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Rare and remarkable: A concise review unmasking the enigmas of fungal Rhinosinusitis

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Abstract

Fungal rhinosinusitis is a rare and complex form of rhinosinusitis, and it has been traditionally associated with immunocompromised individuals. However, recent reports have shown a rising incidence even among immunocompetent patients. The disease presents with a broad spectrum of clinical manifestations, ranging from mild non-invasive forms to invasive types that can be life-threatening. Diagnosis remains challenging due to non-specific clinical signs and imaging findings, often requiring histopathological examination for confirmation. Management strategies are highly variable and depend on the subtype, involving a combination of surgical intervention, corticosteroids, antifungal agents, and, in some cases, biologic therapies. Despite its clinical significance, literature on fungal rhinosinusitis remains limited. This review aims to provide clinicians with a concise summary of current knowledge on diagnosing and managing fungal rhinosinusitis, aiming to improve awareness and guide effective clinical practice.

Keywords: Allergic Fungal Rhinosinusitis; Anti-Fungal; Bent and Kuhn Criteria; Fungal Rhinosinusitis

1. Introduction

Fungal rhinosinusitis is a pathological inflammatory condition of the nasal cavity and paranasal sinuses caused by fungal infection. Rhinosinusitis is one of the most common otolaryngology diseases, affecting approximately 20% of individuals worldwide.[1] However, fungal rhinosinusitis represents a relatively rare subtype of this condition. In Indonesia, its prevalence is estimated at only 2.89%.[2] However, this prevalence is only for invasive fungal rhinosinusitis. Its exact prevalence may be underestimated.

Despite its rarity, fungal rhinosinusitis can lead to significant physical symptoms, marked reductions in quality of life, and considerable disruption of daily activities. The economic burden is also substantial. In the United States, direct healthcare costs related to rhinosinusitis were estimated at $5.6 billion annually as early as 1996, with indirect costs, such as over 70 million lost activity days per year and reductions in physical and social functioning, further emphasizing its impact.[1,3]

Fungal rhinosinusitis encompasses a broad disease spectrum, from non-invasive to invasive forms. Invasive fungal rhinosinusitis can involve extensive tissue invasion, including the mucosa, bone, neurovascular structures, and adjacent organs, leading to potentially fatal complications such as cavernous sinus aspergillosis or orbital apex aspergillosis.[4] Therefore, early and accurate diagnosis and timely management are critical to improving outcomes.

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To date, there is no established international consensus regarding diagnosing and managing fungal rhinosinusitis. Clinical diagnosis can be particularly challenging due to the variability of symptoms, which often depend on the patient's immune status. Additional investigations, including imaging and histopathological examination, confirm the diagnosis and guide appropriate intervention. Management typically involves a combination of therapeutic modalities, including surgical debridement, corticosteroids, antifungal agents, and, in selected cases, biologic therapies.[5,6]

Given this rarity yet potentially life-threatening nature, this review aims to provide a concise and comprehensive summary of current knowledge regarding diagnosing and managing fungal rhinosinusitis. We hope this overview can equip clinicians with the essential information to effectively recognize and treat this challenging condition in clinical practice.

2. Definition and Classification of Fungal Rhinosinusitis

According to *European Position Paper on Rhinosinusitis and Nasal Polyps* (EPOS) 2020, rhinosinusitis is defined as inflammation of the nose and paranasal sinuses characterized by two or more symptoms, one of which must include nasal blockage/obstruction/congestion or nasal discharge (anterior or posterior nasal drip), accompanied by facial pain/pressure and/or a reduction or loss of smell. Accordingly, fungal rhinosinusitis can be defined as inflammation of the nose and paranasal sinuses caused by fungal infection.[7,8]

Based on the potential of fungal hyphae to invade tissue through the epithelium, fungal rhinosinusitis is classified into non-invasive and invasive forms. Non-invasive fungal rhinosinusitis includes saprophytic fungal infestation, fungal ball, and allergic fungal rhinosinusitis, while invasive fungal rhinosinusitis is further categorized into acute invasive fungal rhinosinusitis, chronic invasive fungal rhinosinusitis, and chronic granulomatous invasive fungal rhinosinusitis.[3]

3. Etiology of Fungal Rhinosinusitis

The etiology of fungal rhinosinusitis is notably diverse and influenced by geographic and host-related factors. A study conducted in Indonesia identified *Aspergillus fumigatus* as the most common causative agent (50%), followed by *Aspergillus spp.* (23.3%), *Aspergillus niger* (13.3%), *Candida sp.* (10%), and *Aspergillus versicolor* as the least frequently isolated species (3.3%). The distribution of the etiologic agent is determined by regional epidemiology and host immune status. For instance, *Aspergillus flavus* has been reported as the predominant species in up to 80% of fungal rhinosinusitis cases in India and over 50% of cases in studies from the Middle East. Conversely, a study from the United Kingdom found dematiaceous fungi to be the most prevalent pathogens, with *Aspergillus* species accounting for only 13% of cases. *Apophysomyces elegans* is frequently identified as the etiologic agent of acute invasive fungal rhinosinusitis in immunocompetent individuals in tropical countries. In contrast, among immunocompromised patients, *Aspergillus fumigatus* and *Aspergillus flavus* are the most commonly implicated organisms in acute invasive fungal rhinosinusitis cases.[1,3] The most common etiologies of fungal rhinosinusitis subtypes are presented in Table 1.

