

Aspergillus Infections in the Head and Neck

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Abstract *Aspergillus* is a chronic colonizer as well as a nidus of infection in the sinuses and ears. In the sinuses, the severity of the disease is classified by the invasiveness of the infection. Invasive fungal sinusitis varies in its presentation based upon the infective organism and shows reduced morbidity if identified early, which requires a high index of suspicion. Allergic fungal sinusitis was recently further classified using a radiologic staging system and was proven to have symptomatic improvement with the concomitant use of surgery and immunotherapy. Finally, fungal ball appears to be a chronic problem that is usually cured with surgery. *Aspergillus* in the ear is a relatively common problem often related to prolonged antibiotic use and almost always successfully treated with topical antifungals.

Keywords Fungus · *Aspergillus* · Rhinosinusitis · Otitis externa

Introduction

Fungal infections in the head and neck are a common problem presented to the general practitioner. In fact, fungal colonization in the nares has been shown to be a normal component of nasal mucus. In 2005, Lackner et al. [1] demonstrated that by the age of 4 months, 94% of infants are colonized with fungus. *Aspergillus* is the most common species of fungus identified. Although colonization occurs

without consequence, the fungus can also be responsible for significant rhinologic and otologic diseases as well as numerous sequelae. Although these problems have been consistent challenges for several decades, this article presents the most recent understanding, advances, treatments, and future research related to the various forms of *Aspergillus* infection in the head and neck.

The sinonasal cavities and ears are two of the primary locations for *Aspergillus* to cause pathology. It has been estimated that fungal rhinosinusitis is encountered in about 10% of the patients requiring surgery for rhinosinusitis and that between 13.5% and 28.5% of all maxillary sinusitis is fungal or mixed fungal and bacterial infections [2]. However, the sinuses present three distinct types of disease, delineated by the invasiveness of the fungus. From most to least invasive, these are invasive fungal sinusitis, allergic fungal rhinosinusitis, and fungal ball [9]. The three diseases also occur at different ages; allergic fungal sinusitis is commonly diagnosed in young adults, whereas fungal ball is almost exclusively found in older individuals. Another differentiating factor is that an immunocompromised state is almost always a prerequisite for an invasive sinonasal mycosis. Table 1 shows the relationship between the type of paranasal fungal infection and the immune status of the typical presenting patient.

Furthermore, the different diseases vary in presentation, treatment, and long-term sequelae. We begin by examining the forms of fungal rhinosinusitis and their various subtypes.

Invasive Fungal Sinusitis

Invasive fungal sinusitis (IFS) presents with diagnostic and therapeutic challenges. It can be classified into three categories: acute fulminant, chronic invasive, and granulo-

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Table 1 Immune status in fungal rhinosinusitis conditions

Syndrome	Immune status
Invasive fungal sinusitis	
Granulomatous invasive fungal sinusitis	Immunocompetent
Chronic invasive fungal sinusitis	Often diabetes mellitus
Acute fulminant fungal sinusitis	Immunocompromised
Noninvasive fungal sinusitis	
Fungus ball	Immunocompetent
Allergic fungal sinusitis	Immunocompetent

matous invasive fungal sinusitis. These three varieties differ in pathophysiology and the patient population they most often affect.

Acute Fulminant Invasive Fungal Sinusitis

This type of IFS is a sinonasal infection that presents as a rapidly progressive and locally invasive infection in patients with prolonged altered immune function (ie, diabetes mellitus, AIDS, bone marrow transplant, or hematologic malignancies) [3]. It is most often a result of infection with either *Aspergillus* or *Mucor* spp. Early clinical symptoms frequently mimic those of bacterial sinusitis (ie, nasal congestion, discharge, facial pain, and headache). Later symptoms are the result of extrasinus extension and include facial swelling, orbital involvement and visual compromise, dental involvement, facial anesthesia, and neurologic symptoms. Additionally, physical examination often reveals ischemic mucosa, initially appearing pale at early stages and eventually turning black. Radiologic studies are useful but not diagnostic. CT scan without contrast can identify early changes, such as asymmetric soft tissue swelling of the nasal mucosa in early IFS, and bony erosion or extrasinus extension in advanced IFS. Definitive diagnosis rests with biopsy results showing fungal invasion into mucosa and bone. MRI is helpful in defining extrasinus extension.

