Association of Allergic Biomarkers in Patients with Chronic Rhinosinusitis With or Without Asthma

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ABSTRACT

Background

Chronic rhinosinusitis and asthma are considered under unified airway diseases which describes the shared epidemiologic and pathophysiologic relationship among the chronic inflammatory diseases of the upper and lower airways

Objective

To assess the asthma in patients with chronic rhinosinusitis and determine the relationship of allergic biomarkers, tissue eosinophilia and radiological bone changes in patients with chronic rhinosinusitis with or without asthma.

Method

Prospective study involving 74 adult patients attending the Department of Otorhinolaryngology and Pulmonology at the Kathmandu University Dhulikhel Hospital for treatment of chronic rhinosinusitis and / or asthma and for functional endoscopic sinus surgery between May 2023 and May 2024. Absolute eosinophil count, total serum IgE and spirometry tests were performed. Radiological evidence of osteitis and tissue eosinophilia from surgical samples was evaluated. Correlations between allergic biomarkers,spirometry values, tissue eosinophilia, and radiological bone changes were determined in patients of chronic rhinosinusitis with or without asthma using the Mann Whitney U test, Student t test and the chi square test.

Result

A positive association was observed between the radiological bone score with tissue eosinophilia ($p=.018$), and smoking ($p < 0.001$) in between the two groups. Chronic eosinophilic rhinosinusitis was observed in 39 (52.7%) patients. 15 patients with Chronic rhinosinusitis had asthma ,and among these asthmatic patients 11 had eosinophilic chronic rhinosinusitis. Mild osteitis was evident in 34 (45.9%) ,moderate osteitis in 39 (52.7%) and severe in 1 (1.4%). Among 15 asthmatic patients, 10 had moderate osteitis and 5 had mild osteitis.

Conclusion

A rigorous exentration of osteitic bony nidus appears necessary for successful treatment outcomes in all chronic rhinosinusitis patients and to prevent acute exacerbation in the asthmatic group of chronic rhinosinusitis patients.

KEY WORDS

Asthma, Chronic rhinosinusitis, Osteitis

INTRODUCTION

Asthma and chronic rhinosinusitis (CRS) are considered in the context of unified airway theory, which describes the upper and lower airways as a single functional unit.[1-4] It is estimated that 20-33% of patients with chronic rhinosinusitis also have asthma.[5]

Previous studies have shown that in patients with severe asthma, inflammatory biomarkers such as sputum and blood eosinophils and a higher functional residual capacity are correlated with the radiological severity of concomitant chronic rhinosinusitis. A direct relationship was also observed between the extent of sinus disease, measured as the thickness of the sinonasal mucosa on computed tomography and bronchial inflammation, reflected both by the presence of eosinophils in the bronchi and blood.[6] Therefore, for optimal care of patients with chronic rhinosinusitis, a multidisciplinary team approach is absolutely necessary involving pulmonologists and otolaryngologists.

There has been a paucity of research related to this subject in our country. The aim of this study was to assess the asthma in chronic rhinosinusitis in the hospital population and to determine the relationship of allergic biomarkers, tissue eosinophilia, and radiological bone changes in patients of chronic rhinosinusitis with or without asthma.

METHODS

This was a quantitative, analytical and prospective, hospital-based study conducted in patients who attended the Department of Otorhinolaryngology and Pulmonology of the Kathmandu University Dhulikhel Hospital, Kavre for the treatment of chronic rhinosinusitis and/ or asthma. All participants were informed about the nature and purpose of the study. Consent was obtained and recorded by signature or fingerprint. The Institutional Review Committee of KUSMS (approval No. 228/23) approved the study protocol.

A cohort of 74 consecutive patients diagnosed as chronic rhinosinusitis determined by guidelines using the European position paper on rhinosinusitis older than or equal to 18 years of age and who underwent Functional Endoscopic Sinus Surgery (FESS) between May 2023 and May 2024 constituted the study population.[7] Patients were also evaluated in the Pulmonology Unit of Department of Internal Medicine at the Dhulikhel Hospital, Kathmandu University Hospital, Kavre for the diagnosis of asthma based on clinical criteria provided by the Global Initiative for Asthma (GINA 2023) specifically based on symptoms such as cough, wheezing, chest tightness, and shortness of breath, which are variable in intensity and frequency, along with spirometry/peak flow measurement demonstrating variable airflow limitation.[8] Patients with sinonasal malignancy, trauma to the skull base or facial bone, and those with other respiratory diseases other than asthma were excluded.