Table 1 The most common etiologies of fungal rhinosinusitis 1

Fungal rhinosinusitis subtypes	**Commonly isolated fungi**
Granulomatous invasive fungal rhinosinosinutis	*Aspergillus flavus*
Chronic invasive fungal rhinosinosinutis	*Aspergillus fumigatus, Aspergillus flavus* (less common)
Acute invasive fungal rhinosinosinutis (fulminant/necrotizing)	*Zygomycetes: Rhizopus oryzae* *Aspergillus fumigatus, Aspergillus flavus* *Apophysomyces elegans* (terutama di India)
Local colonization (sporadic infestation)	*Aspergillus fumigatus, Aspergillus spp.* lainnya
Fungal ball (Mycetoma/Aspergilloma)	*Aspergillus fumigatus, Aspergillus fla*vus, dan terkadang *P. boydii*.
Allergic fungal rhinosinusitis	*Dematiaceous fungi* in United States *Alternaria alternata, Bipolaris spp., Drechslera spp., Curvularia lunata, Exserohilum, Aspergillus flavus* in India and Middle East

4. Risk Factors of Fungal Rhinosinusitis

The main risk factor of fungal rhinosinusitis is an immunocompromised state, such as older patients and patients with cancer, diabetes, or *Human Immunodeficiency Virus* infection/ acquired immunodeficiency syndrome (HIV/ AIDS). However, recent studies showed that the incidence of fungal rhinosinusitis is increasing in immunocompetent hosts. In several studies from Sudan and northern India, allergic fungal rhinosinusitis was more common in young adult males from rural areas than in others. It is thought that young adult males who regularly travel to the field in hot, dry climates often experience paranasal sinus mucosal injury and acquire agents from the field. In some studies, allergic fungal rhinosinusitis has been claimed to be associated with African-American race and poverty, although these findings have not been consistently demonstrated across studies.[1]

5. Pathophysiology of Fungal Rhinosinusitis

The pathophysiology of fungal rhinosinusitis remains incompletely understood, particularly in immunocompetent individuals. Fungal colonization requires the penetration of fungal spores and hyphae into the paranasal sinuses, a process often associated with impaired mucociliary clearance (MCC) and/or obstruction of the sinus ostia. A deeper understanding of the epithelial processes involved, including innate and adaptive immune responses, and the physiological and pathological mechanisms underlying fungal rhinosinusitis is needed to identify potential therapeutic targets.[9]

Several proposed hypotheses aim to explain the development of fungal rhinosinusitis, focusing primarily on the host's immune response to airborne fungal elements. The first hypothesis suggests that inhaled fungal proteins are presented to sensitized T cells, leading to a cytokine-mediated activation of eosinophils on the mucosal surface. The second, the barrier hypothesis, posits that eosinophilic degranulation directed against fungi represents a dysregulated immune response, resulting in tissue damage and the clinical manifestations of rhinosinusitis.[8]

6. Clinical Manifestations of Fungal Rhinosinusitis

The clinical manifestations of fungal rhinosinusitis are highly variable and often non-specific. However, detailed and careful history-taking and clinical examination can offer valuable clues for early diagnosis. The signs and symptoms commonly found in each subtype of fungal rhinosinusitis are described below.[10]

6.1. Non-Invasive Fungal Rhinosinusitis

6.1.1. Saprophytic Fungal Infestation

Saprophytic fungal infestation refers to localized colonization of fungi in sinonasal secretions or crusted nasal mucosa. This condition typically arises post-surgically, where residual inflamed or crusted mucosa becomes secondarily colonized by inhaled fungal spores, most commonly of the *Aspergillus* species. It is non-invasive and remains confined to the crust or mucosal surface within the nasal cavity. Symptoms are usually minimal or absent but may include foul nasal odor or expulsion of dry crusts when blowing the nose. Nasal endoscopy may reveal visible fungal growth on dried crusts without evidence of tissue invasion.[4]

6.1.2. Fungal Ball

A fungal ball is a dense collection of hyphae localized outside the mucosa (extra-mucosal), typically causing minimal mucosal inflammation or reaction. Formerly known as "aspergilloma" due to the frequent involvement of *Aspergillus* species, fungal balls commonly affect a single sinus, most frequently the maxillary sinus (94%), followed by the sphenoid sinus. Unlike invasive fungal sinusitis, fungal ball occurs primarily in immunocompetent individuals and is more frequently reported in older women. The exact pathogenesis remains unclear, but as with saprophytic infestation, inhalation of spores and a history of prior mucosal injury or sinus surgery may play a role. Dental procedures, particularly endodontic treatments or dental implants, have been associated with fungal balls, and a dental history should be obtained. Symptoms typically result from mass effect, including nasal obstruction, purulent rhinorrhea, post-nasal drip, and facial pain or pressure. Endoscopic findings may show mild mucosal inflammation.[4]

6.1.3. Allergic Fungal Rhinosinusitis (AFRS)

Allergic fungal rhinosinusitis is considered the most common form of non-invasive fungal rhinosinusitis and shares many clinical and radiological features with chronic rhinosinusitis. Diagnosis is based on clinical, radiologic, and histologic criteria, with the most widely used system proposed by Bent and Kuhn (see Table 2.3). However, some debate

exists around the specificity of these criteria. AFRS typically affects younger individuals (aged 21–33 years) who are immunocompetent, and it is more prevalent among atopic populations. A hallmark feature is the production of thick, dark-colored mucus known as eosinophilic mucin, which contains inflammatory eosinophils and Charcot-Leyden crystals. Clinical symptoms are similar to those of chronic rhinosinusitis and may include nasal obstruction, hyposmia, post-nasal drip, facial pressure, and nasal polyps.[4]

Table 2 Bent and Kuhn Criteria for Allergic Fungal Rhinosinusitis (AFRS) 4

Major Criteria	**Minor Criteria**
Type I hypersensitivity	Asthma
Nasal polyposis	Unilateral disease
Characteristic CT findings	Bone erosion
Eosinophilic mucin without invasion	Fungal cultures
Positive fungal stain	Charcot-Leyden crystals
	Serum eosinophilia