Acute fulminant IFS is a potentially life-threatening disease that often presents with involvement of the orbit, skin, palate, and intracranial structures, and can ultimately result in an overall mortality of 18% to 20% [4, 5]. However, the clinical presentation as well as the morbidity and mortality rate recently were shown to be directly related to the type of fungus causing the infection. Parikh et al. [5] noted that *Aspergillus* was the causative fungus 80% of the time in patients with neutropenia, whereas *Mucor* was the causative fungus in 20% of these patients. Conversely, in diabetic patients, *Aspergillus* was responsible only 20% of the time, with *Mucor* being the more common fungus, occurring in 80% of cases. In 2006, Ingley et al. [6•]

showed that patients with *Mucor* more often presented with orbital and neurologic symptoms (eg, periorbital cellulitis, proptosis, cranial nerve palsies, and altered mental status) when compared with patients with *Aspergillus* infections. Also, patients with *Mucor* were shown to have higher rates of permanent neurologic and orbital morbidity than patients with *Aspergillus* (73% vs 37%, respectively) as well as higher IFS-related mortality rates than patients with *Aspergillus* (32% vs 11%, respectively). This relationship stresses the importance of a heightened sense of awareness when diagnosing IFS in those patients infected with *Aspergillus* because it is often presents more subtly. However, although the diagnosis of *Aspergillus* as the causative agent in IFS results in a lower rate of permanent sequelae and lower mortality, aggressive treatment is still required to decrease the fungal load until the patient's immune system recovers.

Because of the rapidly progressive nature of this disease, differentiation between causative agents is irrelevant unless an early diagnosis is made. Recently, DelGaudio et al. [7•] proved the efficacy of initiating an early detection protocol for the diagnosis of invasive fungal sinusitis. This multidisciplinary protocol involved the hematology service identifying any inpatient with neutropenia and either rhinosinusitis symptoms or fever of unknown origin, performing a sinus CT scan, and obtaining otolaryngology consultation. The otolaryngologists would then review the CT scan, perform nasal endoscopy, and biopsy any ischemic or necrotic tissue, looking for evidence of fungal invasion. The institution of this protocol resulted in lesser extent of disease spread at presentation, fewer surgeries per patient, and less long-term morbidity. However, it should be noted that the protocol had no effect on overall mortality, because the main prognostic factor in recovery from IFS is improved neutrophil count, a factor that the initiation of this protocol does not affect.

This protocol is also important because it stresses the need for imaging of the sinuses as well as endoscopic examination and biopsy for the diagnosis of acute fulminant IFS. In 2003, DelGaudio et al. [8] described early CT scan findings in patients with IFS. CT scans for immunocompromised patients with IFS were compared with those of immunocompromised patients with non-IFS rhinosinusitis in an attempt to delineate specific radiographic findings of IFS. It was noted that most early IFS patients do not exhibit the "classic" IFS CT findings (eg, bony erosion or extrasinus extension). Instead, severe unilateral thickening of the nasal cavity mucosa was the most consistent finding. The degree of mucosal thickening found in the IFS patients was far greater than that seen in the immunocompromised non-fungal sinusitis patients, and predominantly involved the lateral nasal wall, nasal floor, and nasal septum (Fig. 1). Therefore, the clinician cannot rely solely on CT imaging, but rather must use endoscopic examination, biopsies, imaging, and a



Fig. 1 Early acute fulminant invasive fungal sinusitis. Note the unilateral nasal soft-tissue thickening

heightened clinical awareness for an accurate and expeditious diagnosis of IFS.

Following diagnosis, standard of care currently involves initiation of intravenous antifungals, most commonly, amphotericin B in high doses—between 2 and 4 g—for 7 to 10 days, as well as early surgical debridement of the involved tissues. Recently, the azole class of antifungals (ie, voriconazole) was shown to be more effective than amphotericin B when specifically treating IFS caused by *Aspergillus* []. Additionally, surgical debridement should involve thorough, but conservative, resection of involved tissue. The goal of surgery is to reduce the fungal burden until immune function is recovered. However, the ultimate recovery from IFS is dependent on recovery of adequate functional neutrophils. This can be attained more rapidly through the use of granulocyte colony-stimulating factor, which works by stimulating production of functional neutrophils. Frequent endoscopic surveillance is necessary to monitor for persistence or progression of disease while the patient is neutropenic. Repeat debridements may be necessary. Subsequently, after initial control of the disease, recent studies examined how long to continue to monitor patients' progress and disease resolution. Otto et al. [10] recommended long-term follow-up for patients with IFS, until regeneration of mucosa on previously debrided tissues, resolution of crusting, and cessation of bony sequestration. This prolonged follow-up is recommended

