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Research Article

TO STUDY ALLERGIC MUCIN IN ALLERGIC FUNGAL RHINOSINUSITIS IN SOUTH INDIA

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ABSTRACT

Allergic fungal rhinosinusitis (AFRS) is one of the more commonly encountered forms of noninvasive fungal rhinosinusitis, seen in immune competent individuals. Allergic fungal rhinosinusitis (AFRS) is a relatively new and incompletely understood clinical entity with characteristic clinical, radiographic, and histopathologic findings. AFRS is often misdiagnosed. Recognition and understanding of this unique disease will lead to efficient diagnosis and treatment of this curable process. It is caused by a Gell and Coombs Type I, IgE mediated (and possibly Type III) hypersensitivity reaction to an extra mucosal fungal antigen. It bears striking similarities to Allergic Broncho Pulmonary Aspergillosis (ABPA), in terms of pathogenesis as well as treatment. It commonly presents as nasal polyposis. Most current treatment protocols for this condition are based on a combined medical and surgical approach. This is a single-centre prospective study, undertaken to determine the incidence of allergic mucin in patients with AFRS, and its role in the outcome after treatment with systemic anti-fungals and steroids. In this article we have recapitulated the history, epidemiology, etiology, clinical features, diagnostic investigations and treatment protocols for this disease. AFRS is a unique disease process that differs from other forms of sinusitis and as such requires that physicians understand its diagnosis and management to provide care for patients with this condition.

Keywords :- Nasal polyps, hypersensitivity, sinusitis, Aspergillosis, steroids, itraconazole.

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INTRODUCTION

Allergic fungal rhinosinusitis (AFRS) has been reported worldwide with an incidence of 5 to 10% of all cases of chronic rhinosinusitis requiring surgery. [1-2] It represents an allergic/hypersensitivity disorder. Although anecdotal, there have been numerous suggestions in literature, linking an upper airway hyper-reactivity and chronic rhinosinusitis. Due to its pathophysiological similarities with allergic bronchopulmonary aspergillosis (ABPA), AFRS probably forms one such link. AFRS is coupled with the clinical entity of fungus ball (mycetoma) as a form of noninvasive fungal sinus disease, separate from and unrelated to invasive fungal sinus pathology. AFRS is a truly unique pathologic entity, defined largely by the presence of allergic fungal mucin, which is a thick, tenacious, eosinophilic secretion with characteristic histologic findings. This mucin is grossly and microscopically similar to that found in the lungs of patients with allergic bronchopulmonary aspergillosis (ABPA), and this pulmonary correlate helped guide the early understanding of the pathogenesis of AFRS.[3] Since its initial characterization in the 1970s, AFRS has been the subject of much debate and controversy regarding its pathogenesis, diagnosis, classification, and optimal management.

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Diagnosis begins with a thorough clinical history. Commonly, the patient will present with a history of sinus disease strongly recalcitrant to traditional medical and even surgical therapy aimed largely at bacterial rhinosinusitis.[4] Several courses of antibiotics and topical nasal preparations may have been tried with little success. Unique features of AFRS that can alert the clinician to a possible diagnosis include a young (mean age is 22 years), immunocompetent patient with unilateral or asymmetric involvement of the paranasal sinuses, a history of atopy, nasal casts, and polyposis, and a lack of significant pain.[5] Nasal casts are green to black rubbery formed elements made of allergic mucin. The presentation may be dramatic, with a significant number of patients presenting with proptosis, telecanthus, or gross facial dysmorphia.[6] AFRS occurs throughout the United States, with increased prevalence in the Mississippibasin and southwestern states.[7] The diagnostic dilemma is differentiating AFRS from other fungal entities involving the paranasal sinuses, including saprophytic fungal growth, mycetoma, eosinophilic mucin rhinosinusitis, and invasive fungal sinusitis. The major criteria include a history of type I hypersensitivity by history, skin testing, or in vitro testing; nasal polypo sis; characteristic computed tomography (CT) scan findings; the presence of eosinophilic mucin without invasion; and a positive fungal stain of sinus contents removed at the time of surgery. The minor criteria include a history of asthma, unilateral predominance of disease, radiographic evidence of bone erosion, fungal cultures, presence of Charcot-Leyden crystals in surgical specimens, and serum eosinophilia.

