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CLINICAL ANALYSIS OF ROLE OF BLOOD EOSINOPHIL AND BASOPHIL LEVELS AS PROGNOSTIC MARKER IN ALLERGIC FUNGAL RHINOSINUSITIS (AFRS)

Poojitha, R. Bhanu Murthy *, P. Sravani and S. Muneeruddin Ahmed

Department of ENT, Viswabharathi Medical College and General Hospital, Penchikalapadu, Kurnool - 518003, Andhra Pradesh, India.

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Correspondence to Author:
Dr. S. Muneeruddin Ahmed

Professor,
Department of ENT, Viswabharathi Medical College and General Hospital, Penchikalapadu, Kurnool - 518003, Andhra Pradesh, India.

E-mail: ahmedmunirent@gmail.com

ABSTRACT: Background: Allergic Fungal Rhinosinusitis (AFRS) is a common disease and denoted as Chronic Rhinosinusitis with polyps (CRSwNP). Presents as Eosinophilic nasal polyps, and allergic mucin in the nose and sinuses demonstrable with Functional Endoscopic sinus surgery (FESS) surgery. The biological markers predicting this disease entity are uncertain. Physicians experience difficult to predict the outcomes of various methods of treatment adopted to treat AFRS. Sometimes involvements of blood inflammatory cells were used to predict the recovery of the disease and its prognosis. **Aim of the Study**: To study the levels of pre-operative blood Eosinophils and Basophils in patients with AFRS and compare them postoperatively in terms of recurrence of polypi and allergic symptoms. **Materials and Methods:** 69 adult patients diagnosed with AFRS at the tertiary teaching Hospital in Andhra Pradesh were included. Patients were treated with FESS for AFRS. The final outcomes were assessed on the basis of blood Eosinophils and Basophils and correlating with the recurrence of symptoms and polypi. **Results:** Recurrence of polypi in 14 of 69 patients with overall review during study period showed that there was a statistically significant positive correlation between recurrences and blood Eosinophils and Basophils counts. But there was no correlation between the blood and tissue Mast cells. **Conclusions:** The study pointed to the patients at higher risk of AFRS recurrence with high counts of blood Eosinophils, Basophils. Further investigations are needed to study the role of higher levels of Blood Eosinophils, Basophils and Tissue Mast cells in AFRS patients during their follow up period of medical or surgical protocols of treatment.

INTRODUCTION: Allergic fungal rhinosinusitis (AFRS) is a chronic sinus inflammation first recognized around 40 years ago. Early reports described the patients suffering from with Broncho-pulmonary Aspergillosis (ABPA) due to allergy had nasal casts, and Millar documented cases of allergic aspergillosis of the paranasal sinuses [1]. In 1983, Katzenstein started using "Allergic Aspergillus sinusitis," by linking key features to define AFRS as a distinct clinical entity [2].

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Initially, AFRS was considered a nasal manifestation of ABPA as it shared clinical features of type I hypersensitivity to Aspergillus by producing thick, tenacious nasal secretions. However, it was later found that AFRS rarely coexists with ABPA, and non-Aspergillus fungal allergies can also trigger similar sinusitis, establishing AFRS as a separate condition [3].

AFRS is a fungal sinusitis but not so invasive, predominantly affected the younger adults, frequently with a history of Atopy and a type I hypersensitivity to fungi [4]. It is typically a subset of chronic rhinosinusitis with nasal polyposis (CRSwNP) [5]. Up to 24% of AFRS patients have asthma, though this is less common compared to other forms of CRSwNP, where asthma occurs in

up to 50% [6]. AFRS was driven by Type-2 immune response, leading to the production of thick eosinophilic mucin, often described as “rubbery” or “peanut butter-like,” and varying in color from green to black. The affected sinuses may expand and erode bony structures, occasionally causing external deformities like proptosis [7]. Despite these significant changes, patients often experience mild symptoms, with disease progression typically occurring slowly over several years. Imaging plays a crucial role in diagnosing AFRS. CT scans typically showed expansion of sinuses, opacity in them giving a "double density" sign. This was as a result of highly attenuated sinus contents against inflamed mucosa [8].

