REVIEW ARTICLE

Epidemiology and Medical Mycology of Fungal Rhinosinusitis

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Abstract

Fungal rhinosinusitis (FRS) refers to a spectrum of disease ranging from benign colonization of the nose and sinuses by pathogenic fungi to acute invasive and fatal inflammation extending to the orbit and brain. FRS is classified into two categories: invasive and noninvasive. Invasive FRS may again be subcategorized into acute invasive (fulminant) FRS, granulomatous invasive FRS, and chronic invasive FRS; while noninvasive FRS is subcategorized into localized fungal colonization, sinus fungal ball and eosinophil related FRS (including allergic fungal rhinosinusitis, eosinophilic fungal rhinosinusitis). This classification is not without controversies, and intermediate and semi-invasive forms may also exist in particular patients. Acute invasive FRS is an increasingly common disease worldwide among the immunocompromised patients and caused most frequently by *Rhizopus oryzae*, and *Aspergillus* spp. Granulomatous invasive FRS has mostly been reported from Sudan, India, and Pakistan and is characterized by noncaseating granuloma formation, vascular proliferation, vasculitis, perivascular fibrosis, sparse hyphae in tissue, and isolation of *A. flavus* from sinus contents. Chronic invasive FRS is an emerging entity occurring commonly in diabetics and patients on corticosteroid therapy, and is characterized by dense accumulation of hyphae, occasional presence of vascular invasion, sparse inflammatory reaction, involvement of local structures, and isolation of *A. fumigatus*. While localized fungal colonization describes the most benign of all fungal sinusitis in the superficial nasal crusts, sinus fungal ball is a dense mycetoma like aggregate of fungal hyphae in diseased sinuses. Common in southern Europe, especially France, majority of them are sterile on culture while 30-50% may yield *Aspergillus* spp. The definitions and pathogenesis of the group of syndromes in eosinophil related FRS (AFRS, EFRS) are contentious and a matter of intense research among otolaryngologists, pathologists, immunologists and microbiologists. While dematiaceous fungi are the foremost initiators of these syndromes in the west, *Aspergillus flavus* is the predominant pathogen in India and the Middle-East.

Keywords: Fungal sinusitis, epidemiology, Aspergillus, allergy, fungi.

INTRODUCTION

Rhinosinusitis is defined as the inflammation of nasal and paranasal sinus mucosa and is associated with mucosal alterations ranging from inflammatory thickening to gross nasal polyp formation.[1,2] This inflammation of the nasal and sinus mucosa may be due to microorganisms (bacteria and fungi), allergic and nonallergic immunological inflammation, and noninfectious, nonimmunological causes.[3] The subset of rhinosinusitis cases where the etiological role of fungi is proven or is considered to be important (due to its isolation from tissue biopsy samples) is referred to as fungal rhinosinusitis (FRS). FRS is being increasingly recognized in persons of all age groups, resulting in great socioeconomic effects, including both direct and indirect costs to the society.[4,5] The patients have high morbidity and even may have high mortality especially those having acute invasive FRS. The impact of FRS not withstanding, the disease is often neglected and misdiagnosed especially in developing countries like India, where FRS is one among the neglected diseases.

HISTORICAL PERSPECTIVES

Way back in the 18th century, Plaignaud in 1791 described 'fungus tumor' in the maxillary sinus of a 22-year-old soldier.[6] After a long gap of period, Oppe described *Aspergillus* species causing sinusitis in 1897 in a patient with infection of sphenoid sinus. The lesion in that patient had extended to the cerebrum through erosion of the bony wall.[7] Mackenzie in 1894 described what is probably the first case of apparent noninvasive fungal sinusitis.[8] However, it was only in 1965, Hora recognized two categories of fungal sinusitis: One noninvasive behaving clinically like chronic bacterial sinusitis, and the other invasive, in which the infection results in a mass that behaves like malignant neoplasm, eroding bone and spreading into adjacent tissue.[9] Baker et al in 1957 reported for the first

time an acute invasive (fulminant) type of FRS caused by *Zygomycetes* in immunocompromised patients.[10] Later a similar acute invasive FRS was also attributed to *Aspergillus* spp. in 1980.[11] Milosev et al first recognized the chronic granulomatous type of invasive FRS in Sudan in 1969.[12] Finby and Begg did the documentation of the benign entity of fungal ball or sinus mycetoma in 1972.[13] Safirstein in 1976 noted a combination of nasal polyposis, crust formation, and sinus cultures yielding *Aspergillus* spp. in a few patients and observed the clinical similarity that this constellation of findings shared with allergic bronchopulmonary aspergillosis (ABPA).[14] Similarly in 1981, Miller et al[15] and in 1983 Katzenstein et al[16] independently recognized a pathophysiological resemblance between a few cases of chronic rhinosinusitis (CRS) associated with a mucosal plug in the sinuses and patients with ABPA. This fourth type of FRS was first named as allergic *Aspergillus* sinusitis. However, later it became apparent that melanized fungi are also common etiological agents of this allergic sinusitis and hence the entity was renamed as allergic fungal sinusitis or rhinosinusitis (AFS or AFRS).[17-19] In a landmark article, Ponikau et al, 1999, using novel diagnostic techniques, demonstrated the presence of fungi and eosinophils in 96% of CRS, and coined the new entity eosinophilic fungal rhinosinusitis (EFRS).[20] If their findings are true, this will effectively mean that nearly all patients of CRS have a fungal etiology. Increasing interest in the field of CRS and FRS has now stimulated workshops and international cooperation for meaningful discussion on the topic: First the American Academy of Otolaryngology Head and Neck Surgery and other related societies through a workshop attempted a consensus of definition, classification of the condition and suggested clinical research strategies for patients with rhinosinusitis[3]; and very lately the International Society for Human and Animal Mycology (ISHAM) convened a working group to attempt consensus on terminology and disease classification.[21]