6.2. Invasive Fungal Rhinosinusitis

6.2.1. Acute Invasive Fungal Rhinosinusitis (AIFRS)

Acute invasive fungal rhinosinusitis is defined by fungal hyphae invasion in the sinonasal mucosa, submucosa, blood vessels, or bone within one month or less of symptom onset. It most commonly occurs in immunocompromised patients, such as those with uncontrolled diabetes mellitus, neutropenia, HIV/AIDS, hematologic malignancies, or those receiving chemotherapy. Despite its rarity, AIFRS is clinically significant due to its aggressive course and high mortality rate (approximately 50–80%), which has remained unchanged over the past two decades.[4]

Unlike non-invasive forms, AIFRS is characterized by rapid fungal invasion of neurovascular structures beyond the mucosa. Inhaled fungal spores proliferate in the nasal mucosa in the setting of impaired immune defenses, subsequently invading blood vessels and neural structures, leading to thrombosis, localized and extensive ischemia, and necrosis. Necrotic tissue facilitates further spread to adjacent bones and soft tissues.[4]

The most common causative organisms are species of *Aspergillus* and *Zygomycetes*. AIFRS is typically observed in two major patient groups. The first includes patients with poorly controlled diabetes (about 50%), particularly those in diabetic ketoacidosis, where *Zygomycetes* species are frequently isolated due to their affinity for acidic, glucose-rich environments. The second group comprises immunosuppressed individuals, including those with neutropenia, HIV/AIDS, hematologic malignancies, or undergoing chemotherapy. In this group, *Aspergillus* species are more commonly identified. Other conditions associated with AIFRS include iron overload or renal failure, particularly in patients receiving deferoxamine, which can act as a siderophore for *Rhizopus* species. Common symptoms include fever (50–90%), rhinorrhea, headache, facial pain, and ocular symptoms such as diplopia. Diagnostic workup should include imaging studies and biopsy to confirm tissue invasion.[4]

6.2.2. Chronic Invasive Fungal Rhinosinusitis

Chronic invasive fungal rhinosinusitis shares pathological features with the acute form but progresses over a more extended period, often months to years. It occurs more frequently in immunocompetent individuals. Due to its indolent course, it often presents subtly, with non-specific symptoms such as blood-tinged nasal discharge, unilateral nasal obstruction, cacosmia, or as a mass in the nasal or paranasal region that may cause proptosis. Involvement of the maxillary sinus can result in skin changes, while extension to the anterior cranial fossa may lead to neurological symptoms. These findings can be mistaken for malignancy. *Aspergillus* and *Mucor* species are commonly implicated.[4]

6.2.3. Chronic Granulomatous Invasive Fungal Rhinosinusitis

Chronic granulomatous invasive fungal rhinosinusitis is rarely seen in Western countries but is more commonly reported in North Africa, the Middle East, and Asia, affecting both immunocompetent and immunocompromised individuals. Like other invasive forms, it involves submucosal invasion, typically caused by *Aspergillus* species. Histologically, this subtype is distinguished by the formation of non-caseating granulomas. Clinically, patients may

present with proptosis due to an enlarging mass in the nasal cavity or cheek extending into the orbit. Other symptoms resemble those of chronic invasive fungal rhinosinusitis.[4]

7. Diagnostic Tests for Fungal Rhinosinusitis

7.1. Histopathology of Fungal Rhinosinusitis

Histopathological examination is conducted to isolate and identify fungal organisms. Accurate sampling is essential and should be obtained from the edge of the lesion using sterile swabs. Transporting the specimen in appropriate conditions and media (e.g., formalin-fixed and moistened Bouillon environment) is crucial for optimal diagnostic results.

Pathological evaluation is performed on tissue and mucus to identify fungal organisms, inflammatory cells, and specific reactions (such as Charcot-Leyden crystals). Staining methods include hematoxylin-eosin (HE), periodic acid-Schiff (PAS), and Gomori methenamine silver staining, which can better delineate fungal morphology. Histopathological examination remains a rapid and relatively cost-effective method, allowing the detection of fungal presence and confirmation of tissue invasion.[10]

7.1.1. Non-Invasive Fungal Rhinosinusitis

Saprophytic Fungal Infestation

Saprophytic fungal infestation describes superficial fungal colonization of the sinonasal tract, often following surgical procedures or trauma that led to mucosal inflammation, ulceration, or crust formation. This condition involves surface fungal colonization without tissue invasion. Although this subtype is rarely discussed in the literature, it may precede the development of a fungal ball.[11]

Fungal Ball

Histologically, a fungal ball is characterized by dense fungal masses embedded in necrotic fibrinous exudate, with minimal mucosal inflammatory response (Figure 1). By definition, there is no tissue invasion or granulomatous reaction in the surrounding tissue. Microscopically, fungal balls can appear similar to allergic fungal rhinosinusitis due to their laminated appearance.[11]

