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Original Article

A Prospective Clinical Study on Types and Diagnostic Criteria of Fungal Rhinosinusitis used in Tertiary Teaching Hospital of Telangana

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Abstract

Background: Fungal rhinosinusitis (FRS) is a disease of a wide spectrum of immune and pathological responses and includes invasive, chronic, granulomatous, and allergic variants. Consensus on its terminology, pathogenesis, and optimal management is not uniform among the surgeons. Based on the criteria of the International Society for Human and Animal Mycology, a clinical study was conducted on FRS.

Aim of the Study: The aim is to study and determine clinically and radiologically the various types of FRS and analyze them with the help of laboratory tests for confirmation in a clinical setting.

Materials and Methods: A total of 237 patients with FRS were included, and a detailed clinical history, demographic data, clinical examination, and direct sinonasal endoscopy were done. Radiological evaluation was done and the findings considered were air-fluid levels, opacities, mucosal thickening, and sinus wall erosion; expansion of the sinus walls, variegated densities, and other sinuses involved were studied. Fungal studies and histopathological studies were done. Treatment given to all the patients was recorded, and all the patients were followed up for 12 months. All the data were analyzed using standard statistical methods.

Observations and Results: Among the 237 consecutive patients included, there were 144 males (60.75%) and 93 females (39.24%). The mean age in males was 37.62 ± 4.73 years, and in females, it was 39.18 ± 3.64 years. 69/237 (29.11%) belonged to 33–42 years, 53/237 (22.36%) belonged to 23–32 years, 35/237 (14.76%) patients to 13–22 years, 23/237 (9.70%) patients to 53–62 years, and 20/237 (8.43%) patients to 63–72 years age group. Construction workers were 29/23 (12.23%), factory workers were 45/237 (19.40%), agriculture workers were 50/237 (21.09%), students were 23/237 (9.70%), office-goers were 50/237 (21.09%), and homemakers were 40/237 (16.87%) in number**.** Allergy was present in 94/237 (39.66%) and bronchial asthma in 52 (21.94%) patients. Diabetes mellitus was present in 44/237 (18.56%), tuberculosis in (6.32%), previous surgeries in 74 (31.22%), malignancies in 21 (8.86%), and psychiatric illnesses in 32 (13.50%) patients.

Conclusions: The diagnosis of FRS is challenging due to its wide spectrum of clinical symptoms and signs. Radiological features such as hyperattenuation, neo-osteogenesis, air-fluid level, bone erosion, and extra sinus extension are the parameters that will help routinely assess and differentiate fungal sinusitis from non-fungal sinusitis with considerable accuracy. Thorough clinical history, clinical examination, and laboratory evaluation hold the key to successful provisional diagnosis. Post-treatment assessment in India is difficult due to non-availability of patients for follow-up.

Key words: Allergic fungal sinusitis, Chronic sinusitis, Functional endoscopic sinus surgery, Fungal ball and invasive fungal sinusitis, Fungal rhinosinusitis

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INTRODUCTION

Fungal rhinosinusitis (FRS) can be acute invasive FRS (AIFRS) refers to disease of <4 weeks duration in immunocompromised patients; chronic invasive rhinosinusitis and granulomatous rhinosinusitis are terms denoting locally invasive disease over at least 3 months'