CATEGORIZATION OF FUNGAL RHINOSINUSITIS

Though a lot of controversies surround the categorization of FRS,[21,22] most commonly accepted system divides FRS into two categories (Table 1): Invasive and noninvasive depending on the invasion of fungi across mucus membrane. Invasive FRS is subcategorized as into three groups: acute invasive (fulminant), granulomatous invasive, and chronic invasive. Noninvasive FRS is also further subcategorized as into three groups: Localized colonization, fungal ball (sinus mycetoma), and eosinophil related FRS (including allergic fungal rhinosinusitis, eosinophilic fungal rhinosinusitis).

1. Invasive Fungal Rhinosinusitis (FRS)

a. ***Acute invasive (fulminant) FRS:*** Commonly caused by members of the class *Zygomycetes* or by *Aspergillus* spp. This disease occurs more often in the immunocompromised patients,[23-29] and associated with a mortality rate exceeding 50%. The disease is characterized by a time course of less than 4 weeks with predominant vascular invasion. Histopathology demonstrates hyphal invasion of blood vessels, which may include the carotid arteries and cavernous sinuses, vasculitis with thrombosis, hemorrhage, tissue infarction and acute neutrophilic infiltrates.[22] The disease has also been termed as acute necrotizing FRS because necrotizing pathological reaction may be seen in some patients with only minimal inflammation (Fig. 1), and plenty of fungi in the necrotic tissue.[23]

b. ***Granulomatous invasive FRS:*** This disease has been described primarily in Sudan, India, Pakistan and Saudi Arabia, and rarely in the United States, and is characterized by a time course of more than 12 weeks.[22,30,31] The entity presents with an enlarging mass in the cheek, orbit, nose, and paranasal sinuses in immunocompetent hosts. Proptosis is often a prominent feature. Histopathologically a granulomatous response is seen with considerable fibrosis (Fig. 2A). Non-caseating granuloma with foreign body or Langhans' type of giant cells may be seen, sometimes with vasculitis, vascular proliferation, and perivascular fibrosis. Hyphae in many occasions are scanty and are present inside the giant cells (Fig. 2B), and *A. flavus* is the primary agent isolated. The presence or absence of precipitating antibodies against antigens from the etiological fungi correlates well with disease progression.[32]

c. ***Chronic invasive FRS:*** Chronic invasive FRS is a slowly destructive process that most commonly affects the ethmoid and sphenoid sinuses but may involve any paranasal sinus. The disease typically has a time course of more than 12 weeks. However, in contrast to granulomatous invasive FRS, the entity is characterized

TABLE 1: Categories of fungal rhinosinusitis

Category		*Host immune status*	*Role of fungus*	*Major fungus isolated*	*Course*
Invasive	• Granulomatous invasive	Immunocompetent	Pathogen	*A. flavus*	Indolent, chronic
	• Chronic invasive	Often diabetes mellitus, steroid therapy	Pathogen	*A. fumigatus*	Chronic
	• Acute invasive (Fulminant/necrotizing)	Immunocompromised	Pathogen	Zygomycetes, *Aspergillus* spp.	Acute
Noninvasive	• Localized colonization (Saprobic infestation)	Immunocompetent	Saprobe	*Aspergillus* spp.	May or may not progress to other forms especially sinus fungal ball
	• Fungal ball (Mycetoma/Aspergilloma)	Immunocompetent	Saprobe	*Aspergillus* spp.	Chronic
	• Eosinophil related – AFRS	Atopic	Allergen	Dematiaceous fungi, *A. flavus*	Chronic
	– EFRS	Majority nonatopic	Activation of eosinophil	Dematiaceous fungi	Chronic
	– EMRS	Asthmatics, aspirin sensitive individuals, IgG_1 deficiency	Unknown	Not present	Chronic

AFRS = Allergic fungal rhinosinusitis; EFRS = Eosinophilic fungal rhinosinusitis; EMRS = Eosinophilic mucin rhinosinusitis.