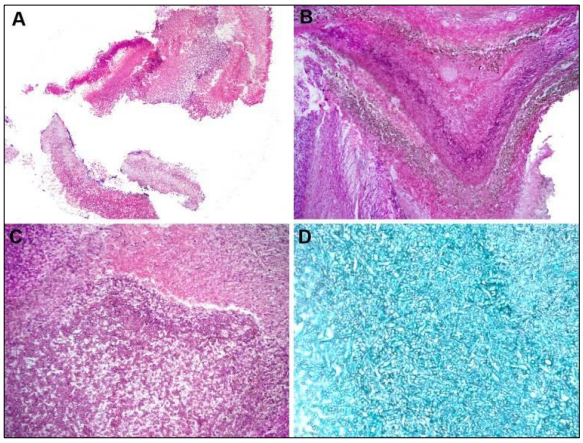

Figure 1 Histopathology of a fungal ball. (A) A low-power view of a fungal ball of the maxillary sinus. Fungal ball consists of encapsulated fungal mass (Hematoxylin and eosin; original magnification ×10). (B) A low-power view of a fungal ball shows a layered appearance and pigmented fungi. Culture shows Aspergillus niger (Hematoxylin and eosin; original magnification ×25). (C) High power view of fungal ball shows encapsulated fungal mass with minimal inflammation (Hematoxylin and eosin; original magnification ×50). (D) Silver stain shows fungi in fungal ball (Grocott stain; original magnification ×100)[4]

Allergic Fungal Rhinosinusitis (AFRS)

A hallmark of AFRS is the presence of clay-like, greenish-brown, or gray mucus. Microscopically, this eosinophilic mucin contains desquamated epithelial cells, eosinophilic degranulation, Charcot-Leyden crystals, and other inflammatory

cells arranged in a layered pattern, often associated with scattered fungal hyphae (Figures 2). While fungal elements may be visible on, HE stains, they are more clearly observed with histochemical stains such as PAS or silver stain.

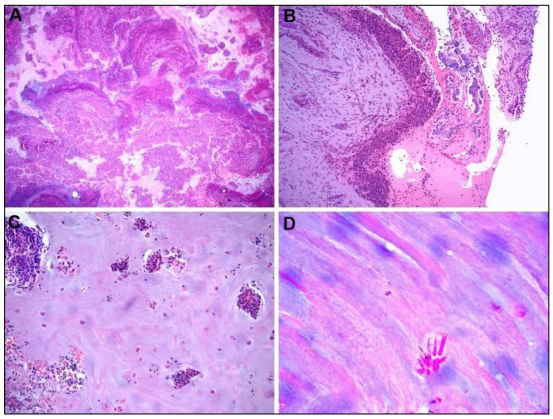

Figure 2 Histopathologic features of allergic fungal rhinosinusitis. (A) A low magnification view of allergic fungal rhinosinusitis showing a layered appearance with mucin mixed with inflammatory cells and debris (Hematoxylin and eosin; original magnification ×10). (B) Eosinophilic mucin showing clusters of eosinophils and detached epithelial cells (Hematoxylin and eosin; original magnification ×50). (C) Eosinophilic mucin showing single and clustered eosinophils (Hematoxylin and eosin; original magnification ×50). (D) Eosinophilic mucin showing Charcot-Leyden crystals (Hematoxylin and eosin; original magnification ×200)[4]

7.1.2. Invasive Fungal Rhinosinusitis

Acute Invasive Fungal Rhinosinusitis

Histologically, acute invasive fungal rhinosinusitis shows mucosal vascular thrombosis and minimal inflammatory cell infiltration. Angioinvasion by fungi can be seen as fungal elements invading vessel walls, leading to vascular occlusion. Although fungi may be seen with H&E staining, PAS and silver stains more clearly highlight fungal organisms, particularly within the vessel wall or vascular lumina mixed with fibrin (Figure 3). Rapid diagnosis is critical, as fungal elements can extend into vital structures, including the orbit and cranial cavity, significantly increasing morbidity and mortality.[11]

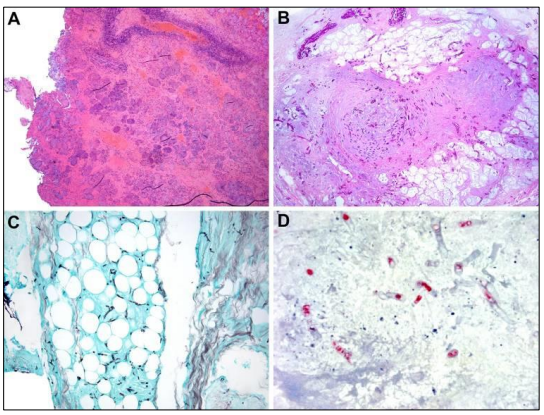

Figure 3 Histopathological features of acute invasive fungal rhinosinusitis. (A) A low magnification view shows infarction without significant inflammatory reaction in an immunosuppressed patient with acute leukemia with acute invasive fungal rhinosinusitis. Culture shows Rhizopus sp. (Hematoxylin and eosin; original magnification ×12.5). (B) Histopathological examination of acute invasive fungal rhinosinusitis shows fungus invading blood vessels and soft tissues. Culture shows Aspergillus fumigatus (Hematoxylin and eosin; original magnification ×100). (C) Silver stain shows fungal hyphae in soft tissues of acute invasive fungal rhinosinusitis. Culture shows A. fumigatus (Hematoxylin and eosin; original magnification ×100). (D) In situ hybridization for Aspergillus ribosomal RNA shows extensive necrosis (Fast red tetrazolium violet; original magnification ×100)[4]

Chronic and Chronic Granulomatous Invasive Fungal Rhinosinusitis

Chronic invasive fungal rhinosinusitis is a slowly progressing infection marked by fungal infiltration into the sinonasal mucosa with rare angioinvasion. It differs from chronic granulomatous invasive rhinosinusitis, which is more commonly seen in patients with immunodeficiency, organ transplants, diabetes, or long-term corticosteroid use. *Aspergillus fumigatus* is the most commonly isolated species in these cases. Compared to the granulomatous form, there is often a greater fungal burden, minimal inflammatory infiltrate, and occasional vascular invasion (Figure 4). Chronic granulomatous invasive fungal rhinosinusitis is characterized by submucosal granulomatous inflammation, sparse fungal hyphae, and extensive fibrosis. The most frequently associated fungal species is *Aspergillus flavus*.[11]

