

A Prospective Study on Clinicopathological Profile of Fungal Rhinosinusitis

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Abstract

Introduction: Kerala being agriculture based state with warm moist climate, favorable for fungal growth and fungal rhinosinusitis (FRS) is relatively common here. This study was conducted to evaluate the clinical and pathological profile of FRS with respect to symptomatology, age group, immunological status, category, risk factors, radiological presentation, treatment regimen, and recurrence.

Materials and Methods: The study was conducted on 50 patients suspected of having FRS and treated as in patients in Government Medical College, Calicut, for 2 years. Clinical, radiological, microscopic, and microbiologic features were documented. Treatment modalities were also evaluated, and patients were followed up at 1 and 3 months.

Results: Out of 50 patients 33 (66%) were diagnosed to have non-invasive FRS which include eosinophilic FRS (50%) and sinus fungal ball IN 16%. 12 (24%) patients were with invasive FRS, 5 (10%) with eosinophilic mucin rhinosinusitis among invasive FRS 8 (16%) acute fulminant type, 3 (6%) chronic, and 1 (2%) patient with granulomatous type. 11 out of 12 invasive FRS patients (91.67%) were diabetic. Computed tomography findings were suggestive of FRS in 54% of cases. Patients with invasive FRS underwent surgical debridement and systemic antifungal therapy. Those with non-invasive FRS underwent surgical clearance, and none had any type of recurrence. *Aspergillus* was found to be the most common pathogen in both groups. Mortality rate in invasive group was 16.67% and 3 had persistent blindness.

Conclusion: FRS is common in warm humid areas. Allergic fungal rhinosinusitis is the most common subtype of FRS associated with allergy. Type 2 diabetes is a major risk factor in acute fulminant invasive fungal sinusitis. Intra orbital and intracranial extension denote poor prognosis. Blindness due to orbital involvement is not reversible even after aggressive treatment.

Key words: Allergic fungal rhinosinusitis, Eosinophilic mucin rhino sinusitis, Fungal rhinosinusitis, Invasive fungal rhinosinusitis, Sinus fungal ball

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common disorder affecting about 20% of the population in India and approximately 31 million people annually.¹ It is defined as any chronic inflammation of mucosal lining of the nose and paranasal sinuses lasting for at least 12 weeks.² Several factors extrinsic and intrinsic contribute for this. Extrinsic etiology may be infection by viral, bacterial,

fungal, or allergic which includes both IgE and non-IgE mediated. Intrinsic factors include genetic, autoimmune, or structural causes.³ About 30% of CRS can be attributed to fungal etiology. Fungi are eukaryotic organisms in the ecosystem aiding decomposition and recycling of organic matter, and these exist as yeast or molds.⁴ They produce spores to tide over unfavorable conditions and aids fungal dissemination.³ Under favorable conditions fungal colonization and proliferation occur in the nose and paranasal sinuses leading clinical presentations.⁴ Type of fungal rhinosinusitis (FRS) and associated fungal pathogen vary with geographical distribution. FRS is broadly classified into two major groups; invasive and non-invasive forms. Distinction between these two forms is based on clinical presentation, imaging evidence and or histopathology, also an extension of fungal elements beyond the paranasal sinuses. Non-invasive form typically

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presents with chronic sinusitis that fails to respond repeated medical and usual surgical procedures. Acute invasive forms have fever, nasal mucosal ulceration. Chronic invasive disease demonstrates progressive worsening of symptoms with orbital and neurological involvement. Invasive forms are seen in immunocompromised patients.⁵ The current definitions require histopathology that shows hyphae in eosinophilic mucin for diagnosis of allergic fungal rhinosinusitis (AFRS) or nonallergic eosinophilic FRS (NAEFRS) rather than positive fungal cultures and the by-products of eosinophils, such as major basic protein.⁶ NAEFRS is based on non-IgE mediated immune response to fungus and showed no response to antifungal agents. Causative fungal species is of less importance than host's immunologic response or nonresponse to the fungus.⁷ Determination of the fungal species by culture aids in antifungal selection.⁸ High index of suspicion is needed for FRS when chronic sinus infection shows resistant to conventional medical therapy. The present study attempts to analyze clinical, radiological, and microscopic features, along with an evaluation of various treatment modalities available for FRS in this setting.