because of the high rate of complications, including bacterial rhinosinusitis, chronic osteomyelitis, or even blindness. Using frequent outpatient follow-ups as well as CT imaging, these complications can quickly be identified and treatment begun.

Overall, acute fulminant IFS is an aggressive and potentially lethal disease that has been found to progress more slowly when caused by *Aspergillus* as opposed to *Mucor* spp. In turn, because of its virulence, an expeditious diagnosis through the use of imaging, endoscopic examination, and biopsies is essential to lessen morbidity and the need for subsequent surgeries. Finally, these patients should be followed until complete resolution of the disease is confirmed to minimize the likelihood of developing dangerous, even fatal, sequelae.

Chronic Invasive Fungal Rhinosinusitis

Chronic invasive fungal rhinosinusitis is similar to acute fulminant IFS in many ways, including diagnostic criteria, causative organisms, and treatment techniques. However, the difference is that the affected population is often immunocompetent, but with diabetes or a low level of immunocompromise [11]. Furthermore, in contrast to the acuity mentioned above, this disease (as the name would imply) develops over months to years and is often persistent and recurrent. Finally, chronic invasive fungal rhinosinusitis more often presents with a hyperattenuating soft-tissue collection on CT imaging with significant bony destruction because of the often long-standing chronicity of the disease prior to diagnosis (Fig. 2). Treatment involves surgical debridement

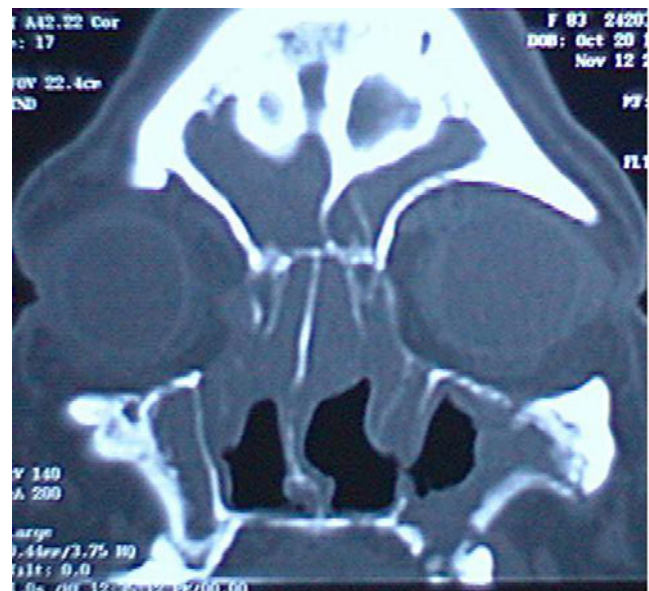


Fig. 2 Chronic invasive fungal sinusitis with evidence of bony erosion in the left maxilla

of affected tissues and systemic antifungal medications, as mentioned above, because of the similar threat of significant morbidity. Orbital and neurologic involvement is also present in this form of fungal sinusitis, but does not usually progress to visual compromise as in acute fulminant IFS. The underlying risk factors for developing this form of invasive fungal disease are not fully understood.

Granulomatous Invasive Fungal Rhinosinusitis

Granulomatous IFS, primarily caused by *Aspergillus*, is mainly localized to Africa and Southeast Asia with only a few cases reported in the United States [12]. Additionally, controversy exists as to whether this disease is its own distinct entity or should be classified as a type of chronic IFS. Granulomatous IFS is characterized by noncaseating granulomas in the tissues, which often extend into the orbit and cranium. Otherwise, CT imaging and treatment techniques mimic that of chronic IFS [11].