The physicians of the Department of Pulmonology and Critical Care Medicine and Otolaryngology conducted a structured face-to –face interview and clinical examination. With the help of a study questionnaire, the age, sex, history of previous sinus surgery, co-factors of the disease such as asthma, signs and symptoms, and findings of anterior rhinoscopy were observed. Written informed consent was obtained from each patient by the principal investigator or the co-investigators. The objectives and protocol of the study were properly explained to the patient. A detailed clinical data form was completed. Diagnostic nasal endoscopy was performed after packing the nasal cavity with 4% Xylocaine for 15 minutes. Nasal decongestant was also used before endoscopy to make it easier to negotiate the endoscope sometimes due to congested turbinates and mucosa. The endoscopy was performed using a 4 mm 0 degree and 45 degree endoscope by the same surgeon for all patients to avoid interobserver bias.

Pulmonologists evaluated patients for comorbid asthma with chronic rhinosinusitis. Patients were diagnosed as asthmatic according to the Global Initiative for asthma management and prevention guidelines if they complained of asthma-related symptoms such as cough, dyspnea, chest tightness, and/or wheezing with the presence of reversible airway obstruction.[8] All the patients underwent a spirometry, and blood analyses for absolute eosinophil count and Serum IgE. Spirometry was performed to assess pre and post bronchodilator FEV1 according to the recommendations of the American Thoracic Society/ Europeran Respiratory Society using an office spirometer (Spirolab spirometer).[9]

Using the parameters-120 kV, 500 mA, a complete coronal CT scan with 3 mm slices was taken that focused on the osteomeatal complex and paranasal sinuses. The CT images were read by a single radiologist. Bony thickness and pattern of bony involvement in each sinus was calculated to obtain an aggregate score called the Global osteitis scoring scale as proposed by Georgalas et al.[11] If less than 50% of the sinus walls involved and the osteitis was < 3 mm wide, it was considered as grade I. Less than 50% of the sinus involvement and 3-5 mm width was designated as grade II. Less than 50% of the sinus involvement, wider than 5mm or greater than 50% of the sinus wall involvement and < 3 mm wide osteitic changes were considered as grade III. More than 50% of sinus wall involvement and 3-5 mm was considered grade IV. Similarly, more than 50% of sinus wall and thicker than 5 mm were designated as grade V.

In this way, each sinus was given a rating ranging from 0 to 5. The scores of all 10 sinuses (right and left frontal, anterior ethmoid, posterior ethmoid, maxillary, and sphenoid) were added, producing a global osteitis score ranging from 0 to 50. Osteitis was therefore classified as, not significant if < 5,

mild if the total score was 5 to < 20, moderate if it was 20 to ≤ 35 and severe if it was greater than 35.

Patients were taken up for functional endoscopic sinus surgery and CRS was stratified according to the presence or absence of nasal polyps (CRSwNP and CRSsNP, respectively). The sinus tissue samples were evaluated by a single histopathologist blinded with symptoms, CT findings and investigation results. The number of eosinophils per high power field (HPF, 400X) was evaluated .Patients with an eosinophil count ≥ 5/HPF in the samples will be considered to have tissue eosinophilia.[12-14]

Data collection was done by using the clinical data proforma. Non-probability convenient sampling technique was used. Statistical package for social science software (version 25.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data were expressed as numbers and percentages for categorical variables and mean (standard deviation) for continuous variables. Data analysis was performed using the Mann Whitney U test, the Chi square test and the student t test. A p-value < 0.05 was considered to indicate statistical significance in all calculations.

RESULTS

Of 74 patients, 46 (62.2%) were men and 28 (37.8%) were women with a mean age of 39.74 years (standard deviation 12.2). The sociodemographic information of the patients is depicted in table 1. There were 25 (33.8%) smokers and 49 (66.2%) non-smokers. The eosinophilic type of CRS was observed in 39 (52.7%) of patients. A total of 15 patients with CRS had asthma, and among these asthmatic patients 11 had the eosinophilic type of CRS. Mild osteitis was evident in 34 (45.9%) of patients, moderate osteitis in 39 (52.7%) and severe in 1 (1.4%) patients. Among 15 asthmatic patients, 10 had moderate osteitis and 5 had mild osteitis. Ten patients gave a history of the previous FESS and one had Samter's triad. The radiological Global Osteitic Scoring Scale (GOSS) and histopathological types in patients with CRS with or without asthma are shown in table 2. The various clinical and upper and lower airways characteristics of participants are presented in table 3. When association between radiological global osteitis scoring scale(GOSS) with tissue eosinophils score was assessed by using chi square test, it was also found to be significant (p=.018). Smoking showed a significant association (p < 0.001) in between the two groups. However, there were no significant differences between the spirometry values, radiological GOSS score, tissue eosinophilia and gender between the asthmatic and non-asthmatic group of patients with CRS as shown in table 2. Similarly, the levels of allergic biomarkers such as total serum IgE and absolute eosinophil count were also similar between the two groups.