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duration, with differing pathology and clinical settings; fungal ball of the sinus is preferred to either mycetoma or aspergilloma of the sinuses. Localized fungal colonization of nasal or paranasal mucosa refers to localized infection visualized endoscopically; eosinophilic mucin refers to allergic mucin; and allergic FRS (AFRS), eosinophilic FRS (EFRS), and eosinophilic mucin rhinosinusitis (EMRS) are imprecise and require better definition.[1] In 1965, Hora published to classify FRS into two categories: Noninvasive, clinically similar to chronic bacterial sinusitis, and invasive, in which the infection results in a mass that behaves such as malignant neoplasm, eroding bone, and spreading into adjacent tissue.[2] The invasive nature of the disease was further confirmed on histopathology.[3,4] A fulminant type of rhinosinusitis with rapid and malignant course was reported by McGill *et al*., in 1980, in immunocompromised patients.[5] Allergic bronchopulmonary aspergillosis (ABPA) was reported by Safirstein[6] in 1976 which was a combination of nasal polyposis, crust formation, and sinus cultures yielding Aspergillus species. This clinical similarity with a constellation of findings was shared in 1981 by Millar *et al*.[7] In 1983, Katzenstein *et al*.[8] independently described a pathophysiologic resemblance in few cases of CRS associated with a mucosal plug in the sinuses of patients with ABPA leading to the description of a fourth type of FRS, namely allergic *Aspergillus sinusitis*. It became apparent later that melanized fungi are common etiological agents of this allergic type of sinusitis, which led to the renaming of this type of FRS as allergic fungal sinusitis or rhinosinusitis (AFS or AFRS).[9-11] With the demonstration of fungi in eosinophilic mucin independently from Type I hypersensitivity in most cases of CRS in recent years, the definition of AFRS has faced a greater challenge.[12,13] Hence, Ponikau *et al*.[12] proposed a new term for this condition, namely EFRS, to reflect the striking role of eosinophils.[12] The granulomatous invasive type of rhinosinusitis has to be differentiated from chronic invasive FRS (CIFRS). The former occurs in the patients who are immunocompetent, exclusively identified with *Aspergillus flavus*, and present as non-caseating granuloma with proptosis, whereas the latter often occurs in subtly immunocompromised patients, such as those with diabetes mellitus and corticosteroid treatment, with dense accumulation of hyphae invading tissue, and sometimes in association with the orbital apex syndrome.[13] The non-invasive FRS disorder consists of three types: Saprophytic fungal infestation, fungal ball, and fungus-related eosinophilic rhinosinusitis including AFRS.[14] Fungal ball is more or less a clear-cut entity. However, the confusion surrounds fungus-related eosinophilic rhinosinusitis and the definition of AFRS. As originally described, the detection of fungi in allergic mucin is considered important in the diagnosis of AFRS, although occasionally hyphae are sparse in the sinus contents. This leads to confusion and potential overlap with EMRS, as described by Ferguson in 2000.[15] Ferguson speculated that EMRS is a systemic disease with dysregulation of immunological control where eosinophilic mucin could be present without the presence of fungi.[15]

Type of the Study

This was a prospective, cross-sectional, and analytical study.

Institute of the Study

The study was conducted at the Department of ENT and Head and Neck Surgery, Gandhi Medical College/Gandhi Hospital, Hyderabad, Telangana.

Period of the Study

The study duration was from July 2013 to June 2015.

MATERIALS AND METHODS

A total of 237 consecutive patients attending the OPD of the Department of ENT, Gandhi Medical College/Gandhi Hospital, tertiary teaching institutes, were selected. Patients with FRS were included in this study over 2 years. An Ethical Committee Clearance was obtained before the commencement of the study. An Ethical Committee cleared consent form was used during the study.

Inclusion Criteria

1. Patients aged between 13 and 75 years were included.
2. Patients with acute as well as chronic FRS (CFRS) were included.
3. Patients with immunocompromised status were included.
4. Patients with diabetes mellitus and immunosuppressive drugs were included.
5. Patients with all types of FRS were included.
6. Patients with recurrent disease were included in the study.

Exclusion Criteria

1. Patients below 13 years and above 75 years were excluded.
2. Patients with bacterial chronic or acute rhinosinusitis were excluded.
3. Patients with acute fulminant systemic diseases were excluded from the study.

Patients included in this study were enquired about their detail clinical history and demographic data followed by clinical examination including direct sinonasal endoscopy. This was followed by plain and/or contrast-enhanced computed tomography (CT) paranasal sinuses (PNS), with axial, coronal, and sagittal cuts in all patients. The radiological findings that were observed were, air-fluid levels, opacities, mucosal thickening, and sinus wall erosion,

Expansion of the sinus walls, Variegated densities, other sinuses involved, Anatomical abnormalities, intra-cranial extension, orbital involvement and laterality to classify the types of AFS.