MATERIALS AND METHODS

The present study was conducted in the Department of ENT, Government Medical College, Calicut, from October 2014 to October 2015. Institutional Ethical clearance was obtained for the conduct of the study. All patients with chronic sinus symptoms treated as inpatients were documented with a detailed history, associated comorbidities, imaging studies computed tomography (CT) and magnetic resonance imaging (for intracranial and orbital extension), microbiology, histopathology, and treatment regimen.

RESULTS

Among the 50 patients symptoms were nasal obstruction in 78%, nasal discharge in 56%, headache in 56%, facial pain in 14%, allergy in (14%), postnasal discharge in 14%, proptosis in 7%, bleeding from nose in 6%, diminished vision 6%, diplopia in 2%, ptosis in 2%, fever in 2%. All patients with proptosis, diplopia, ptosis, diminished vision, fever belonged to the invasive type of FRS. 11 patients (69%) with Type 2 diabetes mellitus had invasive FRS. Other factors contributing immunosuppression were not found out. Clinical examination showed nasal discharge in 60%, polyp 42%, peripheral nervous system tenderness in 32%, ophthalmoplegia in 14%, defective vision in 12%, cranial nerve palsy in 12%, nasal ulceration crusting 10%, proptosis in 10%, and orbital cellulitis in 6%. All patients with polyps belonged to eosinophilic FRS. No significant correlation was seen between erythrocyte sedimentation rate

(ESR) level and type of FRS though 20% had elevated ESR. 50% patients had eosinophilia and allergy with eosinophilic FRS. 54% of cases showed positive CT radiological finding diagnostic of AFS. All 8 patients with fungal ball showed heterodensity of sinus. 14 out of 30 (46%) of AFRS patients also showed heterodensity. 9 patients had orbital extension, 4 had intracranial extension, 2 had orbit with cavernous sinus involvement, and all were invasive type of FRS. 38 patients (76%) underwent surgery alone whereas 12 (24%) underwent surgery and antifungal therapy and the latter belonged to the invasive type of FRS. 27 patients underwent unilateral FESS, 12 bilateral FESS, and 10 cases of endoscopic debridement for invasive FRS, and 1 Caldwell Luc surgery. 41 patients (82%) needed surgical intervention only once. 6(12%) needed 2 interventions, and all are invasive FRS. others are AFRS group (Table 1).

Table 1 showing the sinuses affected with FRS. Among the sinuses, maxillary and ethmoid sinuses were commonly involved in eosinophilic mucin rhinosinusitis (EMRS). Multiple sinuses were involved in AFRS and EMRS. All specimens were subjected to potassium hydroxide wet mount and fungal culture (Sabouraud's dextrose agar) incubated at 25-37° for 4 weeks. Table 2 summarizes the distribution of the different fungi in this study.

Absence of growth culture was always not taken as negative but may be due to poor culture techniques. Among 50 patients 12 (24%) had invasive FRS, and 33 (66%) are non-invasive FRS and 5 (10%) had EMRS. Among invasive subtypes, acute 67%, chronic 25%, and granulomatous 8% were found out. Non-invasive subtypes are AFRS in 76% and fungal ball in 24%.

Table 1: The incidence of sinuses involved in the study

Sinus affected	Non invasive	Invasive
Maxillary	28	5
Ethmoid	15	4
Sphenoid	4	5
Frontal	0	1

Table 2: The distribution of the different fungi in the present study (n=50)

Organism	Number (%)
<i>Aspergillus</i>	20 (40)
<i>Penicillium</i>	8 (16)
Dematiaceous	8 (16)
No growth	6 (12)
<i>Mucor</i>	2 (4)
<i>Rhizopus</i>	2 (4)
<i>Candida</i>	2 (4)
<i>Chrysosporium</i>	1 (2)
<i>Scopulariopsis</i>	1 (2)

