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Clinico Mycological Profile of Fungal Rhinosinusitis in A Tertiary Care Hospital

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Abstract

A Retrospective study of an Mucormycosis in patients with rhinosinusitis

Problems considered: Opportunistic fungal infections are emerging as the significant cause of morbidity & mortality amongst the patients. The objective of the study was to analyse the prevalence, predisposing factors & also to corelate histopathological & radiological findings with microscopy and culture results for accurate clinical diagnosis & classification of fungal rhinosinusitis.

Methods: This was a retrospective analytical study in which evaluation of 157 cases with fungal rhinosinusitis (FRS)was done. Specimens collected were subjected to standard microbiological procedures, relevant data was collected including predisposing factors, clinical, histopathological and radiologic features which was then analysed.

Results: The prevalence of fungal rhinosinusitis in our study was 12%. Aspergillus was the most commonly isolated species (38.88%) of fungus. Acute invasive fungal rhinosinusitis (AIFRS)(63.15%) was the most prevalent entity in the spectrum of fungal rhinosinusitis according to histopathologic classification whereas Chronic granulomatous invasive fungal rhinosinusitis (CGFRS) was observed to be 26.31% in our study. The prevalence of fungal rhinosinusitis was found to be higher among individuals who were immunocompromised. A seasonal trend in prevalence of FRS cases was observed in which maximum number of cases were

noted in winter months in our study. The most common predisposing factor was Diabetes mellitus.

Conclusions: Mycological identification plays a crucial role in diagnosing and categorizing rhinosinusitis. KOH and fungal culture are gold standard for early diagnosis and identification of the etiological agent, respectively. Unilateral involvement of paranasal sinuses is more in favour of fungal etiology.

Keywords: Fungal rhinosinusitis**,** sinusitis, paranasal sinuses.

Introduction

Fungal infection of paranasal sinuses is an increasingly recognized entity both in immunocompetent and immunocompromised individuals. A variety of different causative organisms are responsible for paranasal mycosis, Aspergillus species being the commonest. Rhino-nasal mucormycosis commonly, but not exclusively, affects patients with diabetes mellitus (DM), blood dyscrasias, chronic kidney disease (CKD), prolonged steroid use, neutropenia, malignancies, acquired immunodeficiency syndrome (AIDS), and patient on chronic deferoxamine or immunosuppressive therapy. [1] Fungal rhinosinusitis (FRS) comprises a variety of different disease processes which vary in presentation, histological appearances, and clinical significance.

Disease is most commonly classified as being non-invasive or invasive based on whether the fungi have invaded into the sinonasal submucosal tissue resulting in tissue necrosis and destruction. Invasive disease is characterized as either acute or chronic based on duration of the symptoms existing before presentation. If the duration of symptoms is less than three weeks, it is classified as acute fungal rhinosinusitis and if the symptoms persist more than 3 weeks, it is classified as chronic fungal rhinosinusitis. Invasive diseases are differentiated into (1) acute invasive FRS, (2) chronic invasive FRS and (3) granulomatous type. The non-invasive diseases are further categorized into three different clinical forms: (1) localized colonization, (2) fungal ball and (3) eosinophil-related FRS that includes AFRS.[2]

Fungal sinusitis is caused by a variety of host and environmental factors, with sinus blockage being the most common cause, as it impairs ventilation. Given that fungi are both common and elusive in the natural world, environmental conditions are also quite significant.[3] They can be found in plants, soil, dust, air and decomposing organic materials. They stick to dust particles, get inhaled and land on the sinonasal mucosa, multiply in the perfect warm, humid environment of the upper respiratory tract in healthy people, and becoming pathogenic in individual who are at risk. Accurate diagnosis and prompt treatment are crucial for improving patient outcomes and survival.

The present study was carried out to further understand the clinical behaviour, incidence, prevalence, predisposing risk factors, clinical course, outcome, mortality & morbidity of the disease as well as to study the mycological profile of fungal isolates in clinically suspected rhinosinusitis.

