Fungal Rhinosinusitis: An Overview

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Abstract

Fungal rhinosinusitis (FRS) once considered a rare disease. This global rise in the burden of fungal disease is a consequence of an increment in the population with weakened immune systems. Increased life expectancy with rise in conditions like diabetes mellitus, medical advancements with invasive interventions, use of steroid, wider uses of broad-spectrum antibiotics, immunosuppressive treatments for transplantation and autoimmune diseases, increased incidence of immune deficiency disease. Fungal infections of the paranasal sinuses are in fact a spectrum of diseases rather than one distinct entity. As such, there has been much published on the classification of fungal rhinosinusitis (FRS) Early classifications of FRS used the causative organism as the descriptor, i.e., aspergillosis, mucormycosis, etc. Rapid diagnosis and prompt treatment may save at least some of these patients. When fever with neutropenia and sinonasal symptoms are seen in patients with impaired immune function maintaining a high index of suspicion is essential, and the appropriate diagnostic work up should involve imaging studies and nasal endoscopy with a possible biopsy so as to initiate treatment in a timely manner.

Clinical and histopathologic features of fungal rhinosinusitis are specific to each form, and criteria for diagnosis have been developed. This review of fungal sinus diseases summarizes invasive and noninvasive fungal rhinosinusitis forms but concentrates on AFS because of its high prevalence and the fundamental role the allergist-immunologist plays in its diagnosis and treatment.

Introduction:

Fungal rhinosinusitis (FRS) once considered a rare disease. This global rise in the burden of fungal disease is a consequence of an increment in the population with weakened immune systems. Increased life expectancy with rise in conditions like diabetes mellitus, medical advancements with invasive interventions, use of steroid, wider uses of broad-spectrum antibiotics, immunosuppressive treatments for transplantation and autoimmune diseases, increased incidence
of immune deficiency disease. The categorization of disease into acute and chronic and invasive or noninvasive is important factor with implications in disease management and prognosis and this has been emphasized greatly in recent years. Diagnosis of FRS has been a challenge as the presenting clinical signs and symptoms and radiographic manifestations are often nonspecific. Definitive diagnosis requires direct fungi identification and hence culture and microscopic examination remain the gold standard.

**Classification:**

Fungal infections of the paranasal sinuses are in fact a spectrum of diseases rather than one distinct entity. As such, there has been much published on the classification of fungal rhinosinusitis (FRS) [1–4]. Early classifications of FRS used the causative organism as the descriptor, i.e., aspergillosis, mucormycosis, etc. [5]. The shift from the causative organism to the pathology of the disease process occurred in 1965, when Hora described two broad categories. These are invasive or non-invasive, dependent on the potential of the fungal hyphae to invade the tissues through the epithelium (invasive) in comparison to the infection being confined to the superficial epithelium (non-invasive) [1,3]. As its name suggests, invasive FRS can result in dramatic tissue invasion through mucosa, bone, neurovascular structures and surrounding organs [6]. This has resulted in further subdivision of FRS acute (less than four weeks) or chronic (greater than four weeks) [1]. Pictorial Flow Chart Classification of Invasive Fungal Rhinosinusitis & Non-Invasive Fungal Rhinosinusitis are shown in Fig-01 & Fig-02 respectively. With these subdivisions highlighted, FRS is further categorized into six main subgroups:

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**1A. Acute invasive fungal rhinosinusitis [aka acute fulminant/necrotizing fungal rhinosinusitis, rhino cerebral mucor mycosis]:**

Acute invasive fungal rhinosinusitis is a relatively rare condition mostly seen in immunocompromised patients [7]. The disease can have a rapidly progressing dramatic clinical course over a few days to weeks (<4 weeks).

Rapid spread of the infection can occur into the adjacent orbits and brain parenchyma and vascular cavernous sinus pathways. AIFRS is a lethal form of fungal sinusitis with reported mortality of 50–80% [8,9]. Aspergillus sp. and fungi of the Mucoraceae family (Zygometes order) are implicated in most cases. In poorly controlled diabetics, especially patients with diabetic ketoacidosis and those receiving Deferoxamine, the zygomycetes fungi, including Mucor, Rhizopus, and Absidia predominate and is termed Zygomycosis or Mucormycosis while in neutropenic patients, Aspergillus sp. account for almost 80% cases [8].
**Clinical Presentation:**

The initial presenting symptoms of the disease are nonspecific and similar to acute bacterial sinusitis. Rhinorrhea, headache, fever with spikes along with facial pain and diplopia are the most common findings. There may be painless, necrotic nasal septal ulcer or eschar. Extension of disease across the skull base or via skull base foramina indicates severe disease and presents with ominous signs of cranial nerve palsies, stroke and mental status change. Cavernous sinus thrombosis, internal carotid artery thrombosis, acute subdural hematoma may indicate rhino cerebral mucormycosis. Invasion of the carotid arteries can cause cerebral ischemia and prove fatal.