CT scan of Para nasal sinuses also helped to identify pathological anatomy and bony erosions if any. But fine-cut CTs are highly essential for surgical navigation. MRI scans on T2 sequences often showed mucosal edema with hypo-intensities in the sinuses due to the presence of high protein of eosinophilic mucin and low water content [9]. High total serum IgE (>500 IU/mL) and elevated fungal-specific IgE levels were observed on Lab tests [10]. Peripheral Eosinophils counts may also be raised, though less common. Histopathology of the mucin showed eosinophilic inflammation and necrotic debris, with Charcot-Leyden crystals from degranulated eosinophils. Special stains like GMS stain (Gomori Methenamine Silver) sometimes is required to detect fungal elements, which are otherwise not seen on routine stains [11]. Bent and Kuhn’s 1994 criteria: They are very important and used by many pathologists and required five major features for diagnosis: type I hypersensitivity to fungi, nasal polyposis, characteristic CT signs, eosinophilic mucus without fungal invasion, and a positive fungal stain on surgically removed sinus contents [12].

The other minor criteria were bone erosion on CT scans, fungal cultures positive, disease being unilateral, Charcot-Leyden crystals, and peripheral eosinophilia [13]. After Bent and Kuhn's criteria, alternate diagnostic criterions were set in by DeShazo, who proposed that to diagnose AFRS; one should focus on the absence of immuno-compromise or fungal invasion rather than excluding fungal hypersensitivity and nasal polyposis [14]. However, Bent and Kuhn's criteria are used by many ENT surgeons even today for diagnosing classic AFRS, despite limitations. All the above-described advancements showed that AFRS is not a single entity but a spectrum of disease caused by environmental or host factors, resulting in overlap with other chronic rhino-sinusitis (CRS) phenotypes [15]. A study by Ponikau et al. showed that fungal elements were detected in 81% of CRS patients, both with and without polyps. They also found that 96% of their patients had positive fungal cultures, including all healthy controls. The trypsin was used to enhance fungal detection rates which suggested that fungi are not as specific to AFRS as previously thought [16].

Eosinophilic mucus is found in both AFRS and other CRS types, including aspirin-exacerbated respiratory disease (AERD). It was confirmed that the CRS in the Western world was due to type 2 inflammation, leading to eosinophilic mucin production [17]. This shared mechanism means eosinophilic mucin is not unique to AFRS and does not distinguish it from other CRS subtypes. Despite this, AFRS remains distinct due to features such as expanded sinuses and bony erosions, which are not present in other CRS types. Type I hypersensitivity to fungi is a key criterion in the Bent and Kuhn diagnostic framework for AFRS [18]. However, elevated fungal-specific IgE levels are also found in patients with allergic rhinitis and fungal sensitization, which could complicate the diagnosis if the patient has CRSwNP with type 2 eosinophilic inflammation. While fungal-specific IgE is typically higher in AFRS than in non-AFRS CRS patients, the absence of specific cut-off levels reduces its diagnostic precision [19]. Staphylococcus-aureus, often present in eosinophilic mucin with fungi, can amplify this response through super-antigens, increasing serum IgE levels typical of AFRS [20].

The present study was conducted with an aim to post-surgery, oral steroids are limited due to side effects, and topical steroids or compounded nasal saline solutions are now preferred. Allergen immunotherapy is considered only for recalcitrant cases. While antifungal treatment is an option for persistent AFRS, current evidence is insufficient to support widespread use. Recent FDA-approved biologics for CRSwNP, such as dupilumab, may also benefit AFRS patients, but clinical trials

specific to AFRS are ongoing. More research is needed to refine treatment strategies based on a better understanding of AFRS pathophysiology. The present study was conducted to study the levels of pre-operative blood Eosinophils and Basophils in patients with AFRS and compare them postoperatively in terms of recurrence of polypi and allergic symptoms.

MATERIALS: A retrospective study was conducted in the Department of ENT, Viswabharathi Medical College, Kurnool, A P on 69 consecutive adult patients who underwent endoscopic sinus surgery for AFRS. Functional Endoscopic Sinus Surgery (FESS) was performed in all these patients earlier (2 years back). An Institute Ethics Committee approval was obtained prior to the study with the number: vmc&GH/eth-23/2024. An Ethics committee approved consent form and proforma were used for the purpose. The period of study was between March 2023 and February 2024.

Inclusion Criteria: Patients aged above 25 years and below 65 years were included. Patients of both genders were included. Patients satisfying the Kuhn's criteria for the diagnosis of AFRS were used to include the patients. Patients who have not undergone FESS earlier were only included.