Materials and Methods

In this retrospective analytical study, sinonasal specimens from 157 patients with clinically suspected fungal rhinosinusitis in a tertiary care hospital in Mumbai were evaluated in the time frame of May 2023 to May 2024. Information regarding age, gender, associated co-morbid diseases, clinical presentation

and immune status of the patient were retrieved from records. Seasonal variation of fungal rhinosinusitis was also noted. Samples included were nasal crust and tissue specimens collected during surgical excision. A portion of surgically excised specimens was received in sterile normal saline into the mycology laboratory. The tissue specimens were subjected to 10% KOH, 20% KOH & Grams staining. Irrespective of direct KOH positivity, the specimens were subjected to fungal culture. According to the standard mycological practice, the specimens were inoculated into two sets of Sabouraud's Dextrose Agar (SDA), in duplicates, one with gentamicin and cycloheximide and another without cycloheximide. One set was incubated at 37°C and another set at 25°C for 30 days. In culture-positive samples, the isolate was identified by detailed gross examination of culture characteristic like growth rate, colour, texture, diffusible pigments, exudates aerial & submerged hyphae and colony topography followed by noting microscopic characteristic by performing lactophenol cotton blue (LPCB) tease mount and slide culture technique. Fungal slide cultures were further subjected to LPCB stain. Results of fungal cultures were reviewed and correlated with clinical and histopathological findings.[4,5]

Result and Discussion

In our study the age of the patients varied from 32 to 59 years with the median age being 52 years as indicated in (Fig 1). Male to female ratio was observed to be 0.8:1. In our study, maximum positive cases(69%) were found to be in the winter months, i.e., from September to February, indicating a seasonal trend in disease incidence.(Fig 2) Patients presented with varied symptoms such as nasal obstruction, nasal discharge, facial swelling, headache, etc. with facial swelling being the most common (66.66%) symptom, followed by nasal obstruction (58.33%). In our study, Diabetes mellitus was found to be the most common predisposing factor among KOH/Culture positive isolates as shown in (Fig 3).

Out of 157 cases of clinically suspected rhinosinusitis, 19(12.1%) cases were either fungal culture or KOH positive. KOH smear positivity in this study was observed to be 8 (42.10%), out of the 19 sinonasal specimens. 18 samples were culture positive out of a total of 157 samples. The correlation between KOH and culture findings is shown in [Table 1].

7 out of 18 culture-positive fungal pathogens were Aspergillus species (38.88%) which was the most common species isolated in our study as shown in [Table2] On the basis of histopathological findings, 12(63.15%) were acute invasive fungal rhinosinusitis was the most common type observed in our study which is indicated in [Table 3]

Rhinosinusitis is defined as the inflammation of nasal and paranasal sinus mucosa, and it is a common disorder affecting approximately 20% of the population at some time of their lives. The prevalence is even greater in tropical countries like India.[6]

A study by Michael et al.[7], conducted at Vellore reported fungal rhinosinusitis in patients with mean age of 45.7 years ranging from 11 to 79 years with male to female ratio 0.8:1 which is concordant with our study in which the age of patients ranged from 32 to 59 years with mean age being 46.66 years with male to female ratio being 0.8-1.

The disease is more common in temperate regions than in tropical ones, especially in places with abundant rainfall, which provide ideal growing

conditions for mold on hay. Depending on the farming methods and climate, it usually happens in the late winter and early spring. Raghunath Shanbag et al.[8] noted a rise in cases of fungal rhinosinusitis during monsoon season in South India, whereas in our study there was a sudden hike in FRS cases during winter season followed by monsoon and least cases were noted in summer season. Several environmental & geographical factors like moister, temperature, humidity affects the growth & asexual & sexual reproduction of the fungi, our locality from where study is conducted is just 10 to 15 meters above the sea level, and the average relative humidity is around 75% this in turn promotes fungal rhinosinusitis in susceptible individuals.