**Based on disease extension disease may be clinically staged into**

Stage 1 Rhinomaxillary  
Stage 2 Rhino-orbital  
Stage 3 Rhino-orbito-cerebral

**Imaging Features**

CT scan of the sinus and orbits is the imaging modality of choice, but in the early stages due to the fulminant nature of disease process changes may be very subtle or may not be evident in as many as 12% patients. Hypoattenuating thickened mucosa with partial or complete opacification within a unilateral nasal cavity or sinus is the most consistent but nonspecific imaging feature. In a patient with immunosuppression, the finding of hyper-attenuation areas within opacified sinuses should raise a red flag for a possible underlying fungal cause. These fungi also have a tendency to spread along the vascular structures, and extension beyond the sinuses may occur with intact bony walls. While CT is ideal to assess bony changes, MRI is superior in evaluating retro-antral, intra-orbital or intracranial extension. As invasion progresses cerebritis, cerebral abscess and granulomas may be noted. Intracranial granulomas would appear hypointense on T1/T2-weighted images with minimal enhancement on contrast CT.

**Diagnosis**

Rapid diagnosis and prompt treatment may save at least some of these patients. When fever with neutropenia and sinonasal symptoms are seen in patients with impaired immune function maintaining a high index of suspicion is essential, and the appropriate diagnostic work up should involve imaging studies and nasal endoscopy with a possible biopsy so as to initiate treatment in a timely manner.

On nasal endoscopy mucosa would appear pale with ulceration and tissue necrosis depending on severity. Commonly affected area is painless. Definitive diagnosis is made with microscopic identification of biopsy from suspicious tissue and culture of the tissue. The middle turbinate is the most commonly affected, hence is a high-yield target site for nasal biopsy.
The Aspergillus species on the other hand demonstrate acute branching patterns with narrow septate hyphae. Cultures in AIFRS have been reported to be positive in over 70% cases. Diagnosis-based exclusively on histopathology is not reliable and species identification condition with the use of rapid in situ hybridization for rRNA targets may be a useful method to identify fungal species.

**Management**

Prompt and aggressive surgical debridement, appropriate antifungal therapy along with simultaneous elimination of underlying causes of immunosuppression and risk factors are the mainstays of AIFRS management. Timely but difficult surgical decisions with disfiguring outcomes like maxillectomy and orbital exenteration can be lifesaving. Intraoperative frozen section examination may provide prompt diagnosis and improve prognosis exponentially. Intravenous high-dose amphotericin B deoxycholate (dosage: 1–1.5 mg/kg daily) was widely administered but lately liposomal amphotericin B with better tolerance and lower nephrotoxicity (dosage: 5-10 mg/kg/day) has become the empiric drug of choice in management of AIFRS generally and mucormycosis specifically. Amphotericin B shows activity against Mucorales as well as many Aspergillus species but high drug costs with liposomal amphotericin B remains the biggest obstacle in its prolonged use. FDA approved promising newer azole, Posaconazole is the secondary drug of choice in Mucormycosis (also effective against Aspergillus species) as it can be taken orally (dosage: 800 mg/day in 4 divided doses) with low incidence of side effects. When histopathology or culture results confirm Aspergillus, azoles like Voriconazole are the optimum drug choice. Itraconazole has also been used as alternative therapy.

**1B. Chronic invasive fungal rhinosinusitis (CIFRS) [Non-granulomatous chronic invasive fungal rhinosinusitis]**

Chronic invasive fungal infection is a reportedly rare disease which can have an insidious progression over several months to years (>12 weeks). The condition is characterized by tissue invasion and necrosis but minimal inflammatory reaction. There may be dense accumulation of fungal hyphae resembling mycetoma the disease is often associated with orbital apex syndrome in which there is extension into posterior aspect of the orbit with decreasing vision/blindness. Extension into the cranium can be fatal. While some authors opine that this form has no specific geographic predilection others state that it is uncommon in the United States and is reported more from India and the Middle East. The most commonly reported fungal pathogen is Aspergillus fumigatus. CIFRS though mostly seen in patients with mild forms of immunosuppression may occur in immunocompetent individuals.