DISCUSSION

Human fungal infections are superficial, deep seated/systemic. Opportunistic infection occurs in patients with debilitating diseases as cancer or diabetes, or in whom the physiological state has been upset by immunosuppression. Opportunistic infections are caused by fungi that are avirulent such as *Aspergillus*, penicillium, and *Mucor*. *Aspergillus fumigatus* is the type which causes aspergillosis of lung, paranasal sinus, orbit, etc., mucormycosis is an invasive disease caused by phycomycetes mainly by species of *Rhizopus*, *Mucor*, and *Absidia*. Conditions predisposing to mucormycosis are uncontrolled diabetes, severe neutropenia, long-term use of steroids³ chronic invasive FRS is suspected in patients with immunocompromised with complications. *Aspergillus flavus* also the pathogen in such cases and show histologically granuloma with giant cells containing hyphae.⁴ 22% of patients were in 5th decade. 75% of IFRS cases belonged to 7th and 8th decade. 50% with AFRS were in the 3rd and 4th decade. This is similar to study conducted by Schuber *et al.*,⁵ where they found that AFRS cases were young. 54% of patients were females. There was no statistically significant relationship between sex and type of FRS either. Symptoms of extra nasal spread such as proptosis, diplopia, and diminished vision exclusively seen in invasive FRS. This is in accordance with the study of Chandrasekhar *et al.*, where orbital involvement was seen with invasive fungal sinusitis.⁶ All patients with acute fulminant invasive fungal sinusitis (AFIFS) were diabetic. It was found that patients with poorly controlled diabetes especially DKA were having a risk of invasive mucormycosis.⁷ *Aspergillus* (40%) was the most common fungus retrieved similar to study by Vennewald *et al.*⁸ Histopathology is very important for classification of FRS. In the invasive type, histopathology shows widespread necrosis of all involved structures and inflammatory infiltrate consisting of variable numbers of giant cells, lymphocytes and neutrophils depending on the level of host immune competence. Gomori's methenamine silver (GMS) or Periodic acid-Schiff histologic fungal stains highlight fungal hyphae invading mucosa, blood vessels, or bone. *Aspergillus*, *Rhizopus*, and *Mucor* spp. are common offending organisms, but virtually any fungus can be causative. In AFRS with nasal polyps, characteristic inspissated greenish allergic mucin is seen during surgery. H and E stains show hypertrophic, edematous sinus mucosa containing lymphocytes, plasma cells, and eosinophils. Epithelium is often desquamating with basement membrane thickening and no evidence of necrosis, granulomas or giant cells. The extra mucosal allergic mucin is composed of strongly staining masses of numerous eosinophils surrounded by thin eosinophilic mucin where Charcot Leyden crystals can often be seen. GMS staining shows small areas of