Numerous host-related predisposing factors, including as uncontrolled diabetic mellitus, immunosuppressed states, dust allergies, allergic rhinitis, bronchial asthma and structural risk factors such a deviated nasal septum, have been recognized for the rising frequency of FRS. Risk factors such as hematologic malignancies, solid organ transplants, bone marrow transplants, chemotherapy, radiation, chronic corticosteroid usage and acquired immunodeficiency syndrome (AIDS) have been found to gradually promote immunosuppressive states. Systemic lupus erythematosus and autoimmune disorders are among the other risk factors. Furthermore, by inhibiting bacterial flora and promoting fungal overgrowth, the broad-spectrum antibiotics, antihistamines, and corticosteroids used to treat sinusitis and nasal allergies may actually contribute to the pathophysiology of the condition. In an 18-month study conducted by Jain et al.[9] in north India, it was observed that an increase in incidence of FRS has been attributed to various host predisposing factors like uncontrolled diabetes mellitus, immunosuppressed states, allergy to dust, allergic rhinitis, bronchial asthma and anatomical risk factors like deviated nasal septum. Similar observation was made in our study where predisposing factors such as diabetes mellitus, hypertension, chronic kidney disease and epilepsy can be attributed to precipitating FRS, diabetes mellitus being the most common predisposing factor.

Site of sample collection & quality of sample collected plays a major role for isolating pathogen from specimen submitted for culture. Tissue sample is most appropriate for isolation of pathogens compared to nasal crust, debris, secretions or swabs. Unilateral involvement of paranasal sinuses is more in favour of fungal etiology. Maxillary sinus was most commonly involved in fungal rhinosinusitis in our study which is probably because the sinus ostium is located lowest in the middle meatus compared with other sinus ostia, which provides easy excess to microorganisms.[10]

On histopathology, there is necrotic tissue invaded by plenty of fungal hyphae with acute neutrophilic infiltrate. Acute non-invasive FRS is more commonly seen in immunocompetent middle-aged and elderly females. The diagnostic criteria include radiological evidence of sinus opacification, mucopurulent cheesy or clay-like material within the sinus, a dense conglomeration of hyphae separate from the sinus mucosa, non-specific chronic inflammation of the mucosa, no predominance of eosinophils or granuloma or allergic mucin and no histopathological evidence of fungal invasion of mucosa. Granulomatous invasive FRS is usually seen in young adults and is described by a time course of >12 weeks

presenting with an enlarging mass in the cheek, orbit, nose and paranasal sinuses and proptosis in immunocompetent hosts. Histopathology shows granulomatous response with considerable fibrosis. Non-caseating granuloma with foreign body or Langerhans-type giant cells may be seen with scanty number of hyphae. Panda et al.[11], in their study, categorized 178 patients diagnosed as having paranasal sinus mycoses into three disease groups- Allergic (8), non-invasive (92) and invasive (78) on the basis of histopathological and mycological investigations. In a prospective study of 176 cases of fungal rhinosinusitis, Chakrabarti et al.[12] classified the patients into allergic (12 patients), non-invasive without bony destruction (81 patients), non-invasive destructive (16), chronic invasive (55) and fulminant (12).We, in our study, on the basis of clinical, radiological, histopathological and mycological findings, classified 19 positives for fungal rhinosinusitis and following observations were made: all 19 cases (100%) were of invasive fungal rhinosinusitis of which 12 cases were of acute invasive fungal rhinosinusitis (63.15%), 5 cases of chronic granulomatous invasive fungal rhinosinusitis (26.31%) and 2 cases of chronic invasive fungal rhinosinusitis (1.05%). These invasive type of fungal infections are highly angioinvasive & causes tissue infraction, necrosis & thrombosis. This accounts for blackish eschar & its rapid spread. Neutrophils are the main line of defence against the fungi & the patients with neutropenia are particularly affected. Mortality has been reported to be as high as 80 percent. Identification of the population at risk with high index of suspicion for early diagnosis and aggressive medical and surgical intervention is crucial for survival.

Although histopathological and radiological investigations provide substantial evidence in determining presence of fungal etiology in suspected cases of FRS, culture remains the gold standard for confirming diagnosis of FRS. In our study, the prevalence of fungal rhinosinusitis by fungal culture was 12.1% among patients with CRS, this correlates well with a study by Prateek et al. which reported 21 cases of fungal rhinosinusitis out of 100 suspected cases of CRS over a period of one year when compared to our study conducted over a period of one year which reported 19 positives out of a total of 157 cases of suspected fungal rhinosinusitis.