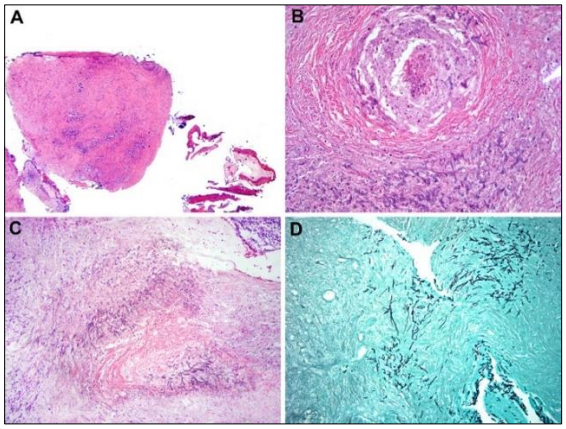

Figure 4 Histopathologic features of chronic fungal rhinosinusitis. (A) Inflamed and fibrotic sinonasal mucosa in a liver transplant patient with chronic invasive fungal rhinosinusitis (Hematoxylin and eosin; original magnification ×12.5). (B, C) Chronic invasive fungal rhinosinusitis with extensive necrosis or infarction of the sinonasal mucosa, with fungal organisms seen in a liver transplant patient with symptoms for more than 3 months. (B) Fungus within blood vessels (Hematoxylin and eosin; original magnification ×100). (D) Silver stain shows fungal hyphae infiltrating the sinonasal mucosa (Hematoxylin and eosin; original magnification ×50)[11]

7.2. Imaging of Fungal Rhinosinusitis

Imaging plays a critical role in the diagnosis of fungal sinus disease. Non-contrast computed tomography (CT) remains the initial imaging modality of choice. However, magnetic resonance imaging (MRI) offers superior visualization of invasive conditions involving soft tissue beyond the sinus boundaries. Non-invasive fungal rhinosinusitis typically presents with sinus opacification and hyperdense secretions on CT and T2 signal voids on MRI. The discussion of CT findings is organized by classifying fungal rhinosinusitis as follows.[5]

7.2.1. Non-Invasive Fungal Rhinosinusitis

Saprophytic Fungal Infestation

There are no specific radiologic findings associated with this subtype.

Fungal Ball

Fungal balls most frequently occur in the maxillary sinus, followed by the sphenoid sinus. The most common bony findings include sclerosis and thickening (osteitis), followed by bone erosion and remodeling. Bone remodeling often leads to expansion of the sinus ostium. As expected for a non-invasive condition, no evidence of tissue invasion.[5]

Allergic Fungal Rhinosinusitis (AFRS)

Diagnosis of AFRS relies heavily on characteristic imaging findings. Bilateral and multi-sinus involvement is the most typical feature, although unilateral multi-sinus involvement may also occur (Figure 5).[5]

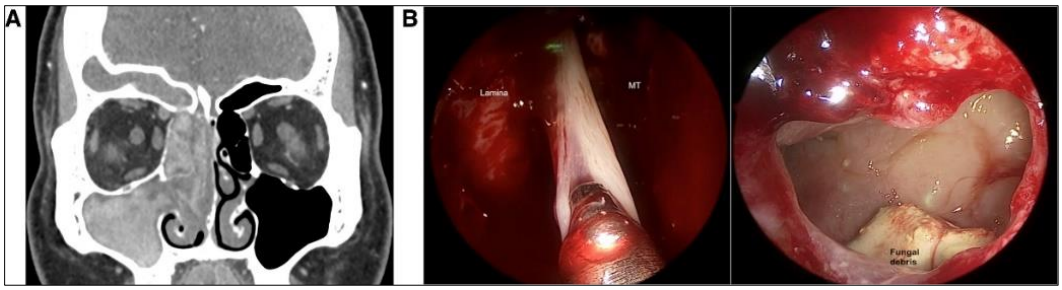

Figure 5 CT images of allergic fungal rhinosinusitis. (A) Coronal post-contrast soft tissue window computed tomography shows unilateral involvement of all sinuses on the right side. It appears to be diffuse within the right maxillary and frontal sinuses and the ethmoid. There is mild expansion of the ethmoid and frontal sinuses with bony remodeling. (B) The endoscopic image shows allergic or eosinophilic mucin originating from the right frontal sinus, and the intraoperative endoscopic image of the right maxillary sinus after antrostomy shows fungal remnants. Lamina, lamina papyracea; MT, middle turbinate[5]

7.2.2. Invasive Fungal Rhinosinusitis

Acute Invasive Fungal Rhinosinusitis

Unilateral mucosal thickening of the nasal cavity is the most consistent early CT finding in acute fungal invasion. Severe mucosal thickening involving the turbinates, nasal walls, and septum is common. These radiologic findings correspond to endoscopic and surgical findings of significant mucosal edema and inflammation around ischemic regions (Figures 6A and B). MRI may reveal the "black turbinate sign," reflecting a lack of contrast enhancement due to mucosal necrosis in mucormycosis, a hallmark of its angioinvasive nature.[5]

Bone erosion or extrasinus extension is highly suggestive of acute invasive fungal rhinosinusitis but is rarely seen in the early stages. Loss of periantral fat is indicative of invasion. When this is the sole radiologic finding, periantral soft tissue infiltration and compatible clinical findings may suggest invasive fungal rhinosinusitis. Intraorbital extension from the ethmoid sinus is also characteristic of this condition. Both periantral and intraorbital invasion can occur without evident bone erosion.[5]