**Clinical Presentation:**

Patients may present with a complaint of unilateral facial pain and swelling. History of chronic sinusitis with nasal polyposis and complaints of nasal discharge and epistaxis are common. Symptoms may include vague sinus pain, anosmia, serous sanguinous nasal discharge, epistaxis and
fever. Intracranial disease extension can present with headache followed by seizures, cranial nerve palsies, neurologic deficits \[25\]. Persistent oral antral fistula may be seen with exposed or necrotic bone in the maxilla and generalized mobility of maxillary teeth on the side of the affected sinus. Orbital involvement is a characteristic association signaled by proptosis, blurring vision, diplopia and ocular immobility \[8\].

**Imaging Features**

CIFRS commonly presents with hyperattenuating soft tissue collection on non-contrast CT with common involvement of one or more adjacent paranasal sinuses \[8\]. Involvement of ethmoid and sphenoid is common. MRI demonstrates T1 intermediate signal with low to very low T2 signal. However, more involvement is seen outside the sinus than within and bone erosion is usually localized to sites of extra-sinus extension \[20\].

**Diagnosis**

Due to the indolent course of the disease diagnosis is often delayed. Chronic invasive fungal sinusitis is distinguished from the other two forms of invasive fungal sinusitis by its chronic course, dense accumulation of fungal hyphae resembling a fungal ball, and association with the orbital apex syndrome, diabetes mellitus, and corticosteroid treatment \[26\]. Endoscopic sinus evaluation can be a useful procedure to obtain biopsy tissue for culture and examine extent of sinus involvement \[20\]. Biopsy and orbital exploration show vascular invasion by fungal elements and minimal inflammatory infiltrate.

**Management**

The optimal treatment of CIFRS is highly debated with no consensus or treatment guidelines. Sinus debridement and aeration are the most important. Complete surgical excavation is quite essential for good prognosis. Partial/incomplete, staged or repeated debridement combined with antifungal regimes has been associated with higher failure rates as compared to radical evacuation \[27\]. Aspergillus species being the most common pathogens, initial therapy with Amphotericin B (dosage and forms same as AIFRS) has been suggested. High rates of relapse and inability to achieve complete infected tissue removal are indications for long-term suppressive therapy in most patients \[8,28\]. Itraconazole has been used for long-term suppression at dosage of 200 mg twice daily and has been reported to reduce relapse \[29\].
(Fig-01): Flow Chart presentation of Invasive Fungal Rhinosinusitis.
(Fig-02): Flow Chart presentation of Invasive Fungal Rhinosinusitis.
1C. **Chronic granulomatous invasive fungal rhinosinusitis (CGIFRS) [Indolent fungal sinus rhinosinusitis/Primary paranasal granuloma]**

This subtype of invasive FRS is characterized by a time course of >12 weeks and is based on characteristic histopathology findings [7]. It is most commonly reported from countries like India, Pakistan, Saudi Arabia and Sudan though cases from the USA are also reported. It was first described by Milosev et al. [30] as primary aspergilloma of paranasal sinuses. This variant is typically seen in patients with intact cell mediated immunity (CMI) which is essential for granuloma formation [31]. Hence it is not reported in patients with diabetes mellitus. Patients are mostly immunocompetent and Aspergillus flavus is the most isolated pathogen.

**Clinical Presentation**

The clinical distinctions between the two types of chronic invasive forms are not clear as both have similar chronic presentations with orbital involvement and prognosis also is similar. Disease course is usually indolent with most common presentation of enlarging cheek mass with involvement of orbit, nose and paranasal sinuses in an immunocompetent patient [26]. Eventual extra-sinus invasion is seen, and the patient may present with diplopia, proptosis due to the mass lesion extending into the orbit [25]. Intracranial extension may also occur rarely.

**Imaging**

Opacification of the involved sinuses and extra-sinus invasion with extension to adjacent soft tissues is seen. Sinus expansion is rare, and involvement of orbits and intracranial compartment may be noted in advanced cases. Findings are analogous to those in malignant lesions.

**Diagnosis**

Patients usually have no predisposing factors. The diagnosis is based on histopathology only. Microscopic examination shows characteristic presence of noncaseating granulomas. Extensive granulomatous response with fungal hyphae within Langerhans-type giant cells and considerable fibrosis are common [26,32]. This unique pathological picture is the main difference between granulomatous invasive fungal disease from the more common CIFRS seen in diabetic patients [25]. CGIFRS is considered by few authors to be part of CIFRS and not a distinct clinical entity [28].