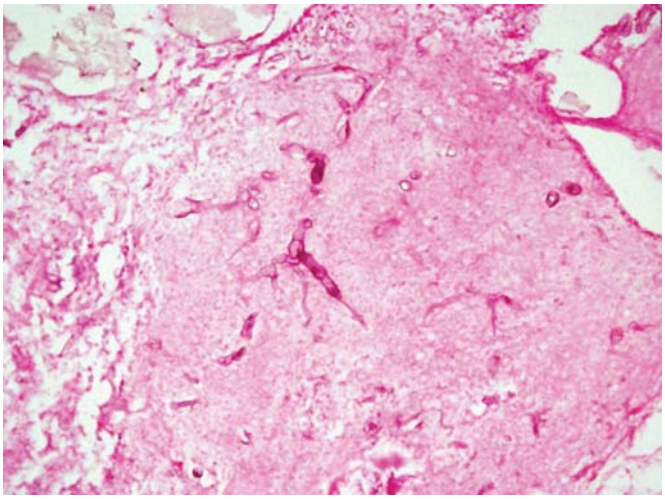


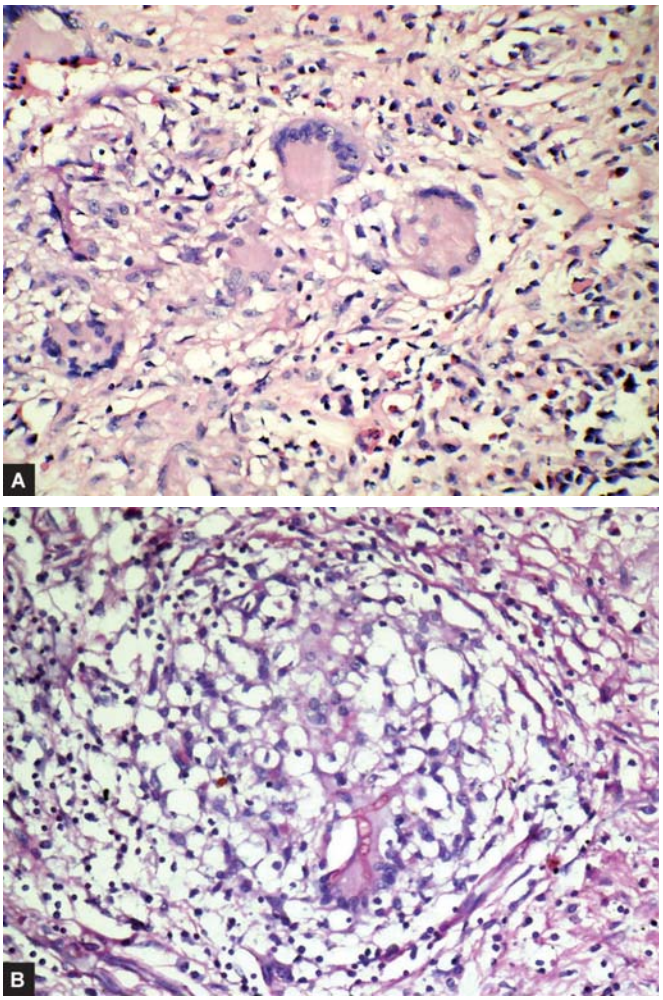
FIGURE 1: Acute invasive fungal rhinosinusitis with bland infarcted area. Plenty of hyphae of zygomycetes (X200)

as dense accumulation of hyphae (Fig. 3), occasional presence of vascular invasion, sparse inflammatory reaction, and involvement of local structures. The entity is usually seen in the patients having diabetes mellitus or on corticosteroid treatment.[22,30,33] Cultures of tissue are positive in >50% of cases and *A. fumigatus* is the most common agent isolated.

The distinction between granulomatous invasive and chronic invasive FRS is not very clear, and indeed some investigators believe both entities to be similar. Granuloma formation, fibrosis, vascular proliferation, scanty fungal infiltration into tissues, absence of vascular invasion, isolation of *A. flavus* and geographical restriction of the disease are probably the important differentiating features for granulomatous invasive FRS from chronic invasive FRS. However, the clinico-pathological distinction between these two types is not sharp. Both have a chronic course and prominent orbital involvement. Moreover, no difference in prognosis or therapy is yet apparent based on this distinction.

2. Noninvasive FRS

a. ***Localized fungal colonization (saprobic infestation):*** This disease entity refers to the asymptomatic colonization of mucous crusts within the nasal cavity by fungi, often in patients who had previous sinus surgery. The possibility of extension of this growth further leading to the formation of fungal ball has been predicted.[34] However most patients have a benign course and treatment may not be warranted in such colonization.



FIGURES 2A and B: Chronic granulomatous fungal rhinosinusitis with (A) extensive granulomatous process on hematoxylin and eosin stain (X400), (B) fungal hyphae inside giant cells on periodic acid schiff stain (X400)

b. ***Sinus fungal ball:*** Sinus fungal ball is described as the presence of noninvasive accumulation of dense conglomeration of fungal hyphae in one sinus cavity, usually the maxillary sinus, though the disease may affect other sinuses or rarely multiple sinuses.[35] Commonly used synonyms in medical literature include fungal ball, sinus mycetoma, aspergilloma of the nasal sinuses, and chronic noninvasive granuloma.[34] The disease is defined by the following criteria: Radiological evidence of sinus opacification with or without radiographic heterogenecity, mucopurulent cheesy or clay-like materials within the sinus, a dense conglomeration of hyphae separate from the sinus mucosa (Figs 4A to C), nonspecific chronic inflammation of the mucosa, no predominance of eosinophils or granuloma or allergic mucin, no histopathological evidence of fungal invasion