Table 1. Sociodemographic variables of patients

Age (years)	Number (Percentage)
≤18-20	3 (4.05)
21-30	17 (22.97)
31-40	20 (27.02)
41-50	17 (22.97)
51-60	14 (18.91)
61-70	3 (4.05)
Gender	
Male	46 (62.2)
Female	28 (37.8)
Total	74 (100)

Table 2. The radiological Global osteitic scoring scale (GOSS) and histopathological types seen in patients with CRS with or without asthma

	Range	Asthma		Total
		Present	Absent	
GOSS	5 to < 20	5	29	34
	20 to < 35	10	29	39
	≥ 35	0	1	1
Histopathological type	Non- eosinophilic type	7	28	35
	Eosinophilic type	8	31	39

Table 3. Clinical and the upper and lower airways characteristics of participants stratified according to the presence or absence of asthma analysed by Mann Whitney U test

Variable	Mean ± SD for CRS without asthma	Mean ± SD for CRS with asthma	p value
Smoking	0.19±0.39	0.93±0.26	<.001
FEV1/FVC	81.65±6.84	77.21±7.54	<.030
FVC	2.40±0.83	2.40±0.65	0.88
FEV1	1.97±0.73	1.87±0.58	0.71
Age	40.34±12.27	37.40±12.08	0.40
GOSS	18.81±7.38	20.53±7.36	0.46
Total serum IgE	807.85±1180.8	932.23±1086.94	0.76
AEC	445.53±261.09	525.13±285.07	0.28
Tissue eosinophilia	6.81±5.68	8.91±6.42	0.26

DISCUSSIONS

A study done in Europe demonstrated that 20-60% of patients with chronic rhinosinusitis (CRS) with nasal polyps (CRSwNPs) have asthma.[15] This indicates that CRSwNP and asthma may share common pathogenetic features. These upper and lower airway conditions are functionally and immunologically associated, and often called "unified airway diseases.[16,17] A local inflammatory reaction in one portion of the airway can reach the systemic circulation and potentially affect distant airway sites.[18]

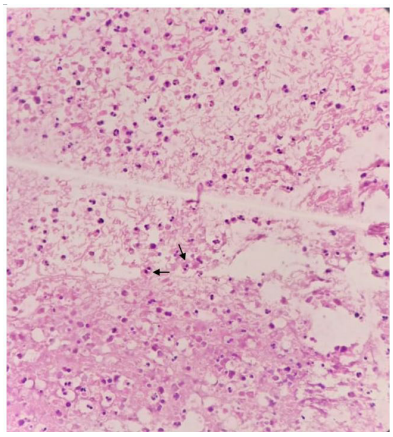

Figure 1. Histopathological section from nasal polyp showing infiltration of stroma with eosionophils (400× magnification); Eosinophils marked by arrow.