The clinical samples obtained after endoscopic sinus surgery (ESS) are cultured on Sabouraud dextrose agar. The Aspergillus species culture takes around 3-4 days to grow. Dematiaceous fungi may take longer time to grow. Identification of fungal isolate is done by the morphological examination of growth and the microscopic examination of the teased LCB mounts made from the fungal colonies. There is increasing evidence that fungi are significantly involved in worsing & sustaining mucosal inflammation. A significant number of patients diagnosed with chronic rhinosinusitis (CRS) often tend to have a final diagnosis of fungal rhinosinusitis. In a study by Chakrabarti et al. 56% KOH mount positivity has been reported which is comparable to 42.10% KOH mount positivity which was observed in our study.

As shown in Table.3, in this study, 9 (5.73 %) samples were KOH positive and fungal growth was found in 18 (11.46 %). 1 (0.63 %) sample was positive for KOH but culture negative which may be attributable

to the presence of non-viable fungi or the presence of possible interfering substances or microorganisms which made culture sterile. On the other hand, in 10 (6.36 %) samples, culture alone was positive, but KOH positivity could not be demonstrated which may be due to less quantity of sample, low fungal content in the sample, non-representative sample for KOH examination, absence of hyphae from the part used for microscopic examination, presence of fungus in an inactive sporulating phase difficult to be detected on KOH that grows when cultured or an otherwise known lower sensitivity of KOH as compared to fungal culture. Therefore, both KOH and culture results should be interpreted for and accurate mycological diagnosis.

It has been observed during reporting that growth of both Aspergillus and Mucormycetes can be noted in sample collected from same site or different samples collected simultaneously from different site from same patient. Interpreting direct smears and fungal cultures in these individuals frequently requires clinical correlation. Since many of the identified fungi are more widely regarded as pollutants, it can be challenging to demonstrate a causal link between the fungal culture results and the clinical presentation of AFS. Occasionally, more than one fungus may grow in the clinical samples, and that could also be important. Aspergillus sp. is a chronic colonizer of paranasal sinuses and ears as well as associated with a variety of different clinical conditions. In our study 38.88 % of fungal rhinosinusitis was caused by Aspergillus sp., and A. flavus (33.33%) was the most common isolate.[13] In a similar study by S. Prateek et al.,[1] Aspergillus sp. (76.19%) was the most common isolated species and A. flavus (57.14%) being the most common fungal isolate among all cases of fungal rhinosinusitis.

In our study, Aspergillus were isolated from chronic forms like CIFRS & CIGFRS cases whereas Zygomycetes like Mucor, Rizopus & syncephalostrum racemosum were responsible for AIFRS cases. While fungi like dematiaceous hyphomycetes like Cladosporium was the causative agent of acute invasive fungal rhinosinusitis.

Surgical debridement is typically used to remove the mucinous concretions and hypertrophic tissue in cases of fungal rhinosinusitis. Corticosteroids, both oral and nasal, are frequently used to control the immunological response.[14] A systematic antifungal therapy might be necessary in instances those were not responding. Ensuring a precise diagnosis of the problem by the growth of the fungal pathogen in culture and the evidence of fungus in KOH is crucial. This will help the surgeon choose the best surgical strategy, the extent of resection, and any necessary perioperative adjuvant antifungal drugs to be given to patients. Control of predisposing factors for secondary instances and endoscopic sinus surgery (ESS), with or without antifungal medications, are advised.[15]

Figure 1:

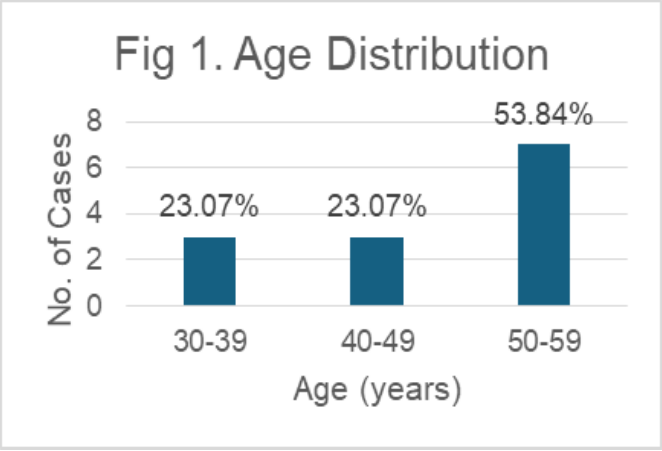

Figure 2:

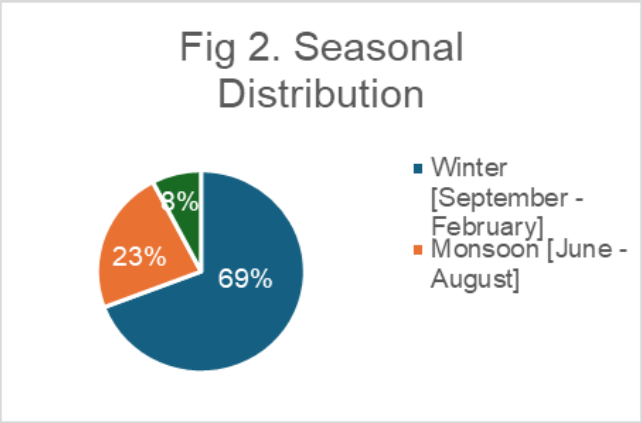

Figure 3:

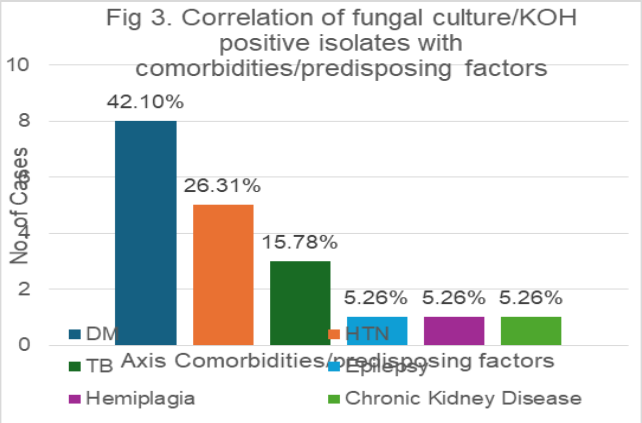

Table 1: Correlation between KOH and culture findings

	KOH Positive (%)	**KOH Negative (%)**
Culture Positive	5.09%	6.36%
Culture Negative	0.63%	87.89%

Table 2: Distribution of fungal isolates identified amongst cases of fungal rhinosinusitis

Species Isolated	**Percentage (n=18)**
Aspergillus flavus	33.33
Aspergillus fumigatus.	5.55
Rhizopus arrhizus	33.33
Mucor sp.	16.66
Cladosporium sp.	5.55
Syncephalastrum racemosum	5.55
Total	100

Table 3: Histopathological classification of cases of fungal rhinosinusitis

Histopathological diagnosis	**Histopathology**	**Percentage (%) (n=19)**
Acute invasive fungal rhinosinusitis (AIFRS)	Fungal Hyphae seen	63.15
Chronic granulomatous invasive fungal rhinosinusitis (CGFRS)	Abundant fungal hyphae	26.31
Chronic invasive fungal rhinosinusitis (CIFRS)	presence of non-caseating granula	1.05

Conclusion

Mycological identification plays a crucial role in diagnosing and categorizing rhinosinusitis. It also provides therapeutic guidance for the other specialities, principally in the case of atypical presentation and in infection with less common agents. KOH and fungal culture are of vital importance for early diagnosis and identification of the etiological agent, respectively.

As each of the clinico-pathological variants of FRS is associated with unique host-related risk factors and different etiological agents, knowledge of the

prevalent fungal agents is important. Hence, a regular monitoring of fungal infections is required to study the prevalent pattern and monitor the emerging pattern of these infections.

Culture is still the gold standard for confirming the diagnosis of FRS, even though histological and radiographic examinations offer significant evidence in identifying the presence of fungal etiology in suspected cases of the disease.

It's crucial to periodically check on the emergence and alteration of the disease pattern in FRS patients as well as to continuously monitor the prevalence of sinonasal fungal infections. Protocol-wise streamlining has produced positive outcomes, a high suspicion index, vigorous medical and surgical intervention, and timely follow-up to ensure early discovery and recurrence prevention.

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