AFRS is a truly unique pathologic entity, defined largely by the presence of allergic fungal mucin in the sinuses. It has characteristic radiological findings in the form of hyperattenuating areas (double densities) within opacified sinuses on CT scan [8]. Fungal-specific IgE (positive allergy skin test), IgG to the etiologic fungus, presence of atopy to common aeroallergens, and immunocompetence are clinical findings that are always present and support the diagnosis of AFRS. The treatment is a multipronged approach including surgery and medical therapy in the form of systemic steroids or antifungals such as Itraconazole [9]. This form of fungal rhinosinusitis has the best prognosis. This is a single-centre prospective study, undertaken to determine the incidence of allergic mucin in patients with AFRS, and its role in the outcome after treatment with systemic anti-fungals and steroids.

MATERIAL AND METHODS:

30 patients of chronic rhinosinusitis fulfilling at least three of Bent and Kuhn's major criteria [10] for the diagnosis of allergic fungal sinusitis, were included in the study and conducted at the department of Otorhinolaryngology, Sri Lakshmi Narayana Institute of Medical Sciences, Pondichery and Sree *Balaji Medical College* & Hospital, Chennai from 2015 to 2016. A diagnostic nasal endoscopy under local aneasthesia was carried out for each patient. Fungal debris, if found, was sent for KOH mount for fungal hyphae and fungal culture. A CT scan of the paranasal sinuses, with axial and coronal cuts, bony and soft tissue windows was done. Sagittal reconstruction was asked for in cases with disease in frontal recess, erosion of posterior wall of frontal sinus or erosion of cribriform plate. Surgical anatomy, sinuses involved, bony erosions of lamina papyracea and skull base were noted. Routine investigations for fitness for general anaesthesia, with differential leukocyte count and absolute eosinophil count were carried out.

Each patient underwent endoscopic sinus surgery with clearing of polyps, allergic mucin and fungal debris from all the paranasal sinuses. Special attention was given to washing out of all the allergic mucin and fungal debris, restoration of sinus ventilation and preservation of mucosa. The obtained allergic mucin and fungal debris were sent for KOH mount for fungal hyphae and fungal culture. Debrided tissue was sent for histopathological assessment. Nasal packs were kept for two days. Post operatively, patients were given tablet Itraconazole (systemic antifungal) 100 mg BD, and Prednisolone (systemic steroid) 1 mg/kg in tapering doses, once in the morning on full stomach along with antacids. After removal of nasal packs, patients were put on steroid sprays and discharged from the hospital. Alkaline nasal douches were given for clearance of nasal crusts.

Each patient was reviewed with Nasal endoscopy immediate 1 week post-surgery, then after 15 days, 1, 2, 3 and 6 months. Decision to continue inhalational steroids and Itraconazole was taken on the basis of the postoperative endoscopic findings. The outcome of the treatment was assessed on the basis of endoscopic findings at the end of 6 months as per Kupferberg staging system [11]. As per this system, in each stage, A represents absence of allergic mucin and B represents presence of allergic mucin.

Stage 0 (A/B) – No mucosal oedema – excellent outcome
Stage I (A/B) - Mucosal oedema – good
Stage II (A/B) - Polypoid oedema – satisfactory
Stage III (A/B) - Sinus polyps - recurrence

Patients with non-resolution of complaints or recurrence of symptoms also underwent endoscopic examination. CT scan was repeated in those cases with recurrence of polyps and those who had intra orbital and intra cranial extension on presentation The study includes thirty patients, out of which twenty were males and ten females; the oldest patient was seventy years old