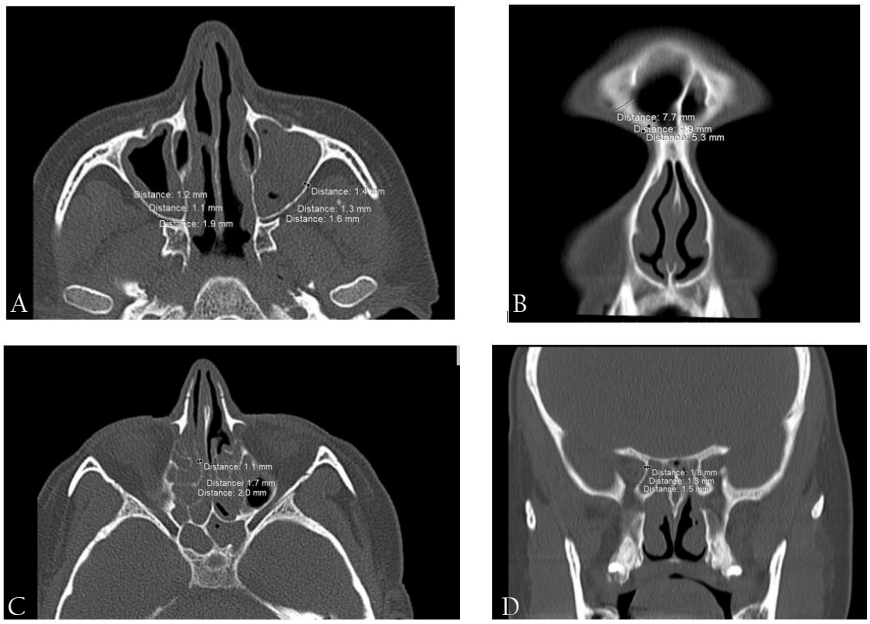

Figure 2. Global Osteitis scoring for A. bilateral maxillary sinus wall thickness, B. Frontal sinus wall thickness, C. Anterior ethmoid air cell bone thickness, D. Spnenoid sinus wall thickness.

To our knowledge, this is the first of its kind to study the prevalence of asthma in CRS in the hospital population of Nepal. The prevalence of asthma in CRS is estimated to be between 20% and 33% in the earlier literature.[5] In our study, the prevalence of asthma in patients with CRS was found to be 20.3% which is comparable to previously published reviews.

Newman et al. also showed an association between extensive sinus disease on CT scanning with a relative increase in the peripheral eosinophil count.[19] Harlin et al. found a significant association between tissue eosinophilia and asthma in adults with chronic sinusitis.[20]

The term osteitis has been used to describe bony thickening of sinus walls present in CRS. Studies done in the past have discussed the role of osteitis in the disease's pathogenesis and refractory.[21] Osteitis has been shown to correspond to substantial endoscopic severity and poorer computed tomography grading.[15,17] It has been recognized as a poor prognostic factor in the surgical management of CRS.[15]

Measurement of the bony thickness of the sinus walls is widely used although there is no consensus on the exact degree of thickening for osteitis.[22]

There is a wide range of variation in the reported incidence rates of underlying osteitis from 36-76% in patients with CRS.[15] A notable finding worth mentioning is that, we observed that all of our patients had some evidence of underlying osteitis in bone. Also ,all the asthmatic group of CRS patients had high grade osteitis ($p < 0.001$).Our findings confirm and extend those of previous literature.[12,23-25] The considerably higher incidence figure of underlying osteitis reported in this study may be due to the late presentation of most patients for surgery. Furthermore, concurrent osteitis in some patients who underwent revision functional endoscopic sinus surgery (FESS) cases may be attributed to previous surgical mucosal trauma and persistent inflammation. This finding has important implications because the presence of coexistent osteitis in CRS may require modifications in both medical and surgical therapeutic approaches. Therefore, more radical approaches involving complete surgical removal of all bone partitions in affected areas may be necessary for successful treatment results as proposed by previous authors.[12,26,27] More importantly, applying functional concepts of FESS and minimally invasive sinus surgeries could be debatable in such situations. It has been hypothesized that remnants of osteitic bony partitions can serve as a continuous nidus to trigger inflammation, inducing recalcitrance of chronic rhinosinusitis.[24,26-28]

More importantly,in recent years, it has been highlighted that the coexistence of asthma in the presence of CRS with nasal polyp is more difficult to treat and control, due to the increased chances of airway obstruction and the higher number of acute exacerbations.[29,30] The key message of this study is the need of applicability of unified airway concept in daily practice. Increased awareness among otolaryngologists of the future risk of developing asthma symptoms in CRS patients and a team approach involving pulmonologists will definitely help in early identification and effective treatment of asthma.

Eosinophilic chronic rhinosinusitis (ECRS) is an allergic inflammatory disease characterized by chronic inflammation of the sinus mucosa, and sometimes, osteitis.[31] Previous reviews have reported that tissue

eosinophilia in CRS is strongly associated with the presence of asthma.[32,33] However, our study did not show such an association. Previous studies showed a significant relationship between eosinophil cell counts in the nose and in the lower airways in mild asthma.[34,35] However ,we found no such relationships.

The potential limitation of this study is the presence of small sample size which could possibly impact the generalizability of the findings.

CONCLUSION

Considering the relatively high prevalence rates of asthma in CRS patients and their association with osteitis, a more vigorous approach involving the exentration of osteitic bony nidus seems necessary for successful treatment results in all CRS patients and to prevent acute exacerbations in the asthmatic group of CRS patients. Increased awareness among otolaryngologists of the future risk of developing asthma symptoms in CRS patients and a team approach involving pulmonologists will definitely help in early identification and effective treatment of asthma.

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