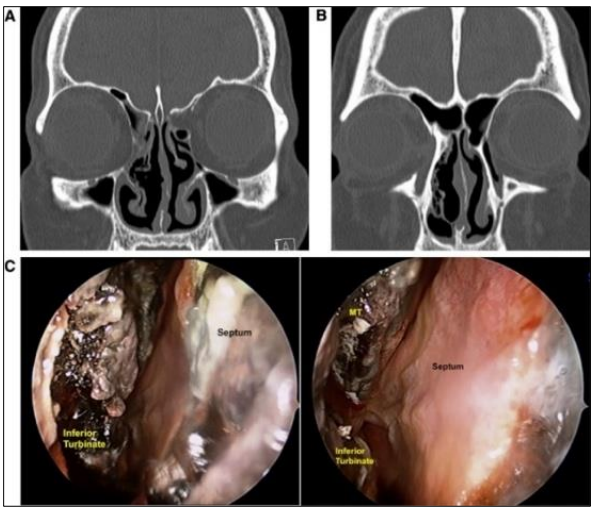

Figure 6 CT images of acute invasive fungal rhinosinusitis. (A, B) A non-contrast CT scan shows submucous emphysema in (A) the right middle and inferior conchae and (B) the lateral nasal wall. (C) Endoscopic examination of the right nasal cavity, showing necrotic tissue in the right inferior conchae and the anterior part of the nasal septum. Endoscopic image of the right nasal cavity also shows necrotic tissue extending to the middle and inferior conchae[5]

Chronic Invasive Fungal Rhinosinusitis

This form frequently involves the ethmoid and sphenoid sinuses. Due to its invasive nature, there is often extension beyond the sinus walls. The orbit is the most commonly involved site of extension, followed by intracranial invasion. In

contrast-enhanced CT, homogenous enhancement of the soft tissue mass may be observed. The affected sinus does not typically exhibit significant expansion, and bone erosion is usually localized to areas of extrasinus extension (Figure 7).[5]

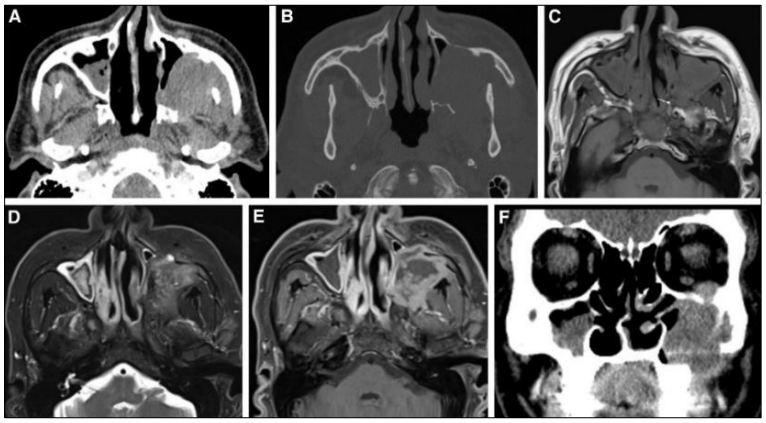

Figure 7 CT images of chronic invasive fungal rhinosinusitis. (A) Soft tissue window and (B) bone window noncontrast computed tomography (CT) images show a mass in the left maxillary sinus with lateral wall erosion. (C) Axial T1-weighted MRI image without contrast shows extension into the pterygopalatine fossa (arrow). (D) T1 postgadolinium fat-saturated MRI shows a low-signal mass. (E) T1 postgadolinium fat-saturated MRI shows peripheral enhancement of the mass, with a nonenhancing central component. Resection shows chronic granulomatous invasive fungal rhinosinusitis with dense fibrous tissue, focal necrosis, and chronic inflammatory infiltrate. (F) Coronal non-contrast CT image shows erosion of the left inferior orbital wall with soft tissue extension into the orbit[5]

Chronic Granulomatous Invasive Fungal Rhinosinusitis

Imaging findings are highly variable and cannot reliably differentiate this subtype from chronic invasive fungal rhinosinusitis. Diagnosis relies on histopathology, with non-caseating granulomas being the defining characteristic. Fungal hyphae may be found within Langerhans-type giant cells. This unique pathology distinguishes it from other invasive subtypes (Figure 8).[5]

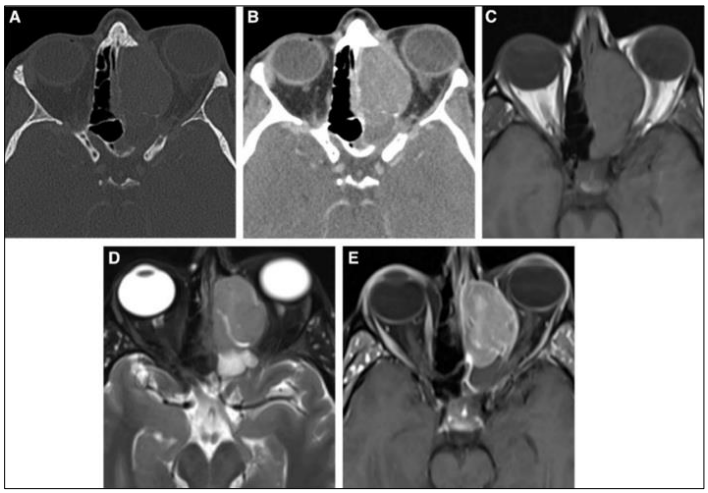

Figure 8. CT images of chronic granulomatous invasive fungal rhinosinusitis. (A) The bone window and (B) soft tissue window contrast-enhanced computed tomography show a mass filling extending into the left ethmoid sinus and the lamina papyracea. Proptosis is noted (left). (C) Axial T1 non-contrast MRI shows a mass isointense to muscle. (D) Axial T2 fat-saturated MRI shows a low-signal mass. (E) Axial T1 post-gadolinium fat-saturated MRI shows a homogeneously enhancing mass. The imaging appearance is similar to chronic invasive fungal rhinosinusitis, but in this case, the biopsy showed a poorly differentiated high-grade carcinoma[5]