Sample Collection

Microbiology and pathology samples were collected such as exudates from nasal debris, discharge, and intraoperative tissue (polyps) sample, respectively. The samples were collected in two sterile containers, one containing normal saline for microbiology examination and the other containing 10% formalin for fixation. Samples received in microbiology were subjected to direct microscopy using KOH and calcofluor white as well as culture onto two sets of tubes of Sabouraud's dextrose agar with and without antibiotics. Samples sent in formalin to the pathology department were put up for histopathological examination (HPE). Fungal elements and yeasts were identified by colony morphology, gram staining, and lactophenol cotton blue standard preparations. Identification of the yeasts was done on the basis of germ tube production and morphology corn meal agar.[16] Treatment given to the all the patients was recorded, and all the patients were followed up for 12 months. All the data were analyzed using standard statistical methods.

OBSERVATIONS AND RESULTS

The study was conducted in a tertiary teaching hospital attached to Gandhi Medical College. The total number of patients attending the ENT department OPD was 86,490 over a period of 3 years. Among them, the patients with nasal complaints were 19,426 (22.46%). Patients with symptoms and signs of chronic rhinosinusitis were 2269 (11.68%). 237 consecutive patients among 2269, who were willing to participate in the study, were included. There were 144 males (60.75%) and 93 females (39.24%). The mean age in males was 37.62 ± 4.73 years, and in females, it was 39.18 ± 3.64 years. The youngest patient was 14-year-old female and the eldest one was 73-year-old male. 69/237 (29.11%) patients belonged to the age group of 33–42 years, 53/237 (22.36%) patients belonged to the age group of 23–32 years, 35/237 (14.76%) patients to the age group of 13–22 years, followed by 23/237 (9.70%) in 53–62 years and 20/237 (8.43%) in 63–72 years age group [Table 1]. In this study, construction workers were 29/23 (12.23%), factory workers were 45/237 (19.40%), agriculture workers were 50/237 (21.09%), students were 23/237 (9.70%), office-goers were 50/237 (21.09%), and home-makers were 40/237(16.87%) in number [Table 1]. Allergy was present in 94/237 (39.66%) and bronchial asthma in 52 (21.94%) patients. Diabetes mellitus was present in 44/237 (18.56%), tuberculosis in (6.32%), previous surgeries in 74 (31.22%), malignancies in 21 (8.86%), and psychiatric illnesses in 32 (13.50%) patients [Table 1].

The study revealed that the complaint of nasal stuffiness was present in 87.76%, rhinorrhea in 76.79%, postnasal drip in 71.72%, cough in 53.58%, purulent rhinorrhea in 49.36%, headaches in 45.52%, fever in 44.72%, facial pains in 33.75%, and toothache in 13.50% of patients [Table 2].

CT PNS with or without contrast showed hyperattenuation in 36.28%, fluid levels in 29.53%, sinuses expansion in 21.51%, variegated appearance in 12.65%, bone erosion in 9.70%, extra sinus extension in 6.32%, and osteoneogenesis in 5.48% of patients [Table 3].

Mucosal thickening, variegated appearance, sinuses expansion, bone erosion, and intracranial or intraorbital

Table 1: The gender incidence and other demographic incidences of the study group (*n* - 237)