**Management**

Timely surgical intervention with complete resection of pathologic tissue is the mainstay of treatment like in the other invasive forms as any delay can worsen prognosis. However, controversy prevails regarding the role of antifungal drugs. Some authors suggest that surgery alone is sufficient while others cite a need for antifungal medication therapy [31,33]. Regime of Amphotericin B for 6 weeks followed by Itraconazole has been recommended [28].
2A. Allergic Fungal Rhinosinusitis

This form of non-invasive fungal sinusitis is allergic fungal rhinosinusitis (AFRS). This is thought to be the most common form of fungal sinus disease\textsuperscript{[34]}. It is similar to CRS however, some specific features which have been included in diagnostic criteria. These are based upon the unique set of clinical, radiological and histological findings\textsuperscript{[35]}. The first recognition of this condition occurred in the 1970s as a result of the similarities in the mucous found in AFRS and allergic bronchopulmonary aspergillosis (ABPA)\textsuperscript{[36]}.

AFRS typically is seen in younger patients (21–33 years) who are not immunocompromised\textsuperscript{[36]}. This highlights the role of type I and type III hypersensitivity reactions to fungal antigens\textsuperscript{[35]}. This has been supported in the literature by Manning and Holman\textsuperscript{[37]}. A type I hypersensitivity reaction is an IgE mediated reaction to an antigen. This results in the release of histamine and inflammatory mediators resulting in an eosinophilia. This has been shown to be the case on mucosal biopsies of patients with AFRS\textsuperscript{[36, 37]}. A type III hypersensitivity reaction occurs as a result of an IgG mediated antigen-antibody complex formation. This results in immune complex deposition and inflammation. It is thought that, via these two mechanisms, inhaled fungi, causing a mucosal reaction resulting in inflammation and importantly mucous production, termed ‘eosinophilic’ mucin.\textsuperscript{[37, 38]} Inflammatory mediators have been shown to have an important role in AFRS (e.g., T-Helper cells, cytokines, interleukin-4 and interleukin-5). For these reasons, the pathogenesis of AFRS is complex, controversial and incompletely understood\textsuperscript{[40]}.

Diagnosis:

AFRS is often suspected in the setting of a patient who is resistant to the routine treatments, including surgical intervention, for CRS. They may, however, show good, but relapsing, responses to oral steroids\textsuperscript{[35]}. Although the disease is non-invasive in nature, it is not uncommon for these patients to show evidence of bony erosion on cross sectional imaging and to have ophthalmological findings e.g., proptosis\textsuperscript{[40]}. To try and create a uniform diagnosis for AFRS, several classification systems have been suggested. The most widely accepted is the one proposed by Bent and Kuhn\textsuperscript{[41]}. This system splits diagnostic criteria into ‘major’ and ‘minor’ criteria. All of the major criteria should be fulfilled to confirm a diagnosis of AFRS, with minor criteria used to support the diagnosis\textsuperscript{[42]}.

Management:

There are roles for both medical and surgical treatments in patients with AFRS. However, patients have often undergone several medical and surgical treatments prior to a diagnosis of AFRS.\textsuperscript{[34, 36, 40, 43]} This includes samples of polyps and the mucin being sent for histology, fungal staining and culture\textsuperscript{[36]}. The mainstay of post-operative medical treatment has been outlined by Gan et al. in 2014.

Steroid therapy: The use of corticosteroids (oral and topical) is widely shown to be beneficial in AFRS for the same reasons as in CRS. Suppression of inflammatory responses, eosinophilia and IgE levels has been shown\textsuperscript{[39, 43]}. An exact regimen for oral steroids has not been reported; short bursts compared with a prolonged course with tapering doses have been described\textsuperscript{[36, 40, 41, 43]}.
While AFRS is not a fungal infection, the aim is to reduce the fungal load and as such reduce the immune response to it [43].

**Leukotriene modulators:** The use of leukotriene modulators (i.e., Montelukast) has been investigated in the setting of AFRS with one case study suggesting that it could be beneficial in AFRS refractory to conventional therapy. [36, 40, 43]. Biological therapies: More recently, the investigation of biological therapies aimed at suppressing inflammatory mediators (e.g., anti-IgE and anti-IL-5 agents) have been a suggested treatment. Early studies focusing on the use of biological therapies (e.g., omalizumab and mepolizumab) have shown promising results [39, 44, 1]. There were improvements in SNOT-22 scores (31%) as well as endoscopic scores (61%) in a patient population treated with omalizumab for AFRS and asthma [39].