7.3. Other Diagnostic Tests

A common diagnostic method in patients with suspected fungal rhinosinusitis is functional endoscopic sinus surgery followed by histopathological analysis. The specimens are cultured and treated with potassium hydroxide (KOH) for microscopic visualization.[6]

Mycological examination is another essential diagnostic step and can be performed with or without staining. Its sensitivity is comparable to that of histopathological methods. Sample collection involves obtaining mucus from the middle meatus or ethmoid region when allergic fungal rhinosinusitis is suspected. Testing is typically done on days 2, 5, 7, 10, and 30. Insufficient or delayed testing may result in false negatives.[10]

Serological testing aims to detect specific immunoglobulins as current or past fungal infection markers. Two conditions are required to detect specific serum immunoglobulin G (IgG): sufficient and prolonged exposure to the fungal antigen, and an intact immune system. This explains why patients with localized fungal infections who are immunocompromised (e.g., AIDS or leukemia) may show negative serological results.[10]

Skin prick testing is another valuable diagnostic tool, particularly in cases of allergic fungal rhinosinusitis. It is now considered standard practice, and the fungal extracts used have been standardized for intradermal testing.[10]

8. Management of Fungal Rhinosinusitis

Until now, there have been no universal international guidelines or consensus statements regarding managing fungal rhinosinusitis. Surgical debridement is the treatment of choice for most forms of fungal rhinosinusitis, as it serves diagnostic and therapeutic purposes. Functional endoscopic sinus surgery (FESS) allows for direct visualization of the pathology and sinonasal anatomy, biopsy of lesions, sinus clearance and irrigation, and correction of underlying structural abnormalities (e.g., fistulas or foreign bodies). Polypectomy should be performed if indicated.[6]

Oral corticosteroids are beneficial in many acute and chronic cases due to their anti-inflammatory effects and ability to reduce circulating IgE levels; however, long-term use is not recommended. Topical nasal steroids should not be used as monotherapy, but are useful in combination with systemic corticosteroids. A study by Fokkens et al. demonstrated that such combined therapy reduces recurrence rates over two years.[6]

Systemic antifungals are not considered first-line therapy for acute or chronic fungal rhinosinusitis, but they may play a role in treating invasive forms. Amphotericin B remains the antifungal of choice for invasive fungal rhinosinusitis. Certain azole-class antifungals are also effective but should be administered under the supervision of an infectious disease specialist. Topical antifungal treatments have shown minimal efficacy and are therefore not recommended.[6]

Fungal immunotherapy has been explored as an adjunct treatment for acute and chronic fungal rhinosinusitis. It works by desensitizing the immune system to fungal allergens. While the short-term benefits may be more pronounced than the long-term outcomes, immunotherapy can reduce dependence on corticosteroids and help mitigate the adverse effects of their prolonged use.[6]

Since most cases of invasive fungal rhinosinusitis occur in immunocompromised individuals, identifying and correcting the underlying cause of immunosuppression is a critical component of comprehensive management.[6]

8.1. Non-Invasive Fungal Rhinosinusitis

8.1.1. Saprophytic Fungal Infestation

This form is hypothesized to be a precursor to fungal ball formation. Symptomatic cases are generally managed surgically via sinus debridement and crust removal. Nasal irrigation can aid in mucosal hydration. Antifungal therapy is not indicated. Given the recurrent nature of this condition, periodic endoscopic evaluation is necessary for follow-up.[4,6]

8.1.2. Fungal Ball

As a non-invasive fungal infection, systemic or topical antifungal therapies are not recommended to manage the fungal ball. The primary aim is to restore ventilation and drainage of the affected sinus. Endoscopic widening or creation of a new sinus ostium may be required to reestablish normal sinus function. In cases where endoscopic extraction of the fungal mass is difficult, external approaches such as a gingivobuccal incision (Luc-Caldwell procedure) may be

considered. Besides, management should address contributing factors such as oroantral fistula or retained dental amalgam. Fungal debris must be thoroughly removed, and the surrounding mucosa biopsied to exclude invasive disease.

8.1.3. Allergic Fungal Rhinosinusitis (AFRS)

Management includes both medical and surgical interventions. Many patients undergo multiple treatments before a definitive diagnosis is made. According to Bent and Kuhn, allergic mucin and fungal debris, usually discovered during surgery, are essential for diagnosis.[4]

The primary goals are effective drainage and restoration of sinus ventilation. Oral and topical corticosteroids are the mainstays of medical therapy. Oral antifungals and immunotherapy are generally reserved for refractory cases. Pharmacologic strategies commonly used include:[4]