Observation	Male - 144 (60.75%)	Female - 93 (39.24%)	Total (%) 237 (100%)
Mean age	37.62±4.73	39.18±3.64	
Age groups			
13–22	22 (15.27)	13 (13.97)	35 (14.76)
23–32	34 (23.61)	19 (20.43)	53 (22.36)
33–42	41 (28.47)	28 (30.10)	69 (29.11)
43–52	16 (11.11)	8 (08.60)	24 (10.12)
53–62	13 (9.02)	10 (10.75)	23 (9.70)
63–72	11 (7.63)	9 (9.67)	20 (8.43)
>72	7 (4.86)	6 (6.45)	13 (5.48)
Profession			
Construction worker	18 (12.5)	11 (11.82)	29 (12.23)
Factory worker	26 (18.05)	19 (20.43)	45 (19.40)
Agriculture	30 (20.83)	20 (21.50)	50 (21.09)
Student	12 (8.33)	11 (11.82)	23 (9.70)
Office-goers	29 (20.13)	21 (22.08)	50 (21.09)
Home-maker	29 (20.13)	11 (11.82)	40 (16.87)
Allergy			
Present	67 (46.52)	27 (29.03)	94 (39.66)
Absent	77 (53.47)	66 (70.96)	143 (60.33)
Bronchial asthma			
Present	31 (21.02)	21 (22.58)	52 (21.94)
Absent	113 (78.47)	72 (77.41)	185 (78.05)
Diabetes mellitus			
Present	34 (14.34)	13 (13.97)	44 (18.56)
Absent	120 (50.63)	80 (86.02)	200 (84.23)
Immunocompromised			
Present	9 (06.02)	7 (07.52)	16 (6.75)
Absent	135 (93.75)	86 (92.47)	221 (93.24)
Tuberculosis			
Present	10 (06.94)	5 (05.37)	15 (6.32)
Absent	134 (93.05)	88 (94.62)	222 (93.67)
Previous surgeries			
Present	46 (31.94)	28 (30.10)	74 (31.22)
Absent	98 (68.05)	65 (69.89)	163 (68.77)
Malignancies			
Present	13 (9.02)	8 (8.60)	21 (8.86)
Absent	131 (90.97)	87 (93.54)	116 (48.94)
Psychiatric illnesses			
Present	20 (13.88)	12 (12.90)	32 (13.50)
Absent	124 (86.11)	81 (87.09)	205 (86.49)

Table 2: The incidence of different symptoms in the patients (*n* - 237)

Observation	Male - 144	Female - 93	Total (%)
Stuffiness	121	87	208 (87.76)
Watery rhinorrhea	103	79	182 (76.79)
Postnasal drips	98	72	170 (71.72)
Coughs	76	51	127 (53.58)
Purulent rhinorrhea	68	49	117 (49.36)
Headaches	67	48	115 (45.52)
Fevers	59	47	106 (44.72)
Facial pains	44	36	80 (33.75)
Toothaches	19	13	32 (13.50)
Diplopia	17	8	25 (10.54)
Visual loss	12	5	17 (7.17)

Table 3: Radiological findings of CT PNS in the study group (*n* - 237)

Observation	Male - 144	Female - 93	Total (%)
Hyperattenuation	61	25	86 (36.28)
Fluid levels	48	22	70 (29.53)
Sinuses expansion	38	13	51 (21.51)
Variegated appearance	19	11	30 (12.65)
Bone erosion	16	7	23 (09.70)
Extra sinus extension	9	4	13 (05.48)
Osteoneogenesis	3	0	03 (01.26)

CT: Computed tomography, PNS: Paranasal sinuses

extensions were more common in AIFRS than in chronic fungal sinusitis. Variegated appearance in soft tissue densities filling the sinuses was noted in AFRS. CT PNS features of bone erosion, invasion into extra sinus areas, and hyperattenuation were seen in CIFRS. Saprophytic fungal infestation patients showed unilateral variegated, circumscribed masses in one or many sinuses, usually maxillary sinus followed by the frontal sinus. EMRS showed mucosal thickening, sinus expansion, and hyperattenuation on CT PNS. Taking into consideration of clinical symptoms, microbiological, pathological, and CT PNS findings, the diagnosis was made and it showed AFRS in 85/237 (35.86%), chronic invasive fungal sinusitis in 58/237 (24.47%), chronic granulomatous sinusitis in 43/237 (18.14%), fungal ball in 20/237 (8.43%), saprophytic fungal infestation in 12/237 (5.406%), EMRS in 10/237 (04.21%), and acute invasive fungal sinusitis in 9 (03.79%) patients [Table 4].