Exclusion Criteria: Patients aged below 25 and above 65 years were excluded. Patients with Diabetes Mellitus, Recent URTI infections, viral pneumonias, Enteric fever or any post traumatic surgeries were excluded. Patients with immunodeficiency diseases were excluded. Demographic data, clinical examination and sinus endocopy findings were collected and analysed.

Patients were graded according to Bent and Kuhn's 1994 criteria requiring five major features for diagnosis: type I hypersensitivity to fungi, nasal polyposis, characteristic CT signs, eosinophilic mucus without fungal invasion, and a positive fungal stain on surgically removed sinus contents. (12) Minor criteria include radiographic bone erosion, positive fungal cultures, unilateral disease, Charcot-Leyden crystals, and peripheral eosinophilia. (13) Laboratory blood tests were done before and after surgery were:

1. Eosinophil counts

2. Basophil counts.

3. Mast cells.

All the patients were subjected to the following Protocol:

1. Pre-operative one-month medical treatment consisting of: Itraconazole 100mg twice daily for one month, Antihistamine and oral decongestant combination tablets for two weeks, Methyl Prednisolone 4mg twice daily in a tapering dose for 10 days and Azithromycin 500 mg for six days for one month.

2. FESS under General Anaesthesia operated by a team of two WNT surgeons. All the patients were followed up for 12 months at monthly intervals for an initial three months followed by three monthly follow up, Post operative nasal endoscopy done to assess the recurrence. Recurrence was confirmed by re appearance of the polypi to an extent of 25% of the previous clinical presentation. Postoperatively the patients with recurrence were subjected to Blood eosinophils, Basophils and mast cells estimation. Comparison was made between the preoperative and post operative counts.

Statistical Analysis: Data was organized in Microsoft Excel and analyzed using SPSS version 16.0. Continuous data is presented as mean ± SD, while categorical data is shown as frequencies and percentages. The Chi-squared test was used to assess the association between categorical variables. Sensitivity, specificity, and 95% confidence intervals (CI) were calculated. A P-value of less than 0.05 was considered statistically significant.

RESULTS: Among the 69 patients there were 53/69 (76.81%) males and 16/69 (23.18%) females with a male to female ratio of 1.3:1. There were 23/69 (33.33%) patients in the age group of 35 to 45 years and number of patients in the age group of 45 to 55 were 29 (42.02%) accounting for more than 75%. Patients' descriptive features, in terms of mean age at diagnosis, gender, asthma status, blood eosinophils (count and percentage), blood Basophils (cells per square millimeter- Mean), and tissue eosinophils (cells per square millimeter-Mean), and Mast cells (cells per square millimeter-Mean) are summarized in **Table 1.**

TABLE 1: SHOWING THE DEMOGRAPHIC DATA AND BLOOD EOSINOPHILS, BASOPHILS AND TISSUE MAST CELLS (N-69)

Observation	Number	Percentage	P value
Age			
25 to 35 Yrs	12	17.39	0.153
35 to 45 Yrs	23	33.33	
45 to 55 yrs	29	42.02	
55 to 65 yrs	06	08.69	
Mean Age	45.68±3.17	--	--
Gender			
Male	53	76.81	--
Female	16	23.18	--
Asthma status			
Yes	31		44.92
No	37		53.62
Blood Eosinophils (cells per square millimeter)- Mean	89.31 ± 21.49	--	--
Blood Basophils (cells per square millimeter)- Mean	03.5± 0.85	--	--
cells per square millimeter)- Mean	25.21 (3.4)	--	--

Recurrence was noted in 11/69 (15.94%) of the patients on basal endoscopy and as per guidelines of the study. Post operative eosinophil counts, Basophil counts and Mast cell counts were tabulated in Table **2.** Recurrent AFRS polyps were documented by endoscope in 11 of 69 patients with a median of 12 months after FESS. In the cohort as a whole, Spearman's rank correlation test was used and the Eosinophil, Basophil and Mast cells counts were significant in predicting the recurrence in the study **Table 2.**

TABLE 2: SHOWING THE MEAN COUNTS OF EOSINOPHILS, BASOPHILS AND MAST CELLS IN THE POST OPERATIVE RECURRENT AFRS PATIENTS (N-11)