- Corticosteroids
    - Both systemic and topical corticosteroids are beneficial due to their ability to reduce inflammation, eosinophilia, and IgE levels—the risk of adverse effects limits prolonged systemic use. Topical corticosteroids are not effective as monotherapy but are more beneficial when used alongside systemic steroids. One study demonstrated a 15% recurrence rate over two years with combination therapy, compared to 50% with placebo.[4,9]
- Antifungal Agents
    - Although AFRS is not a true fungal infection, oral antifungals may reduce fungal exposure and subsequent immune activation. The evidence for efficacy remains mixed. A Cochrane review found no benefit for antifungals in chronic rhinosinusitis with nasal polyps, while Gan et al. reported that itraconazole may benefit select patients by reducing steroid dependency. Given the side effects of systemic antifungals, their use should be reserved for refractory cases.[4,9]
- Immunotherapy
    - Based on the type I hypersensitivity mechanism underlying AFRS, subcutaneous fungal immunotherapy has been studied. A systematic review found Grade C evidence supporting its short-term (3–4 years) symptomatic benefit, though long-term efficacy remains unclear. It may also reduce long-term corticosteroid use post-surgery. Given the limited evidence and high cost, immunotherapy is generally reserved for patients unresponsive to first-line therapies.[4,9]
- Leukotriene Modulators
    - Montelukast and other leukotriene inhibitors have been reported as adjuncts in AFRS treatment. Case studies suggest possible benefits in refractory cases, but more research is needed.[4]
- Biologic Therapies
    - Recent investigations have examined biologics targeting inflammatory mediators (e.g., anti-IgE, anti-IL-5 agents) extrapolated from asthma treatment. Early studies show promise: treatment with omalizumab in AFRS patients with comorbid asthma led to a 31% improvement in SNOT-22 scores and 61% in endoscopic scores.[4,9]

8.2. Invasive Fungal Rhinosinusitis

8.2.1. Acute Invasive Fungal Rhinosinusitis

Management involves three pillars: addressing predisposing factors (e.g., neutropenia, diabetic ketoacidosis), surgical debridement, and antifungal therapy.[4,9]

Surgical intervention is critical for both diagnosis and treatment. FESS facilitates early tissue sampling and aggressive necrotic mucosa and bone debridement until viable, bleeding tissue is encountered. This may involve removal of extensive nasal mucosa, turbinates, and extended sinus access procedures such as medial maxillectomy or Draf III. Repeat debridement is often necessary due to progressive necrosis.[9]

Early initiation of systemic antifungal therapy improves survival. Culture results should be used as a guide for antifungal selection. Amphotericin B (0.25–1.5 mg/kg/day) is the drug of choice, though its use may lead to fever, nausea, hypotension, and significant nephrotoxicity. If Aspergillus is identified, voriconazole is preferred due to a more favorable side-effect profile, though it is less effective against Mucorales. Other agents, such as posaconazole and isavuconazole, are considered second-line and may be used in patients with renal impairment or treatment-resistant cases.[4,9]

8.2.2. Chronic Invasive Fungal Rhinosinusitis

Management parallels the acute form, involving surgical resection and systemic antifungals. The same principles apply to surgical approaches and antifungal selection.[4]

8.2.3. Chronic Granulomatous Invasive Fungal Rhinosinusitis

Management is likewise based on aggressive surgical debridement and systemic antifungal therapy. This form typically requires long-term monitoring due to its indolent but progressive nature.[4,12]

9. Complication and Prognosis Fungal Rhinosinusitis

Complications are frequently associated with invasive fungal rhinosinusitis, particularly in cavernous sinus aspergillosis or orbital apex aspergillosis. Clinical manifestations may include headache, acute unilateral visual loss, and ocular pain, often resulting from cavernous sinus thrombosis or the development of a carotid-cavernous fistula. These life-threatening complications are most commonly observed in immunocompromised individuals, such as patients with diabetes mellitus or malignancy.[6]

Patients with diabetes mellitus have also been reported to be at greater risk for intraoperative complications during surgical management of fungal rhinosinusitis. Documented intraoperative complications include hemorrhage (72.60%), cerebrospinal fluid leak (4.1%), orbital hematoma (0.68%), nasolacrimal duct injury (2.05%), and periorbital hematoma (0.68%). Reported postoperative complications include synechiae (56.16%), oroantral fistula (45.89%), hypoesthesia (25.34%), reduction in visual acuity (16.43%), facial pain (20.54%), facial deformity (20.54%), diplopia (6.8%), headache (30.13%), anosmia (39.72%), toothache (20.54%), otalgia (9.58%), hyposmia (45.89%), periorbital ecchymosis (0.68%), residual disease (16.10%), recurrence (2.05%), and mortality (2.05%).[12,13]

These findings underscore the importance of early diagnosis, careful perioperative planning, and postoperative surveillance, particularly in high-risk patient populations.

10. Conclusion

Fungal rhinosinusitis represents a diverse spectrum of sinonasal disorders ranging from benign, non-invasive conditions to life-threatening invasive infections. Diagnosis relies on a combination of clinical assessment, imaging, histopathological evaluation, and mycological studies. CT remains the imaging modality of choice for initial evaluation, while MRI is valuable for assessing extra-sinus extension, especially in invasive disease. Histopathology not only confirms fungal presence but also identifies tissue invasion, which is key for diagnosing invasive variants. Management must be tailored to the specific subtype. Non-invasive forms generally respond well to surgical intervention, with corticosteroids playing a key role in allergic fungal rhinosinusitis. Invasive forms require aggressive surgical debridement, reversal of predisposing factors, and systemic antifungal therapy. The overall prognosis of fungal rhinosinusitis is generally satisfactory. However, invasive fungal rhinosinusitis carries a significant risk of morbidity and mortality, particularly in immunocompromised patients, and is associated with a poor prognosis if not promptly diagnosed and treated. In conclusion, optimal outcomes in FRS depend on timely diagnosis, precise classification, and individualized, multidisciplinary management. Future research should aim to establish standardized treatment guidelines, explore the role of host-fungal interactions, and evaluate novel therapeutic modalities for refractory and invasive cases.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

This study did not require ethical approval or informed consent, as it is based solely on a review of existing literature.

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