Allergic Fungal Rhinosinusitis

In contrast to IFS, *Aspergillus* can also affect the sinuses in a noninvasive method, as in allergic fungal rhinosinusitis (AFRS). AFRS is a chronic inflammatory disorder of the paranasal sinuses that represents an IgE-mediated hypersensitivity to fungal antigens. It was first characterized by Bent and Kuhn [13], who identified five major criteria: atopy through history, IgE levels, or radioallergosorbent testing was found in 100% of patients, as was the presence of nasal polyposis. Additionally, the presence of radiologic bony expansion or erosion, eosinophilic mucus without fungal invasion, and positive fungal cultures were identified in the majority of AFRS patients. AFRS can be caused by a variety of organisms, the most common of which include *Aspergillus* and *Curvularia* spp [14], and it remains a relatively common disease (10% to 30% of patients with nasal polyps also have AFRS) [15, 16]. Yet, despite its prevalence, AFRS has often been difficult to diagnose accurately because on physical examination it is similar to chronic rhinosinusitis. Recently, Dhiwakar et al. [17] proposed a set of preoperative criteria for the diagnosis of AFRS, which included nasal polyposis on physical examination, hyperattenuation of sinus secretions on CT scan, and increased serum IgE levels to *Aspergillus*. Taken together, these criteria were 70% sensitive and 100% specific for the diagnosis of AFRS.

Although AFRS has been a long-standing and widespread condition, particularly affecting those in the Southern and Southwest regions of the United States [18], recent attempts have been made to objectively rate its severity and understand the specific population the disease more often

afflicts. Recently, Wise et al. [19] discovered a strong correlation between severity of AFRS and race. African Americans were found to have more severe manifestations of AFRS, characterized by nearly twice the degree of bony erosion when compared with Caucasians. This increased severity has been theorized to result from a greater delay in African American patients presenting to an otolaryngologist or possibly an increased genetic or multifactorial susceptibility to bony erosion. These authors also showed a strong correlation between AFRS and the male gender (male to female ratio 1.5:1), with males more severely affected than females. Patients tended to be younger than 30 years old at presentation.

However, an objective means by which to define this “greater severity” of AFRS was described only recently. In 2008, Wise et al. [20•] proposed a radiologic staging system for AFRS disease severity based on the number of paranasal sinus walls that exhibited expansion or erosion. Using this method, any patient with the preoperative criteria mentioned above could be independently graded on disease severity. In turn, this would provide the otolaryngologist with a better system to objectively compare patients for the purpose of clinical research and possibly, in the future, for variations in treatment depending on severity (Fig. 3).

The mainstay of treatment is still based on surgical debridement of all fungal mucin and polyps, as well as the use of systemic and topical steroids, all designed to reduce the antigenic load and inflammatory response. Additionally, because of the obstructive nature of the polyps that occur

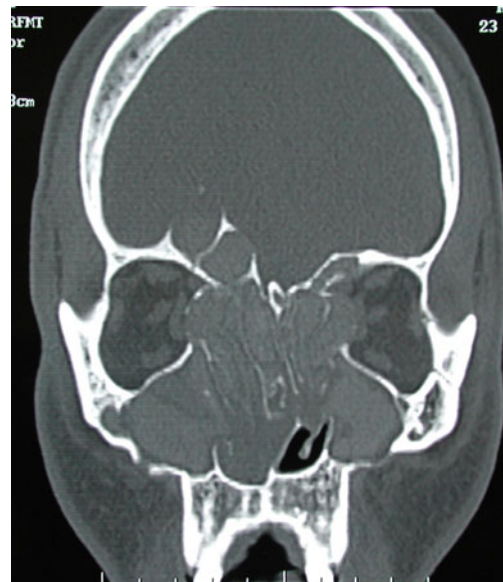


Fig. 3 Advanced allergic fungal rhinosinusitis with intracranial expansion of the ethmoid sinuses with bone dissolution

in advanced AFRS, occasionally a bacterial sinusitis also develops. Bacterial sinusitis more commonly occurs when a mucocoele becomes infected to produce a mucopyocele, with the development of acute pain and possibly orbital edema and proptosis. In this case, treatment with oral antimicrobials and possibly acute surgical intervention is warranted.