**2B. Fungal Ball**

Fungal balls are defined as a densely matted collection of fungal hyphae, which exist extra-mucosally, causing minimal mucosal inflammation or reaction [36,4]. Previously, these have been termed ‘Aspergillomas’, owing to the most commonly encountered fungus being Aspergillus species [23]. However, other fungi have been implicated in fungal ball production and hence the change in terminology to ‘Fungal ball’. [36, 22]

These fungal balls frequently occur in only one sinus with the most commonly affected being the maxillary sinus (94%). The majority of the remaining cases occurring in the sphenoid [36]. The association has been shown to be quite strong, with studies reporting rates as high as 89.2% in patients who have had previous dental work [47]. As such, it has been suggested that panoramic dental imaging should be a mandatory part of the management of patients with suspected fungal balls [48]. It is worth noting that fungal balls might occur alongside other forms of fungal sinus disease [36].

**Diagnosis:**

Presentation of a fungal ball is usually non-specific and indeed it can be asymptomatic. As such, this is often encountered as a part of investigation and treatment for chronic rhinosinusitis (CRS) [46]. Endoscopic examination of the nasal cavity produces a variety of different findings in the setting of fungal balls. This may range from an entirely normal mucosa and nasal cavity, through to crusting, purulent discharge and edematous mucosa with polyp formation [22,46]. This makes it difficult to clinically distinguish this entity from conventional CRS. The sensitivity and specificity of this modality for diagnosing fungal balls are 62% and 99%, respectively [49]. The classical signs on nasoendoscopy are: ‘cheesy’ and ‘clay-like’ inspissated mucous. This is highly sensitive (100%) and specific (99%) [46]. Fungal balls are diagnosed histologically. The classical findings are of matted fungal hyphae, separate from the sinus mucosa.

**Management:**

As fungal balls are not invasive, systemic or topical, medial therapy with antifungals are not appropriate. As such, this disease is primarily managed by functional endoscopic sinus surgery (FESS) [36]. However, other approaches, such as an osteoplastic approach (operating endoscopically via a window in the anterior wall of the maxillary sinus).
2C. Saprophytic Fungal Infestation

Saprophytic fungal infestation is traditionally described as fungal colonization of the secretions of the sinonasal cavity or crusted mucosa. As such, it was not always included as part of the classification of FRS [50]. It has no invasive features and is confined to the crusts/mucosa within the nasal cavity.

**Diagnosis:** This can be an asymptomatic disease process and so often goes undiagnosed. It can, however, present with a foul smell in the nasal cavity [36].

**Management:** The main relevance of this category of FRS is the speculation that it can be the starting point for fungal ball development [51]. There is, however, a paucity of literature on this category of FRS. If symptomatic, generally, this is managed as part of concurrent sinus surgery with the clearance of the crust, or more commonly, non-surgically, with nasal douching; it does not require formal surgical intervention [36].

**Discussion:**

FRS can present as invasive or noninvasive disease. Invasive fungal rhinosinusitis is a true invasive infection where fungal hyphae invade the sinus mucosa, blood vessels, or bone. It presents in three clinicopathologic forms: acute fulminant, chronic, and granulomatous (“indolent”) invasive fungal sinusitis. In noninvasive fungal rhinosinusitis, the fungi play a pathogenic role in the rhinosinusitis disorder but reside within the sinus cavity without penetration of the mucosal barrier. Noninvasive fungal rhinosinusitis presents as fungal ball (“sinus mycetoma”) or allergic fungal sinusitis (AFS). AFS is now thought to be the most prevalent form of diagnosed fungal rhinosinusitis and is analogous in many ways to allergic bronchopulmonary aspergillosis (ABPA).

This appears as a whitish image within involved sinus cavities, close in density to mineral or bone, and can be accentuated on CT by increasing the contrast or attenuation controls. In some cases, sinus CT may show extension of the fungal rhinosinusitis process through juxtaposed bone into the orbit or epidural space. All surgical specimens should be sent to a pathologist if any form of fungal rhinosinusitis is suspected. Histopathologic diagnosis requires both hematoxylin and eosin (H & E) and fungal stains such as Gomori’s methenamine silver stain. Surgical sinus fungal and bacterial cultures should always be obtained, although fungal culture positivity is generally not required for diagnosis because cultures may return negative despite confirmed histopathologic disease. Clinical and histopathologic features of fungal rhinosinusitis are specific to each form, and criteria for diagnosis have been developed. This review of fungal sinus diseases summarizes invasive and noninvasive fungal rhinosinusitis forms but concentrates on AFS because of its high prevalence and the fundamental role the allergist-immunologist plays in its diagnosis and treatment.
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