and the youngest ten. Nineteen had bilateral pathology, eight left sided and three right sided. Four patients had come with recurrent disease, operated elsewhere. One of the patients had been operated with a septoplasty for the nasal complaints. Seventeen patients had used inhalational steroids pre operatively. Seventeen patients had septate hyphae on KOH mount. Itraconazole was given to eleven of those patients. Twenty patients were given postoperative systemic steroids. Post operatively, inhalational steroids were given to all the patients. Twenty patients had Kupferberg grade I A at 6 months. Four had grade II A. one patient had III A. One had I A on same side; IV B on unoperated side - posted for surgery in near future. Five patients operated at the institute developed recurrence. One of them, on the same sites as before underwent surgery and was disease free at the end of six months. One patient developed recurrence three months post-surgery, was treated with systemic steroids and stayed disease free. Two patients had minimal recurrence and recovered with inhalational steroids. The fifth one remained disease free on the operated side, but developed it on the other side.There is a significant correlation between the presence of allergic mucin and AFRS. Allergic mucin was found in 90 percentage of patients with AFRS. Therefore we can conclude that allergic mucin has a strong positive correlation and hence is a major diagnostic criteria for AFRS. These patients responded well to endoscopic clearance and oral Itraconazole. 81 percent of patients with allergic mucin had good outcome i.e minimal mucosal edema at the end of six months. Complete clearance of allergic mucin from the paranasal sinuses leads to better post operative results.

Table 1: Association Between Allergic Mucin and outcome

Allergic Mucin	Outcome			
	Excellent	Good	Satisfactory	Recurrence
Yes(N=27)	-	22	04	01
No(N=03)	-	03	-	-

By Fisher Exact Test P>0.05

Figure1:Endoscopic image of polypsandallergicmucin

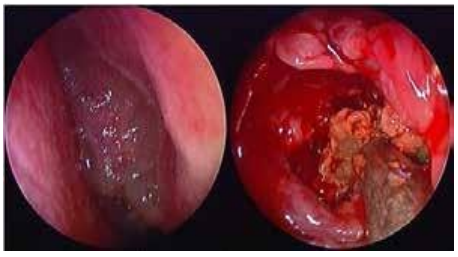


Figure2:Radiological features: CT coronal soft tissue – double densities, Iso to hypo intense on T1 weighted MRI and Signal void in T2 weighted MRI

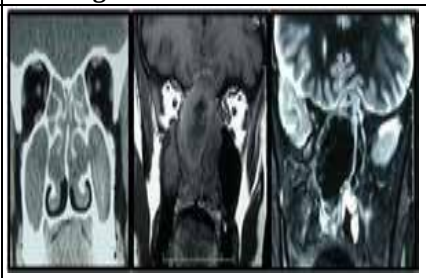
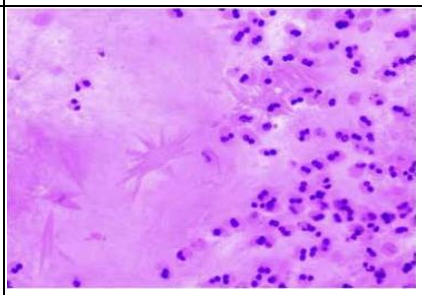


Figure3:Charcot-Leyden crystal sonahematoxylin &eosin stainallergic mucin



DISCUSSION

Laboratory findings are also helpful in the diagnosis of AFRS. Total immunoglobulin E (IgE) levels are generally elevated, often to more than 1,000 U/mL. Mabry and colleagues [13–15] demonstrated broad sensitivity to both fungal and nonfungal antigens, emphasizing that AFRS patients are generally atopic. Interestingly, the reactions were not fungal specific, although typically only one fungus was isolated from the culture. This finding could represent a common fungal epitope to explain the broad reactivity, or possibly—as Schubert described—the presence of a superantigen that could contribute to the nonspecific reactivity of these patients. [16]

AFRS is a truly unique pathologic entity, defined largely by the presence of allergic fungal mucin, which is a thick, tenacious, eosinophilic secretion with characteristic histologic findings. The age group affected is predominantly young adults and adolescents, younger than most CRS patients, with a mean age at diagnosis of 21.9 years [16,17]. Most studies demonstrate a fairly equal male-to-female ratio [16]. Since the causative organism,fungi, thrive well in warm and humid conditions, it is commonly seen in tropical countries such

as India [16]. The common causes of allergic fungal sinusitis are the dematiaceous hyphomycetes including Curvularia sp., Bipolaris sp., Pseudallescheria boydii, and the hyaline hyphomycetes such as Aspergillus sp. and Fusarium sp [18]. Sometimes, this mucin is also encountered in patients with rhinosinusitis, with their clinical profile very similar to that of but without actual AFRS. This mucin is negative for fungal hyphae on histolopathology with negative fungal cultures. They may also show the characteristic hyperattenuating shadows on CT as in AFRS [19-20]. It is important to note that examination of the unique allergic fungal mucin itself, and not the surrounding mucosa, is the most reliable indicator of disease. Grossly, this thick, highly viscous, variably colored mucin has been described as being similar to peanut butter or axle grease and contains laminated accumulation of intact and degenerating eosinophils, Charcot-leyden crystals, cellular debris and sparse hyphae.