Mycological examination revealed fungal elements of Mucor species, *A. flavu*s, and Rhizopus species in the order of frequency in majority of the AIFRS patients. In chronic invasive, FRS <50% showed fungal elements. In addition to the above fungi, *Aspergillus niger*, *Candida albicans,* and Penicillium species were found in CIFRS patients. Histopathological specimens collected revealed fungal colonies in submucosal areas and bony erosion areas. Highly vascular areas and areas of necrosis were found in

Table 4: The final diagnosis of FRS in the study group (*n* - 237)

Observation	Male - 144	Female - 93	Total (%)
Allergic fungal rhinosinusitis - 115	52	33	85 (35.86)
Chronic invasive fungal sinusitis	32	26	58 (24.47)
Chronic granulomatous sinusitis	22	21	43 (18.14)
Fungal ball	14	6	20 (8.43)
Saprophytic fungal infestation	9	3	12 (5.06)
Eosinophilic mucin rhinosinusitis	8	2	10 (4.21)
Acute invasive fungal sinusitis	7	2	09 (3.79)

AIFRS. Fungal colonies were aseptate type in majority of AIFRS and CIFRS specimens. No evidence or evidence of occasional fungal elements was noted in AFRS and EMRS. Treatment consisted of functional endoscopic sinus surgery with debridement and clearance of the diseased tissue with adequate ventilation of all the sinuses, avoiding damage to the normal respiratory mucosa. Intraoperatively, Amphotericin B was given parenterally followed by post-operative antifungal antibiotics for 6 weeks in patients with AIFRS and CIFRS. In AFRS patients, itraconazole combined with steroid and antihistamine nasal spray and systemic steroids like methyl prednisolone was given to the patients for 6 months. Treatment of fungal ball consisted of FESS with middle meatus antrostomy and excision of the fungal ball followed by Antral lavage.

DISCUSSION

Various types of microorganism enter the upper airway tract and tend to colonize in the nasal cavity, PNS, and nasopharynx. In the PNS, fungi are the most common organism which would colonize as their spores are inhaled from the atmospheric air. Absence or minimal immune host reaction toward fungi plays a major role in the symptomatic manifestations of FRS, both invasive and non-invasive.[16] Invasive FRS is of two types: Acute (AIFRS) and CFRS, whereas non-invasive are typed as AFRS, fungal mycetoma (fungal ball), saprophytic variant, and EMRS.[17] Based on the clinical condition, immune status, histopathology, and fungus infection, de Shazo *et al*.[14] suggested a classification for tissue of IFRS as AIFRS, chronic granulomatous FRS (CGFRS), and CIFRS types, with a disease course of <4 weeks which is seen in AIFRS cases in an immunocompromised setting. He proposed that a disease course of >12 weeks, dense infiltration of fungal hyphae, occasional vascular invasion, and sparse inflammatory reaction destroying the local sinus walls are typical of CIFRS cases. The presence of granulomatous