sparsely scattered fungal hyphae within the mucin but not within the mucosa. In describing FRS, it is important to categorize the types because treatment and prognosis differ with manifestation of the disease. Diagnosis and classification were done taking into consideration of clinical features, radiological findings, fungal culture, and the most important histopathology. The cases with polyposis, allergic mucin and other characteristics suggestive of allergic or nonallergic eosinophilic FRS in whom fungal stain came negative were classified as a distinct category of EMRS. Out of 50 cases, 5 (10%) were categorized as EMRS, 33 cases (66%) were classified under non-invasive, and 12 cases (24%) under invasive FRS. Non-invasive type was further classified into sinus fungal ball and eosinophilic FRS. There were 8 cases (24%) of sinus fungal ball and 25 cases (76%) of AFRS/NAEFRS the most important criteria for the diagnosis of AFRS require elevation of IgE antibodies specific to the fungus found on the culture of eosinophilic mucin containing the fungus there must not be evidence of fungal invasion. Patients with histopathological evidence of AFRS without elevated IgE to fungus are classified as NAEFRS.⁹ Levin *et al.* recently showed that NAEFRS may actually demonstrate local immunity in the absence of systemic elevation of fungal IgE.¹⁰ Invasive type of FRS were further classified into acute fulminant 8 cases (67%), chronic 3 cases (25%), and granulomatous 1 case (8%) granulomatous invasive FRS is rare in the Southern area compared to North India. All invasive FRS patients underwent endoscopic debridement as surgical procedure along with antifungal therapy. Granulomatous case underwent 3 times surgical debridement as for recurrence along with oral itraconazole. Scopulariopsis as the causative agent in FRS is rarely reported in literature.¹¹ We had one such case who had uncontrolled Type 2 diabetes and orbital involvement at the time of presentation. Patients with AFRS underwent FESS, and oral steroids started after surgery; dose was titrated depending on endoscopic grading system by Kupferberg. None of them received antifungal agents. However, there are individual studies supporting topical and oral antifungal therapy in AFRS.¹² None of our patients had a recurrence during 3 months follow-up period. Endoscopic sinus surgery and clearance of fungal ball and re-establishment of sinus ventilation was done in sinus fungal ball case. This was the gold standard management of *Aspergillus* fungal ball. Most of the patients with invasive disease were given intravenous amphotericin B 0.25-1 mg/kg/day to a total dose of 3 g over 6-8 weeks. In patients with possible renal toxicity, liposomal amphotericin B at a concentration of 3-5 mg/kg/day. This is reserved for clinically proven fungal infection in immunocompromised host with elevated serum creatinine (>2.5 mg/dl) or progression of disease even after maximum dose of standard amphotericin. IV voriconazole was given in invasive aspergillosis was more

effective than amphotericin B for invasive aspergillosis.¹³ The optimal duration of antifungal drug administration for chronic invasive fungal sinusitis is controversial, and reports vary widely depending on the severity of disease from 1 month to more than 15 months. In our series, all patients received antifungal therapy for 3 months. Around 60% of patients with invasive fungal disease had to undergo surgical debridement more than once. All the patients were followed up for a period of minimum 3 months. Detailed clinical and endoscopic examination was done. AFRS patients were oral steroids, and no recurrence was noted. Persistent disease was noticed in 3 AFIFS patients with orbital involvement. One AFIFS patient with orbital and intracranial extension expired during treatment. Another patient with chronic IFS expired at the end follow-up due to other comorbidities. Thus, patients with orbital and intracranial involvement are less likely to respond to management. In a retrospective review by Parikh,¹⁴ the overall mortality rate as result of fungal sinusitis was found to be 18%. In our series, the overall mortality is 4%, but it is 16.67% of invasive group alone is considered which is in accordance with the current literature. Vision loss persisted in three patients due to optic neuropathy as result of ischemic vasculitis, where certain types of fungi like *Mucor* species have the propensity of invading blood vessels with consequent thrombosis and ischemia.

CONCLUSION

Fungi play a significant role in developing and perpetuating inflammatory disease of the respiratory tract. In this series, we had 50 suspected cases of FRS. Clinical features, radiological features and treatment, prognosis varied according to the subtypes of FRS. FRS is classified as non-invasive and invasive groups. Non-invasive is again into eosinophilic FRS (allergic-AFRS/nonallergic-NAEFRS) and sinus fungal ball. Invasive form is classified as AFIFS, chronic IFS, and granulomatous IFS. AFRS patients are younger age group, while the invasive group was between 6th and 8 decade. Nasal obstruction, discharge and headache were common symptoms. Proptosis, diplopia, defective vision, and ptosis were noticed in invasive disease aggravated by diabetes. CT findings were not characteristic in initial stages but later developed features suggestive of fungal etiology. Fungal ball showed heterodensity of sinus

involved. Bone erosion, orbital, and intracranial extension seen in invasive groups. Maxillary and ethmoid sinuses are the most frequently affected sinuses overall, but maxillary, ethmoid and sphenoid are equally affected in invasive disease. AFRS patients are managed by endoscopic sinus surgery, oral and local steroids. Invasive disease required multiple debridements and systemic antifungal agents. *Aspergillus* species were found to be the most fungal agent in both invasive and non-invasive group. There was a case of invasive *Scopulariopsis* which has been reported as very rare in literature.

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