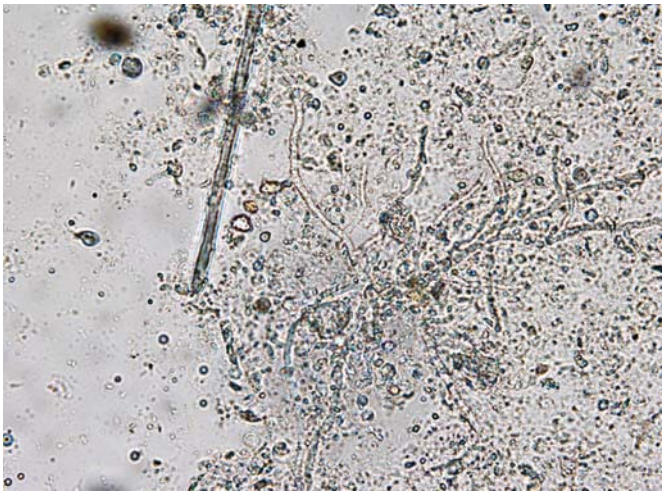
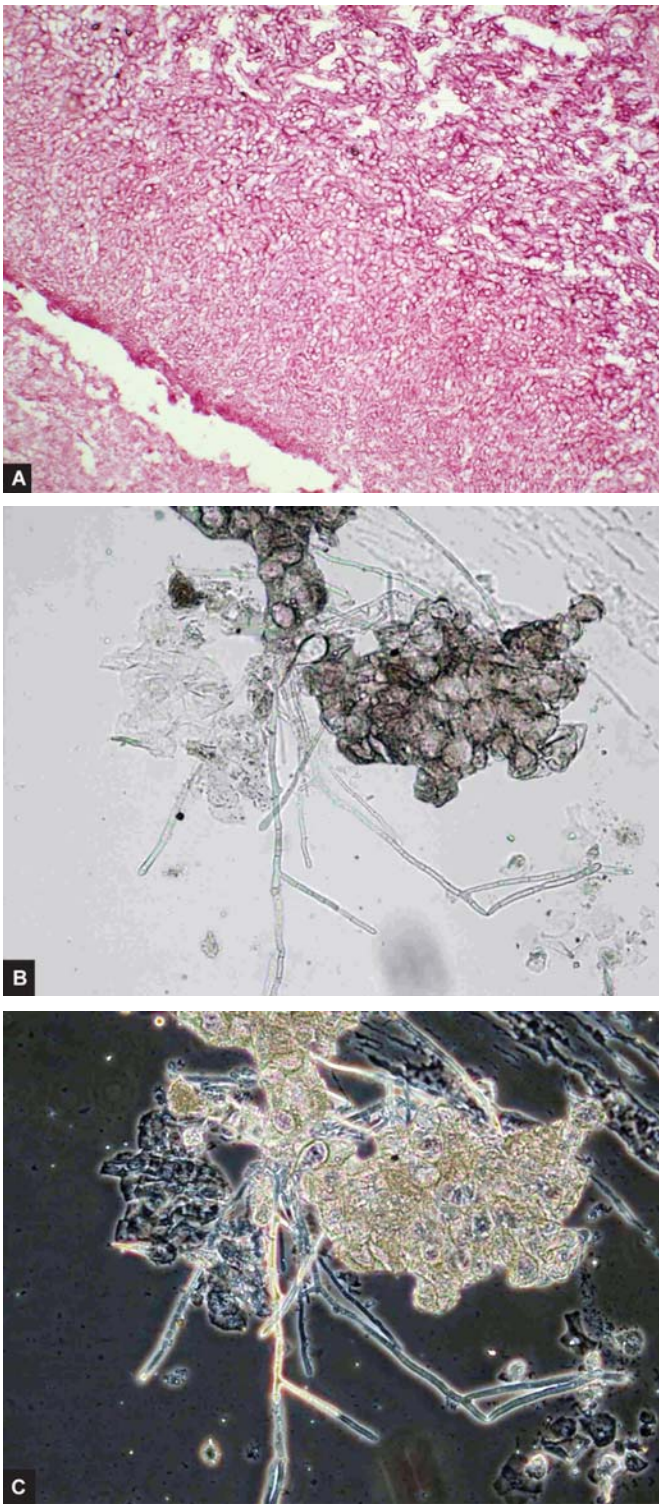


FIGURE 3: Chronic invasive fungal rhinosinusitis with plenty of hyphae on 10% potassium hydroxide wet mount (X200)

of mucosa.[36] Rarely the fungi may become invasive after substantial immunosuppression, such as in renal transplantation.[37] In addition, some patients may develop allergic mucin surrounding the fungal balls when corticosteroids are tapered.[34,38] Fungal balls have a characteristic gritty matted gross appearance to the surgeon.[39]

