion

Blood eosinophil is a crucial biomarker which is in connection with specific endotype and severity of CRSwNP(11, 17). Our previous study has demonstrated that systemic eosinophilia (Blood eosinophil count [?]0.3x10^9/L) were associated with poor treatment outcome of nasal polyps(5). However, the correlation of paranasal sinus CT features and blood eosinophil count was rarely observed in the previous study. Thus, identification of auxiliary clinical parameters strongly linked to blood eosinophilia in CRSwNP could be helpful to assess the prognosis and guide the management. The new finding in the present research is that OC score was positively related to the level of blood eosinophil, and an independently predictor for systemic eosinophilia of nasal polyps. Overall, these results indicate that olfactory cleft opacification in paranasal sinus CT scan could be a feature for the phenotype of CRSwNP with blood eosinophilia.

In this study, the percentage of subjects with blood eosinophilia was 40% while 60% was subjects without blood eosinophilia based on the cutpoint of $0.3x10^9$/L. Nevertheless, the consensus about the cutpoint of blood eosinophilia in CRSwNP has not reached. The results about significant difference in clinical characteristics between two subgroups confirm that eosinophilic inflammation in blood is linked to the comorbidities such as allergy rhinitis and asthma and poor disease control as well, which are in accordance with previous studies(5). Although it is not clear that how blood eosinophilia acts on the pathogenesis of CRSwNP, we could speculate that systemic eosinophilia may contribute to local eosinophilic infiltration in nasal mucosa and relate to structured histopathology in nasal polyps (18, 19).

In clinical practice, blood routine examination is the most direct method that reflect the status of eosinophilic inflammation in blood. However, the count of peripheral blood eosinophil is largely affected by oral glucocorticoid treatment (20, 21). Therefore, finding additional parameters correlated to systemic eosinophilia is necessary. Paranasal sinus CT scan as a widely used and noninvasive test has been used to identify the phenotypes of CRSwNP(7), predict the recurrence(10) and assess the sensitivity of glucocorticoid for the patients(22). but few studies concentrate on the relationship between paranasal sinus CT features and peripheral systemic eosinophilia. Interestingly, our study showed that OC score, PES score, ES score, SS score, ES/MS ratio and PES/AES ratio were higher in the B-high subgroup, but only OC score as the independent risk factor was associated with systemic eosinophilia. And for all we know, this is the first research for reporting the significant correlation between OC area opacification in paranasal sinus CT scan and CRSwNP with systemic eosinophilia.

Previous study has verified that olfactory cleft opacification were associated with olfactory dysfunction(23, 24), and could be a clinical predictor for identifying eosinophilic CRS(25). Chen et al. (16)have confirmed that OC score could be used to identify the airway hyperresponsiveness in CRS, which is positively associated with blood eosinophil counts. These reports indicated that OC score was related to systemic eosinophilia in CRSwNP. Although the reason why OC scores were higher in the patients with systemic eosinophilia is unclear, the finding in this study suggests that the area of olfactory cleft with opacification could be sensitive to the eosinophilic inflammation in the blood.

However, several limitations in our present study are worth considering. The size of sample size was small, and the data in this research were short of validation in prospective cohort study. In addition, the patients in the retrospective cohort were derived from a single tertiary medical center, which may be not generalizable to patients with CRSwNP in other medical institutions. Finally, 22-item Sinonasal Outcome Test score as a clinical parameter was not included for the assessment of disease severity.

To sum up, our study reveals that OC opacification in sinus CT is independently associated with blood eosinophilia, and may be served as a specific indicator of systemic eosinophilia in CRSwNP patients.