Observation	Number	Percentage	P value
Recurrence AFRS	**11**	**15.94**	**0.001**
Blood Eosinophils: (cells per square millimeter)- Mean	89.31 ± 21.49	----	0.001
Pre-operative	112±2.76		
Post operative			
Blood Basoinophils: (cells per square millimeter)- Mean	03.5± 0.85	--	0.001
Pre-operative	07.65± 1.45		
Post operative			
Mast cells: (cells per square millimeter)- Mean	25.21 (3.4)	--	0.001
Pre-operative	31.85±4.11		
Post operative			

DISCUSSION: AFRS is a chronic inflammatory condition of the sinuses and nasal mucosa, characterized by nasal polyps. Functional Endoscopic Sinus Surgery (FESS) offers benefits like surgical precision, minimal trauma, and the removal of diseased tissue while preserving normal structures, making it the primary surgical option for treating chronic rhinosinusitis with nasal polyps when medications are ineffective. However, postoperative recurrence may be influenced by factors such as secondary infections, mucosal edema, vesicle formation, and polyp regeneration during the mucosal healing phase [21]. The evaluation of CRS outcomes includes subjective and objective assessments. According to EPOS2020 and the 2018 Chinese Guidelines for Chronic Nasal Sinusitis, subjective evaluation is done using the Visual Analogue Scale (VAS), while objective evaluation involves the Lund-Kennedy score for nasal endoscopy and the Lund-Mackay score for sinus CT [22]. In the present study Among the 69 patients there were 53/69 (76.81%) males and 16/69 (23.18%) females with a male to female ratio of 1.3:1. There were 23/69 (33.33%) patients in the age group of 35 to 45 years and number of patients in the age group of 45 to 55 were 29 (42.02%) accounting for more than 75%. Patients' descriptive features, in terms of mean age at diagnosis, gender, asthma status, blood eosinophils (count and percentage), blood basophils (cells per square millimeter- Mean), and tissue eosinophils (cells per square millimeter- Mean), and Mast cells (cells per

square millimeter- Mean) are summarized in **Table 1.** In AFRS, fungal antigens interact with the sino-nasal mucosa due to the persistence of fungus in the sinus contents, which is facilitated by the accumulation of allergic mucin in atopic individuals. This triggers the sensitization of T-cells by processed fungal proteins, leading to a Th2 cytokine response [23].

The response activates eosinophils, drawing them to the mucosal surface where they target the fungi in an abnormal defense response, resulting in Eosinophilic degranulation and tissue damage. To patients with non-eCRS8,28. Eosinophilic CRS (eCRS) is known as a more severe and persistent subtype of CRS, often associated with worse clinical outcomes. Elevated levels of eosinophils and related cytokines are common in patients with nasal polyps, typically linked to a T-helper type 2 (Th2) inflammatory responses. In the present study the patients with eCRS (defined as >10 eosinophils per HPF) had significantly worse SIT scores compared to non-eCRS and healthy controls [24]. The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) and the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) recommend including peripheral blood eosinophil count in diagnostic algorithms and assessments of CRSwNP severity [25]. Recurrence was noted in 11/69 (15.94%) of the patients on basal endoscopy and as per guidelines of the study. Post operative eosinophil counts, Basophil counts, and Mast cell counts were tabulated in **Table 2.** Recurrent AFRS polyps were documented on endoscopic examination in 11 of 69 patients a median 12 months after FESS. In the cohort as a whole, Spearman's rank correlation test was used, and the Eosinophil, Basophil and Mast cells counts were significant in predicting the recurrence in the study **Table 2.** A similar study by several authors concluded that blood eosinophils and Basophils play an increasingly important role in various CRSwNP endotypes. The blood eosinophil-basophil ratio (bEBR) appears to be a promising parameter for investigation, as it is significantly higher in patients with allergy, asthma, and aspirin-exacerbated respiratory disease [26].

CONCLUSION: The study pointed to the patients at higher risk of AFRS recurrence with high amounts of blood Eosinophils, Basophils. Further investigations are needed to study the role of higher levels of Blood Eosinophils, Basophils and Tissue Mast cells in AFRS patients during their follow-up period of medical or surgical protocols of treatment.

Limitations to the Study: In the absence of more effective and elaborate investigations to predict the outcome of treatment of AFRS the preliminary data support by simple estimation of Blood Eosinophils and Basophils level was used. But the subject warrants testing in further prospective and larger (preferably multi-institutional) investigations as part of the preoperative work-up for patients and their follow up to predict the recurrence.

CONFLICTS OF INTEREST: The present study has not received any grants or recommendations either for conducting or reporting the results in favour of anybody or organization.

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