However, in the past decade, immunotherapy was introduced as a treatment in the long-term control of AFRS. Thus far, immunotherapy is the only therapeutic option that modifies the basic allergic mechanism by inducing desensitization and an anergy state for the allergen [21]. Recently, its administration through a sublingual route has greatly improved dispensation and compliance. In a randomized, controlled trial in 2006, sublingual immunotherapy showed significant decreases in allergic symptoms, including rhinorrhea, sneezing, and conjunctivitis, and a significant decrease in the use of nasal steroids [22]. Additionally, it was shown to decrease the reoperation rates from 33% in the placebo group to 11% in the immunotherapy group [23].

Although thorough surgery and systemic steroids are the mainstay of treatment for AFRS, several clinical researchers also demonstrated improvement using itraconazole for patients with chronic invasive aspergillosis [24]. Chan et al. [25] evaluated the utility of itraconazole following surgery for patients who were refractory to prednisone. More than half the patients reported improvement in clinical symptoms and more than 90% were found to have improved or stable disease state based on endoscopic examination after 3 months of treatment. However, it should be noted that because AFRS is not an invasive process, the role of systemic antifungals is limited.

Fungal Ball

Aspergillus can also noninvasively affect the paranasal sinuses through the presence of a fungus ball. A fungus ball, which typically affects immunocompetent people, is characterized by an extramucosal mass of fungal hyphae that progressively expands to occupy the sinus cavity, usually without involvement of the underlying mucosa. Although often caused by *Aspergillus*, the term “aspergilloma” has fallen out of favor to describe this pathophysiology because of its numerous and imprecise medical implications.

Recently, specific diagnostic criteria have been defined to confirm the finding of a fungal ball, including radiologic evidence of sinus opacification, mucopurulent or clay-like material in the sinus, a dense conglomeration of hyphae separate from the sinus mucosa, and no predominance of eosinophils, granuloma, allergic mucin, or fungal invasion [26]. Specific patient populations have also been identified as more likely to be affected by fungal balls, including

older individuals, females, and most significantly, those with a history of previous endodontic treatment [27, 28].

The association with previous dental manipulation has been repeatedly verified over the past 20 years. Theories suggest that sinus perforation secondary to endodontic treatments creates an ideal environment for inhaled spores to grow because of the presence of zinc oxide in sealants. The presence of this inert material, in turn, impedes mucociliary clearance, thus preventing fungal spore clearance [26]. More recently, basic scientists have also shown that the fungal-inhibiting component of amalgam—eugenol—becomes inactive after several years, leading to a decreased resistance to fungal growth [29]. However, these theories fail to explain the occurrence of fungal balls in the other sinuses.

The clinical signs of a fungal ball depend on the location. With maxillary sinus involvement (the most common locale), the majority of the fungal ball symptoms mimic those of chronic rhinosinusitis, including nasal discharge and obstruction, facial pain, headache, and hyposmia [26]. Patients with sphenoid sinus fungus balls more often complain of headaches, nasal obstruction, and visual disturbances (Fig. 4).

Therefore, given the numerous and relatively nonspecific array of symptoms, CT imaging has an important role in the diagnosis of fungal balls. The presence of an opacified sinus with central metal dense spots, in the absence of previous history of foreign body, strongly suggests this diagnosis. Research has suggested that these metallic bodies may reflect the metal content of dental sealers that have possibly penetrated into the sinuses [26]. The bony walls of the involved sinus are usually thickened because of



Fig. 4 Sphenoid fungal ball. Note the chronically thickened sinus walls and hyperdense secretions

the chronic nature of the process and the inflammatory reaction of the bone. However, definitive diagnosis is still based primarily on macroscopic visualization and histopathology. For Klossek et al. [30], the intraoperative visualization of a fungal ball, the identification of fungus on histology or cultures, the absence of mucosal invasion, and negative serologic results are the necessary components for an accurate diagnosis. It should be noted that histology has been found to be inconsistent in the diagnosis of fungal ball, with 10% to 70% of specimens positive for fungus. The inconsistency is thought to be related to the difficulty in growing fungal elements once they are removed from the sinus. Systemic antifungal therapy is not required in the treatment of fungal balls given the noninvasive nature of the disease.