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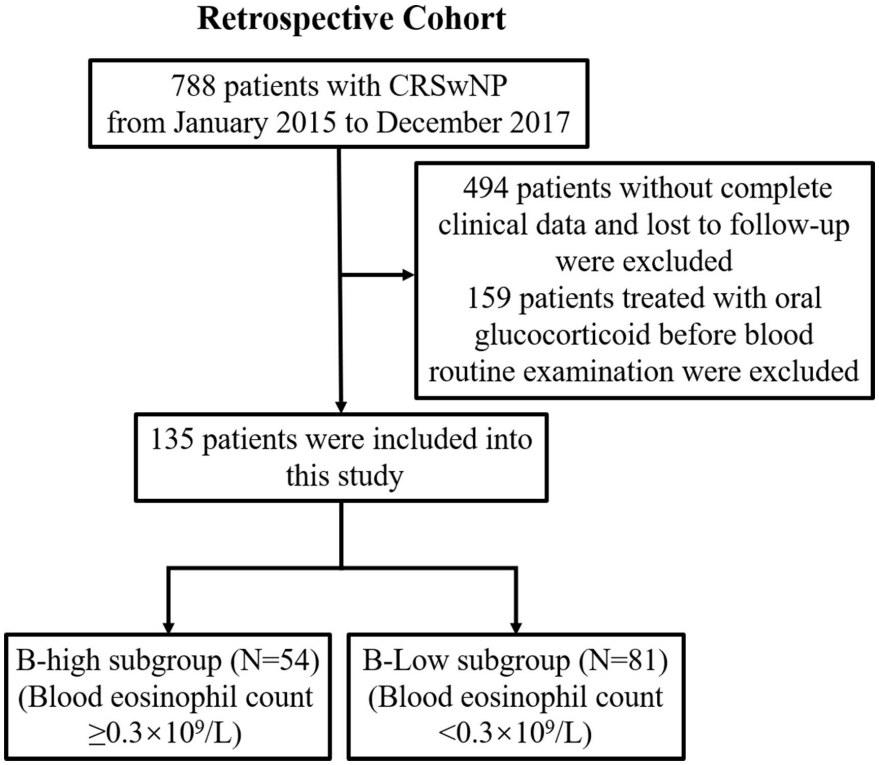
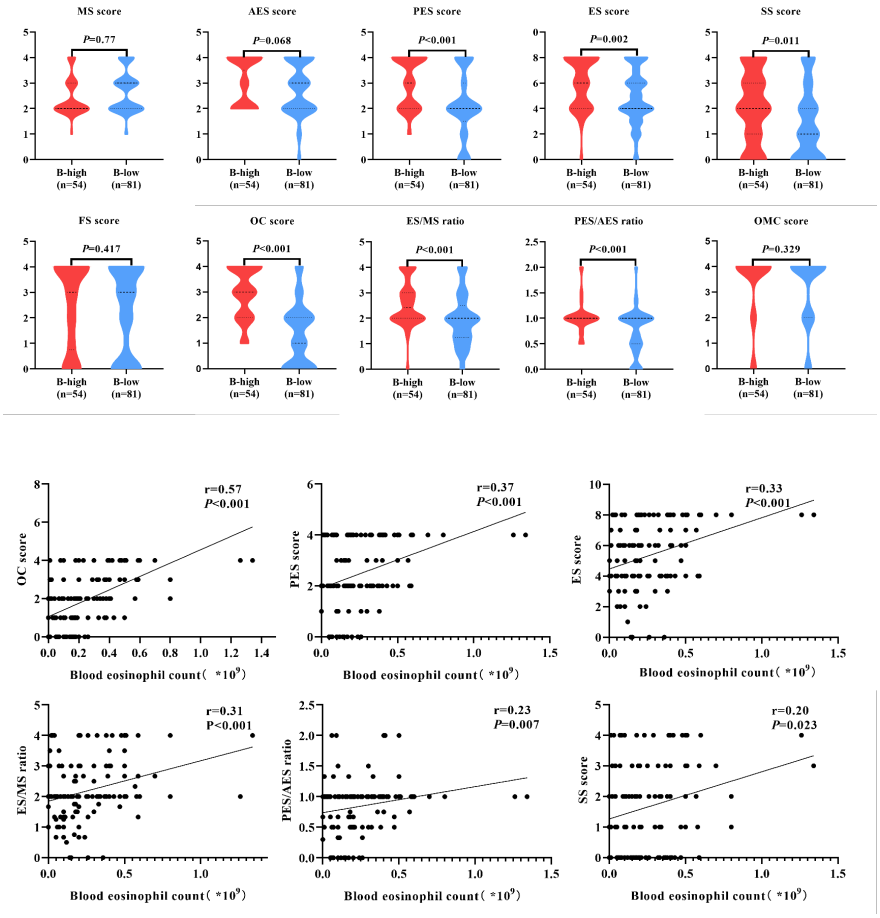
Figure legend:

Figure 1. Flow diagram for patient inclusion and classification

Figure 2. Comparison of L-M CT score and OC score between B-high subgroup and B-low subgroup in CRSwNP. L-M score, Lund-Mackay score; OC score, olfactory cleft score; ES score, ethmoid sinus score; MS score, maxillary sinus score; ES/MS ratio, ES score/MS score ratio; PES score, posterior ethmoid sinus score; AES score, anterior ethmoid sinus score; PES/AES ratio, PES score/AES score ratio; SS score, Sphenoid sinus score; OMC score, ostiomeatal complex score; FS score, frontal sinus score.

Figure 3. Relationship between blood eosinophil levels and OC score, PES score, ES score, ES/MS ratio, PES/AES ratio and SS score. OC score, olfactory cleft score; PES score, posterior ethmoid sinus score; ES score, ethmoid sinus score; ES/MS ratio, ES score/MS score ratio; PES/AES ratio, PES score/AES score ratio; SS score, sphenoid sinus score.





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