c. ***Eosinophil related FRS:***

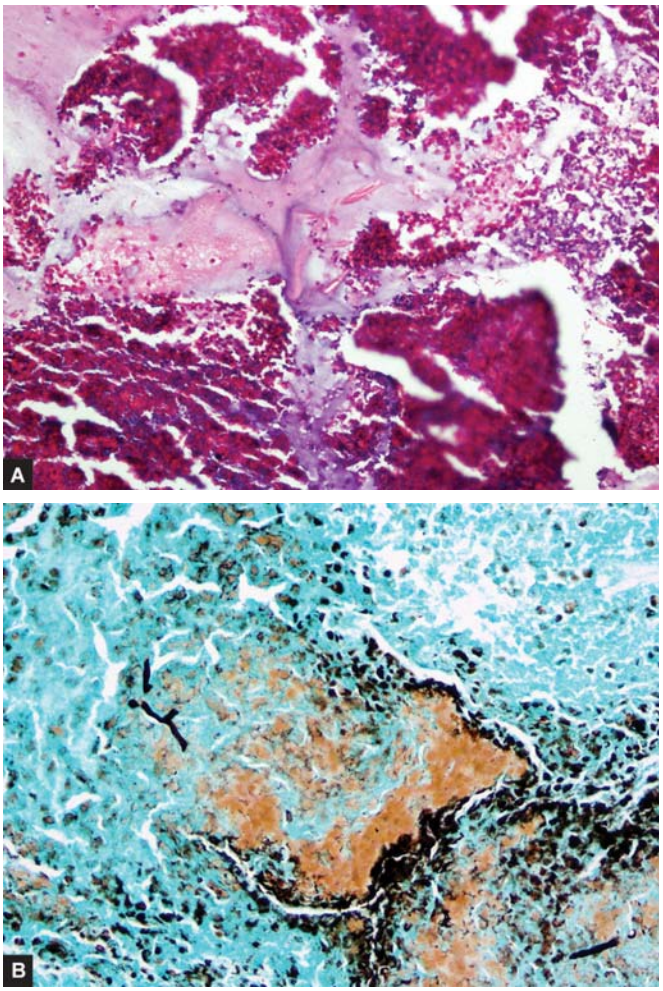
i. *Allergic fungal rhinosinusitis (AFRS):* After the early observations of Safirstein, Millar, and Katzenstein, Bent and Kuhn proposed five diagnostic criteria for the entity of AFRS: type I hypersensitivity, nasal polyposis, characteristic findings on CT scan, presence of fungi on direct microscopy or culture, and allergic mucin containing fungal elements without tissue invasion.[19] The 'peanut-butter' or 'cottage-cheese' like mucin evacuated from sinuses of patients of AFRS is indistinguishable from the mucoid impactions of patients with ABPA.[22] Termed allergic or eosinophilic mucin, it is tan to green, brown or black, and consists of whole and partially degenerated eosinophils, Charcot-Leyden crystals, sparse hyphae and mucus (Figs 5A and B). The adjacent sinus mucosa has a mixed cellular infiltrate of eosinophils, plasma cells, and lymphocytes.[22] However, the most important aspect in the concept of AFRS is the allergy (type-I hypersensitivity) to fungi. It is believed that fungal allergens elicit IgE–mediated allergic reaction (type-I) and possibly type–III (immune complex) mediated mucosal inflammation in the absence of invasion in an atopic host.[40,41] One diagnostic requirement put forth by guidelines for clinical research in CRS was to consider AFRS as a distinct entity categorized by a



FIGURES 4A to C: Fungal ball with (A) fungal hyphae on periodic acid schiff stain (X200), (B) on 10% potassium hydroxide wet mount (X200) in light microscope and (C) in phase contrast microscope

type I hypersensitivity to fungi cultured from eosinophilic mucin containing hyphae and harvested from the patients nose or sinus cavities, and without evidence of tissue invasion by fungus.[3] Moreover, when the sensitized individuals are exposed to an environment of high fungal content, symptoms of upper and/or lower airway hyper-responsiveness increase significantly.[42] Generalized sinonasal inflammation in combination with viscid allergic mucin effectively obstructs the normal drainage pathway. Fungi stimulate locally destructive immune responses. The process then may expand to involve adjacent sinuses and may produce sinus expansion and bony erosion.[43,44] Accumulation of eosinophilic mucin in the expanded sinuses leads to elevation of inflammatory mediators, such as major basic protein, eosinophil peroxidase, eosinophil–derived neurotoxin, tumor necrosis factor β, and interleukin (IL)-4, 5, 10 and 13.[45,46] These early observations, based on less than 20 patients, capture the usual clinical findings of AFRS, although there are exceptions to several of the criteria, particularly presence of nasal polyps. Patients with recurrent AFRS who have had prior surgery frequently lack nasal polyps, although their sinuses contain eosinophilic mucin with hyphae. Current thinking does not support rigid dependence on the presence of all five criteria to establish a diagnosis of AFRS; rather a patient should demonstrate eosinophilic mucin and allergy to causative fungi. Accordingly the clinical examination should consider historical and physical stigma of atopy (hay fever, asthma, eczema, inhalant allergy), as well as nasal polyposis. Radiologic evidence of sinusitis of one or more paranasal sinuses with or without flocculent calcifications is supportive. Characteristically, CT scan findings include central areas of hyper-attenuation within sinus cavity corresponding to areas of hypointensity on T1-weighted MR images, and signal void on T2-weighted MR images. Controversy increased when Type-I hypersensitivity, as a criterion to define AFRS, was removed.[47]

ii. *Eosinophilic fungal rhinosinusitis:* Contrary to the prevailing belief that fungi were responsible for CRS in only a selected group of patients with distinct pathophysiology, Ponikau et al in 1999 demonstrated the presence of fungi in nasal mucus from 96% of patients with CRS and found type I hypersensitivity to be present in < 25% of their study group. They detected fungi along with eosinophil and eosinophil degraded products in mucus.[20] Often the eosinophils detected in the mucus were in clusters along with a few Charcot-Leyden crystals, but sometimes they found the eosinophils in the form of cellular debris and crystals. They termed this mucin 'eosinophilic mucin' and coined the term 'eosinophilic fungal rhinosinusitis' (EFRS). However, they also cultured a diverse array of airborne fungi from the nose of 100% of healthy volunteers.[20] Later, they further improved the detection technique in eosinophilic mucin by using a fluorescein-labeled chitinase staining technique.[48] From Europe, Braun et al in 2003 made a similar observation using sensitive techniques to detect fungi.[49] Similarly, Polzehl et al,