However, despite the inconsistency in diagnostic tools, treatment is relatively straightforward and uncontroversial. The treatment of choice for fungus ball is endoscopic sinus surgery, which removes fungal debris from the affected sinus and reestablishes proper ventilation and drainage [31]. Any external approach (ie, lateral rhinotomy, Caldwell-Luc approach) is no longer justified for treating a fungus ball, which is a noninvasive fungal contamination. Instead, adequate opening of the ostium through endoscopic sinus surgery has been sufficient to prevent recurrence in 95% of cases.

Otomycosis

Otomycosis or fungal otitis externa is a fungal infection of the external auditory canal with infrequent complications

involving the middle ear. It is one of the most common conditions encountered by the otolaryngologist with as high as 9% of all otitis externa stemming from a fungal infection [32]. *Aspergillus* and *Candida* spp are the most common causative agents, although controversy exists about whether the fungi are the true infective hosts or rather a result of compromised immune system from bacterial infection [33].

Similar to many otolaryngologic diseases, presenting symptoms are often nonspecific, including otalgia, otorrhea, hearing loss, aural fullness, and pruritus [34]. Physical examination often shows a thick, fibrinous accumulation of debris, absence of edema in the canal, and small areas of granulation tissue. Several factors have been proposed as predisposing causes, including humid climate, immunocompromised host, history of prior otologic procedure, and most consistently, prolonged use of ototopical antibiotics or steroids.

Fortunately, few complications of otomycosis occur, with even fewer requiring complex treatments. The most frequent complications are serous otitis media and tympanic membrane perforation, affecting 13% and 14% of patients, respectively [32]. Treatment of otomycosis is also relatively easy. Mechanical debridement along with ketoconazole cream has proven to be most successful because of its efficacy against both *Aspergillus* and *Candida* spp and its limited side effects. Treatments with solutions such as cresylate otic drops or boric acid have recently become less used because of the increased pain associated with their application and their potential to cause hearing loss in patients with tympanic membrane perforation [35]. Systemic antifungal therapy is rarely required because invasive disease is an incredibly rare complication of otomycosis.

Table 2 Overview of *Aspergillus* infections in the head and neck

Name	Definition	Symptoms/Signs	Physical examination	Treatment
Acute fulminant invasive fungal sinusitis	Sinonasal fungal infection that presents as a rapidly progressive and locally invasive infection in patients with prolonged altered immune function	Early: congestion, discharge, facial pain, and headaches. Later: facial swelling, orbital involvement and visual compromise, dental involvement, facial anesthesia, and neurologic symptoms	Ischemic mucosa, initially appearing pale at early stages and eventually turning black	Surgical debridement, G-CSF, and systemic antifungals
Allergic fungal rhinosinusitis	Chronic inflammatory disorder of the paranasal sinuses that represents an IgE-mediated hypersensitivity to fungal antigens	Nasal discharge of thick mucus, nasal obstruction, anosmia	Nasal polyposis	Surgical debridement, systemic and topical steroids, and immunotherapy
Fungal ball	Extramucosal mass of fungal hyphae, which progressively expands to occupy the sinus cavity	Depends on the location: eg, maxillary sinus—nasal discharge and obstruction, facial pain, headache	Visualization of a fungal ball on endoscopic examination	Functional endoscopic sinus surgery
Otomycosis	Superficial (noninvasive) fungal infection of the outer ear canal	Otalgia, otorrhea, pruritus, and hearing loss	Thick, fibrinous accumulation of debris and areas of granulation tissue	Topical antifungal creams or drops

G-CSF granulocyte colony-stimulating factor

In summary, given its nonspecific symptoms, otomycosis requires vigilance from clinicians. Prolonged use of otic antibiotics or steroids should heighten awareness for a fungal ear infection. Treatment should involve debridement and a topical antifungal cream, and rarely requires the addition of oral antifungals, except in severe disease that is unresponsive to topical therapy.

Conclusions

Aspergillus has been a long-standing and pervasive pathogen of the sinonasal cavities and ears. Its presentation in disease states varies from acute and invasive to chronic and limited. However, common factors of its presentation in the sinuses include its challenge in diagnosis, and the nearly universal use of surgery as a mainstay of treatment. *Aspergillus* infection in the ears, however, is more easily recognized on physical examination and requires a less aggressive treatment with topical antifungals. In summary, *Aspergillus* is a common pathogen in the head and neck and can manifest itself through a variety of diseases (Table 2).

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