The histopathologic findings in AFRS are critical to the diagnosis. Microscopic review of mucosal specimens on hematoxylin-eosin (H&E) staining will show typical inflammatory infiltrate composed of eosinophils, lymphocytes, and plasma cells.It is important to note that examination of the unique allergic fungal mucin itself, and not the surrounding mucosa, is the most reliable indicator of disease. Grossly, this thick, highly viscous, variably colored mucin has been described as being similar to peanut butter or axle grease. Microscopically, the mucin often takes on a chondroid appearance with sheets of eosinophils, frequently with the presence of eosinophilic breakdown products or Charcot-Leyden crystals6 that can easily be seen with H&E staining. Fungi themselves do not stain with H&E staining; however, their negative image can sometimes be appreciated. Special stains containing silver are usually needed to appreciate the branching, noninvasive fungal hyphae.

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Some of them may not be a topic, but may have NSAID hypersensitivity. This entity has been termed as eosinihilic mucin rhinosinusitis (EMRS) by Ferguson (2000). The disease is usually bilateral (in about 93% cases), and patients of EMRS have a greater incidence of coexistent asthma than seen with AFRS, besides also having a lower serum IgE level as compared to the latter. Allergic mucin that is grossly and histopathologically identical to that found in AFRS has also been reported occasionally in hypertrophic sinus disease patients in the absence of AFRS. The allergic mucin is negative for fungal hyphae on histopathology, and surgical sinus fungal cultures are uniformly negative. The clinical presentation of such hypertrophic sinus disease patients is often similar to that of patients with AFRS, including the finding of intrasinus hyperattenuation on CT. Some of these patients, however, are nonatopic; many also have ASA/NSAID hypersensitivity. It has been suggested that this form of hypertrophic sinus disease be termed eosinophilic mucin rhinosinusitis (EMRS) [22]

Patients with residual allergic mucin have a greater chance of developing recurrence of the disease. Hence it is important to thoroughly wash out the allergic mucin in such patients to minimize the rates of recurrence. AFRS is a medical disease requiring surgical intervention to ensure optimal results. It is a relatively new clinical entity with characteristic features. A high index of suspicion in young immunocompetent patients presenting with chronic rhinosinusitis is required for early diagnosis. Presence of allergic mucin is diagnostic for AFRS. Differentiation from invasive forms of fungal sinus disease is crucial, as the management as well as prognosis

vary in the two. Endoscopic evaluation and radiological assessment are the cornerstones of diagnosis. A multimodality approach is required (medical, surgical and immunomodulation) as the disease is multifactorial. The exact role of anti fungals and systemic steroids in achieving systemic control of the disease can probably be established by larger population studies. Long term follow up is essential so that medical therapy, if required can be continued and recurrence prevented.

CONCLUSION

AFRS is an obstinate, immunologically mediated noninvasive fungal inflammation, with a marked propensity for recurrence. Unlike in other fungal infections of the body, with the exception of ABPA (to which it has been likened), steroids form an important part of therapy, along with surgery. Many a times, despite the best efforts, recurrences have been reported. The answer probably lies in a combination modality treatment protocol, which includes immunotherapy. This study has been undertaken to assess the significance of allergic mucin in AFRS. The study concludes that allergic mucin has a strong positive correlation and hence is a major diagnostic criterion for AFRS. Theories on pathogenesis include hypersensitivity and T-cell mediated reactions as well as a humoral immune response. Treatment is largely surgical, with a strong role for oral corticosteroids and an emerging role for IT. Antifungals, both systemic and

topical, currently have a limited role in treatment, although this area needs further study. It is hoped that the publication of this description will guide many clinicians in the prompt suspicion with accurate assessment,aiding in the proper management of AFRS.

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