FIGURES 5A and B: Allergic fungal rhinosinusitis with (A) allergic mucin (X100), (B) Gomori methenamine silver stain showing hyphae within the mucin (X100)

2005 could detect fungi in 50% of sinus aspirate samples from 77 CRS patients using similar sensitive techniques. However, contrary to the previous two reports, none of their controls had fungi in their sinus contents.[50] Ponikau et al further progressed their hypothesis by demonstrating high levels of toxic major basic protein (MBP) from eosinophils in the mucus of patients with CRS, and postulating that MBP damages the nasal epithelium from the luminal side, permitting secondary bacterial infection on the damaged epithelium.[51] They proposed that certain fungi could elicit eosinophilic inflammation in the absence of type I hypersensitivity reactions in patients with CRS.[20,51] This concept of nonatopic eosinophilia from fungi is supported by studies, which demonstrate that peripheral blood mononuclear cells (PBMCs) from patients with CRS show exaggerated humoral and cellular responses (both Th1 and Th2 types) after exposure to common airborne fungi particularly *Alternaria* species, which are absent in PBMCs from healthy control subjects. The authors claimed that the anomalous immune and inflammatory responses to ubiquitous fungi might explain the chronic eosinophilic inflammation of CRS.[52]

iii. *Eosinophil mucin rhinosinusitis:* At the turn of the new century, Ferguson described the presence of eosinophilic mucin without the presence of fungi in a proportion of rhinosinusitis patients at her center. She named this entity eosinophilic mucin rhinosinusitis (EMRS)[53] and suggested that EMRS is a systemic disease with dysregulation of immunological control. Cases with EMRS were significantly associated with bilateral disease, asthma, increased incidence of aspirin sensitivity, and IgG1 deficiency, and so it was thought that systemic steroids would be a useful adjunct in those patients. However, she predicted fungal immunotherapy and antifungal agents would be ineffective in patients with EMRS. Four potential mechanisms for the pathogenesis of EMRS were proposed: Allergic fungal rhinosinusitis, nonallergic fungal eosinophilic rhinosinusitis, super antigen induced eosinophilic rhinosinusitis, and aspirin exacerbated eosinophilic rhinosinusitis.[53]

The subclassification of eosinophil related FRS is not universally accepted. Though the detection of fungi in allergic mucin is considered important, hyphae may be sparse in sinus content, and take considerable time to visualize with the currently used stains. As such cases of AFRS and EFRS may be misdiagnosed as EMRS.[53] However, the use of much more sensitive diagnostic techniques such as chitin staining[48] or PCR amplification[50] to detect the presence of fungi, may reveal that EMRS is predominantly or completely related to a response to one or more fungi. In a prospective study from India, considerable overlap in findings between AFRS and EMRS were observed, though type – I hypersensitivity, Charcot-Leyden crystals, bony erosion, and heterogeneous opacity with sinus expansion on CT scan were found to be significantly associated with AFRS, whereas asthma was significantly associated with EMRS.[54] It is possible that EMRS and AFRS are differing manifestations of the same pathological process, with considerable overlap.

Previously the role of fungi in the pathogenesis of eosinophil related FRS was unquestioned. Fungi were thought to be the sole and major initiators of inflammation in such disease process. However, with the confusion in discrete definitions of AFRS, EFRS and EMRS, a possibility is that fungi may be bystanders or one of several contributors to the whole process. In the analysis of pathophysiology of eosinophil related FRS, it has been suggested that fungal elements trapped in the mucus in sinuses are the source of antigenic material that stimulates IgE, IgG, and IgA production.[16,55] Numerous stimuli other than fungi, or in addition to fungi, may be responsible for the pathophysiology of this disorder, including the putative role of allergens, bacteria and bacterial derived superantigens.[56]

Various authors propose fungal rhinosinusitis to be a continuous spectrum of disease starting from the noninvasive to the acute invasive varieties with considerable overlap and transition from one form to another in the same patient. In this background, the entity of noninvasive destructive fungal rhinosinusitis may be viewed as an intermediate form of FRS. Rowe-Jones and Moore-Gillon in 1994 proposed chronic destructive but noninvasive (semi-invasive) form of fungal rhinosinusitis.[57] It is categorized by sinus expansion and bony erosion,

but with no histologic evidence of tissue invasion. In this state, the pathogens lead to progressive, chronic inflammation, intermediate between allergic, sinus fungal ball, and chronic invasive state. Even though inflammation and bony erosion were evident, these cases had not progressed to produce facial mass or proptosis associated with invasive disease. Such example of semi-invasive pulmonary aspergillosis also exists.[58] However, this entity may be a variant of noninvasive types in which the fungal mass destroys the sinus wall by pressure.[59,60]