reaction and fibrosis suggests a CGFRS.[18] In the present study, there were 144 males (60.75%) and 93 females (39.24%). The mean age in males was 37.62 ± 4.73 years, and in females, it was 39.18 ± 3.64 years. The youngest patient was 14 years old female and the eldest one was 73 years old male. In this study, AFRS accounted for 85/237 (35.86%) of the total patients with female-to-male preponderance of 1.5:1. In a study from Thailand among the patients of AIFRS, the age range was 22–75 years with a mean age of 54 years and sex ratio (Male:Female) of 1:1.33.[18] Chakrabarthi *et al*.[19] reported a mean age of 54 years (24–82) and Male:Female ratio of 1.5:1; this was similar to the present study. In the same study among CIFRS patients, the age range was 20–63 years, mean age being 45 years and sex ratio (Male:Female) 1:2. In the present study, the Male: Female ratio among the CIFRS patients was 1.23:1. Review of literature showed that patients of CIFRS present clinically with an enlarging mass in cheek, orbit, nose, and PNS regions and intracranial extension will change the clinical picture to associated symptoms such as headache, localizing, neurological findings, seizures, proptosis, and facial pain. Acute fulminant type presents with fever and headache in initial stages and proptosis, blindness, conjugal chemosis, ophthalmoplegia, signs and symptoms of meningeal involvement, cerebral infarction, and multiple cranial nerve palsies on invasion to different sites.[20,21,22] The present study revealed that the complaint of nasal stuffiness was present in 87.76%, rhinorrhea in 76.79%, postnasal drip in 71.72%, cough in 53.58%, purulent rhinorrhea in 49.36%, headaches in 45.52%, fever in 44.72%, facial pains in 33.75%, and toothache in 13.50% of patients, whereas Piromchai from Thailand[23] in 2008 from his study concluded that headache (59.3%) was the most common symptom, followed by visual loss (47.5%), facial pain (35.6%), and fever (33.9%). There were 9/237 (03.79%) patients in this study presenting with AIFRS who were immunocompromised unlike all other types of FRS 228/237 (96.20%), who were immunocompetent. Among the 9 cases of AIFRS, all were immunocompromised accounting to 100%. This was similar to the study conducted in the USA in 2008[22] wherein they found that all their patients with AIFRS were immunocompromised. As described by de Shazo *et al*.,[14] AIFRS occurs in immunocompromised patients most frequently. The comorbidities encountered in this study of FRS were diabetes mellitus, tuberculosis, allergy, bronchial asthma, and malignancies. Allergy was present in 94/237 (39.66%) and bronchial asthma in 52 (21.94%) patients. Diabetes mellitus was present in 44/237 (18.56%), tuberculosis in 15/237 (06.32%). previous surgeries in 74 (31.22%), malignancies in 21 (08.86%), and psychiatric illnesses in 32 (13.50%) patients. In Thailand (2008) study, diabetes mellitus was present in 66.6% of their AIFRS cases. Pagella *et al*.[24] reported that, in AIFRS cases, hematological malignancies represented the principal comorbidity (100%), and Montone *et al*.[22] from the USA also found hematological disorders (84%) to be more commonly associated with AIFRS patients. Furthermore, Michael *et al*.[24] in their patients found an association of diabetes in 62.7% of AIFRS cases. In CIFRS cases, diabetes was present in 22.2% and hypertension in 11.1% of cases, while Pagella *et al*.[25] reported that, in chronic form, diabetes mellitus (87.5%) to be the principal comorbidity. Radiological evaluation in this study showed CT PNS with or without contrast showed hyperattenuation in 36.28%, fluid levels in 29.53%, sinuses expansion in 21.51%, variegated appearance in 12.65%, bone erosion in 9.70%, extra sinus extension in 6.32%, and osteoneogenesis in 5.48% of patients. In AIFRS patients in this study, bone erosions, intraorbital and intracranial extension, mucosal thickening, and variegated opacities on bilateral sides were present. Unilateral homogenous opacities are described as characteristic radiological feature of fungal ball which was significantly present in this study. Aribandi *et al*.[26] documented features of the findings such as heterogeneous opacities, mucosal thickening, and calcifications in patients of fungal ball diseases. All the patients with AFRS in this study showed bilateral sinus involvement with heterogeneous opacities and variegated appearances and calcifications indicating a systemic disease rather than local infection with fungus. This finding is in agreement with the work of authors such as Aribandi *et al*.,[26] Michael *et al*.,[25] and Piromchai and Thanaviratananich.[23] Heterogeneous opacities were the most common finding in CIFRS cases followed by mucosal thickening and calcification. The CT findings seen in this study were showing such changes in CIFRS patients. Review of the study by Aribandi *et al*.[26] showed that the features of CGFRS were similar to CIFRS cases in their study. On HPE of the tissue from AFRS showed necrosis of sub-mucosa, bone, and vascular tissue in all the patients. All patients with AIFRS showed 100% of cases of AIFRS, and 65/85 (76.47%) of the AFRS patients evidenced accumulation of hyphae invading tissue. Only 148/237 (62.44%) patients could be followed up following surgical and medical treatment on this study. The incidence of recurrence among these 148 patients was 11/148 (07.43%). Post-treatment of this study remains the drawback of the present study.

CONCLUSION

The diagnosis of FRS is challenging due to its wide spectrum of clinical symptoms and signs. Radiological features such as hyperattenuation, neo-osteogenesis, air-fluid level, bone erosion, and extra sinus extension are the parameters that will help routinely assess and differentiate fungal sinusitis from non-fungal sinusitis with considerable

accuracy. Thorough clinical history, clinical examination, and laboratory evaluation hold the key to a successful provisional diagnosis. Post-treatment assessment in India is difficult due to the non-availability of patients for follow-up.

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