EPIDEMIOLOGY OF FUNGAL RHINOSINUSITIS

Prevalence of the disease: Rhinosinusitis is a common disorder affecting approximately 20% of the population at some time of their lives. It has been estimated to affect approximately 31 million patients (4% of adult population) in the United States each year.[61] In fact a recent survey reported that 14.1% of adults recalled a health professional's diagnosis of sinusitis.[5] Previously, 5-15% of all these cases of chronic rhinosinusitis cases were thought to be of fungal etiology. However, after the claim of fungus to be the etiological agent in majority of cases of CRS by Ponikau et al, 1999, the impact of FRS seems to be tremendous. FRS causes significant physical symptoms, severe quality of life impairment, and can substantially impair daily functioning. The economic effect is also huge; in the US the direct cost estimated in 1996 at $5.6 billion per year and indirect costs, such as >70 million lost activity days per year and reduced physical and social functioning.[62,63] As the incidence of chronic rhinosinusitis has increased over the last decade, the economic effect is expected to be more. Further it should be noted that in comparison to USA the prevalence of FRS is even greater in tropical countries like India, Sudan and Pakistan.

Geographical distribution: Geographical location is probably an important determinant of the incidence of AFRS and granulomatous invasive FRS. AFRS is found to occur more commonly in India, North Africa, Middle-East, and parts of USA like Mississippi basin and South-East and South-West parts of United States.[4,32,54,64-70] A survey of 20 otolaryngology practices throughout USA found that 23% of all patients in Memphis, Tennessee practice who were referred for sinus procedures had a diagnosis of AFRS. Similarly, practices in Alabama, Georgia, and Texas reported a frequency of at least 10% compared to northern areas where AFRS frequencies ranged from 0 to 4%.[64] Warm, dry climates specifically North India, Sudan, Saudi Arabia, and Arizona record very high number of cases.[32] Granulomatous invasive FRS has been seen exclusively in Sudan, India, Pakistan, and rarely in the United States.[20,30-32] The sinus fungal ball entity may also have geographical restriction to certain extent, as maximum number of cases has been reported from France, Italy, and Taiwan. About 30 cases of sinus fungal ball per year are reported from Poitiers and Toulouse in France.[71] Overall, 173 cases have been reported from a single center in Poitiers, France over a period of 14 years (1989-2002).[72] Italy, another country in southern Europe is also endemic for sinus fungal ball disease. Over a period of 11 years (1994-2005), 81 cases have been reported from a single center in Pavia, Italy.[73] In Asia, the entity of sinus fungal ball has been diagnosed in 126 patients at a single center Taiwan over a period of 8 years (1995-2003).[74]

Host factors: Most forms of fungal sinusitis are found more commonly in males. The exact reason for this predisposition is not known. However, sinus fungal ball has been found more commonly in middle-aged or elderly females.[72,73] Acute invasive FRS is more common in the older age group, possibly due to the risk factors like diabetes and cancer chemotherapy, which are common in that age group. In some but not all studies from Sudan and north India, AFRS has been documented commonly in young adult males from rural areas than others. On basis of these reports it was postulated that young adult males who commonly go to the field in a hot, dry climate sustain frequent mucosal injuries of paranasal sinuses and acquire the agent from the field.[32]

In some studies AFRS is claimed to be associated with African-American race and poverty,[75,76] though these findings were not consistently demonstrated in all studies.[77,78]

Acute invasive (fulminant) FRS occurs predominantly in immunocompromised persons. Patients suffering from diseases associated with impaired neutrophil function, such as uncontrolled diabetes mellitus with or without ketoacidosis, hematologic and solid organ transplant malignancies, aplastic anemia, and hemochromatosis, or those undergoing iatrogenic immunosuppression with systemic corticosteroids or chemotherapeutic agents, are especially susceptible to the development of this disease entity.[24,26,29,39,79-81] Absolute neutrophil counts less than 500 cells/ml are strongly correlated with the development of

invasive fungal disease.[81,82] Inhalation of ubiquitous fungi like *Aspergillus* and *Zygomycetes* is an innocuous phenomenon. However, in the immunodeficient host, these fungi may breach host defenses and propagate within and along the blood vessels and nerves, infecting sinonasal tissue and creating an acidotic area of tissue necrosis that is ideal for continued fungal proliferation.[26] Widespread use of steroid is also an important cause of increased incidence of the disease.[26,81,83] The steroid acts by two ways – suppressing normal inflammatory cell response and by inducing a diabetic stage. Meyer et al. suggested that advanced AIDS and low CD4 cell counts might be associated with invasive FRS. A functional neutropenic state is indeed present in such cases of advanced AIDS, however, further studies are required to confirm such association.[84,85] Other risk factors found to be associated with development of acute invasive fungal rhinosinusitis include long-term antibiotic usage, indwelling catheters, nasal intubations, metabolic abnormalities, prolonged hospitalization, and sinus disease.[79,80] Among the limited number of cases of acute invasive FRS in immunocompetent individuals, *Apophysomyces elegans* seems to be an important etiology and traumatic implantation of this agent mixed in soil becomes an important risk factor in the acquisition of the disease.[86]

For AFRS, atopy defines the condition and persons with type I hypersensitivity to fungi are exclusively affected by the disease. AFRS is also found more in persons with simple asthma and aspirin sensitive asthma. However, both of these associations are said to be more important for the nonfungal EMRS.[34,53] Atopy against fungi has also been found in a few cases of sinus fungal ball. However, prior sinus surgery seems to be a more important risk factor for development of sinus fungal ball. It has been speculated that sinus fungal ball may develop in any poorly ventilated sinus and that fungal exposure and poor sinus ventilation may be the only risk factors that are required.[36] In a case-control study, endodontic treatment on maxillary teeth was found to be a strong risk factor for fungal ball of the maxillary sinus.[87]

Agent Factors: The agents causing different categories of fungal rhinosinusitis are described in Table 2. *Zygomycetes* are by far the commonest cause of acute invasive fungal rhinosinusitis.[31] The predominant *Zygomycetes* causing such disease is *Rhizopus oryzae*.[29,31,70] *Apophysomyces elegans* as a cause of acute invasive FRS in the immunocompetent host is common in tropics, especially in India.[86] The most common septate fungi causing acute invasive FRS in the immunocompromised patient are *Aspergillus fumigatus* and *Aspergillus flavus*.[31] The fungi causing AFRS are diverse and in a review of the English literature, Manning and Holman in 1998 reported of 168 culture positive cases, 87% due to dematiaceous fungi and 13% due to *Aspergillus* spp.[107] Most common dematiaceous fungi implicated were *Alternaria alternata*, *Bipolaris* spp., *Drechslera* spp. and *Curvularia lunata*. Interestingly, in the Indian scenario *A. flavus* is isolated in more than 80% of cases of AFRS, both in southern and northern parts of the country.[32,65-67,69,70] *A. flavus* was also isolated from 50% of patients diagnosed with AFRS in the Middle-East.[68] In granulomatous invasive FRS *A. flavus* is the commonest pathogen isolated. In contrast *A. fumigatus* causes most cases of chronic invasive FRS.[22,30-32] The biopsy samples collected from majority of the cases with sinus fungal ball appear sterile, though fungi are detectable on direct microscopy. Only 30 to 50% of such cultures show the growth of the causative fungi, which are usually *Aspergillus fumigatus* or *Aspergillus flavus* and occasionally *P. boydii*.[110]

CONCLUSION

Despite recognition of fungal rhinosinusitis as a serious disease entity for more than two centuries, our knowledge about the epidemiology and medical mycology of the disease remains incomplete and subject to newer findings and research. FRS can range from the benign localized fungal colonization to the extremely aggressive acute invasive FRS. Though the classification is still confusing, each of the clinicopathological variants of FRS is associated with unique geographical and host related risk factors, and different fungal etiological agents.

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TABLE 2: The fungi causing different categories of fungal rhinosinusitis

Category of fungal rhinosinusitis		*Commonly isolated fungus*	*Rarely isolated fungus*
Granulomatous invasive FRS		*A. flavus*[22,30-32]	
Chronic invasive FRS		*A. fumigatus*, less commonly *A. flavus*	*Mucor, Alternaria alternata, Candida, Drechslera, Bipolaris hawaiiensis, Sporothrix schenckii, Pseudallescheria boydii, Ascotrica chartarum, Exserohilum mcginnisii, Aspergillus avenaceus, Fusarium verticillioides*[88,108,109]
Acute invasive FRS (Fulminant/necrotizing)		Zygomycetes -*Rhizopus oryzae*.[29,31,70] *Aspergillus fumigatus, Aspergillus flavus*.[31] *Apophysomyces elegans* [India][29,86]	Mucorales– *R. rhizopodiformis, Mucor circeneloides, Saksenaea vasiformis, Absidia corymbifera, Cunninghamella bertholletiae, Mucor racemosus.*[88-96] Entomophthorales– *Conidiobolus coronatus, Conidiobolus incongruous, Basidiobolus ranarum.*[88,97] Septate Fungi – *Aspergillus oryzae, Scedosporium apiospermum* (*Pseudallescheria boydii*), *Scedosporium prolificans, Fusarium solani*, other *Fusarium spp., Scopulariopsis acremonium, Scopulariopsis candida, Aspergillus terreus, Exserohilum rostratum, Arthrographis kalrae, Scytalidium dimidiatum, Paecilomyces lilacinus, Valsa sordida.*[88,98-106]
Localized colonization (Saprobic infestation)		*Aspergillus fumigatus*, other *Aspergillus spp.*[113]	*Alternaria alternata, Penicillium rugulosum*, mycelia sterilia,[113] mucoraceous fungi.[116]
Fungal ball (Mycetoma/ Aspergilloma)		*Aspergillus fumigatus, Aspergillus flavus* and occasionally *P. boydii*.[110]	*Chaetomium globosum, Scedosporium prolificans, Aspergillus nidulans, Penicillium* spp.[88] *Schizophyllum commune,*[115] very rarely mucoraceous fungi.[110-112]
Eosinophil related FRS	AFRS	Dematiaceous fungi in USA *Alternaria alternata, Bipolaris* spp., *Drechslera* spp. *Curvularia lunata, Exserohilum.*[107] *Aspergillus flavus* in India[32,65-67,69,70] and Middle East.[68]	*Schizophyllum commune,*[115] *Aspergillus nidulans, Nodulosporium hinnuleum, Myriodontium keratinophilum,*[88] *Epicoccum nigrum,*[114] *Penicillium* sp. and *Cladosporium* sp.[117]
	EFRS	Similar to AFRS	

AFRS = Allergic fungal rhinosinusitis; EFRS = Eosinophilic fungal rhinosinusitis; EMRS = Eosinophilic mucin rhinosinusitis.

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