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*Review*

# Fungal sinusitis in immunocompromised hosts

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**The term "immunocompromised host" is generally applied to a variety of patients with various immune defects. Invasive rhinosinusitis is defined by the presence of local inflammation, with vascular and osseous necrosis with extensive soft tissue extension, and occurs almost exclusively in immunocompromised patients. Fungi have been increasingly recognized as important pathogens in severe acute and chronic sinusitis in immunosuppressed hosts. Earlier recognition of the disease, medical attention specific to the patient's needs are required. After medical remission, significant complications of invasive fungal infection may be seen. Patients should be followed in the long-term, until remucosalization of the sinuses.**

**Key word:** Fungal sinusitis, immunocompromised hosts, rhinosinusitis, immune defects.

## INTRODUCTION

The term "immunocompromised host" is generally applied to a variety of patients with various immune defects. Patients having neutropenia, hematological malignancies, cell-mediated immunodeficiencies, acquired immune-deficiency syndrome, and diabetes mellitus would be considered immunocompromised. Patients receiving immunosuppressive therapy, undergoing systematic chemotherapy, and patients who have received a solid organ transplant or a hematopoietic stem cell transplant would also be considered to be immunocompromised (Derber et al., 2010).

The immunocompromised population is at a higher risk for developing infection and life-threatening clinical syndromes, since they lack the basic mechanisms of cellular defense. The most common complications are bacterial, viral, or fungal infections. Among the fungal infections, aspergillosis is the most common (incidence, 1 to 9%; mortality, 55 to 92%) following organ transplant (Silva et al., 2010).

Fungal infections in immunocompromised patients have elevated and variegated during the last few decades. They are exposed to a large number of fungal pathogens that are ubiquitous, difficult to identify, and very often fatal (Georgala et al., 2006).

Sinusitis is the term representing inflammation of the paranasal sinus mucosa. Like the paranasal sinuses, the entire nasal cavity is lined by a thin layer of respiratory mucosa composed of pseudostratified, ciliated, columnar epithelial cells with goblet mucous cells interspersed among the columnar cells. Due to the contiguous nature of nasal and paranasal sinus mucosa, the term rhino-sinusitis has become a common replacement for the term sinusitis, as well as their interactions and potentially shared involvement in various inflammatory processes. Rhinosinusitis occurs in both acute and chronic forms, and represents a potential heterogeneity of pathophysiologies and prognoses (Schubert 2009). Rhinosinusitis is considered to be a multi-factorial disease, in which a large number of factors may even-tually lead to damaged ciliary function, more mucus with mucosal swelling, and increased viscosity (Fokkens et al., 2009). It is characterized by the presence of distinctive symptoms: nasal blockage, nasal discharge, facial pain and/or reduced sense of smell, and is present for at least 12 weeks without complete resolution and either endoscopic signs or computed tomography (CT) changes characteristic of the disease (Ebbens et al.,

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2009; Polzehl et al., 2009).

## INVASIVE RHINOSINUSITIS

Invasive rhinosinusitis is defined by the presence of local inflammation, with vascular and osseous necrosis with extensive soft tissue extension, and occurs almost exclusively in immunosuppressed patients (Ukkola et al., 2010).

Once considered a rare disorder, fungal sinusitis is now known to be relatively common, and is reported with increasing frequency throughout the world, though it is often misdiagnosed. It is a serious condition, as certain forms of fungal sinusitis are associated with a high rate of mortality. Fungi have been increasingly recognized as important pathogens in severe acute and chronic sinusitis in immunocompromised hosts. They have been detected in more than 90% of nasal lavages in immunocompetent patients with rhinosinusitis (Malani and Kauffman, 2002). Fungal spores, due to their nature, are continuously inhaled and deposited on the airway mucosa. Although they seldom behave as pathogens in the airways of healthy individuals, they may occasionally be the cause of disease in some (Ebbens et al., 2009).

The role of fungi is well established in a few subtypes of rhinosinusitis, such as acute invasive fungal rhinosinusitis, allergic fungal rhinosinusitis, and fungal balls (Chakrabarti et al., 2009) An acute invasive fungal infection of the sinonasal cavities is a potentially life-threatening, systemic infectious disease requiring more urgent attention and treatment by an otolaryngologist–head and neck surgeon, but it is difficult to diagnose and treat (DelGaudio et al., 2003). It is a serious disease, with a rapidly progressing infection seen most commonly in immunocompromised patients and only rarely in healthy individuals. The disease is delineated by a time course of < 4 weeks, with predominant vascular invasion. Patients typically are immunosuppressed, and the infection leads to widespread facial and paranasal tissue necrosis with high morbidity and mortality rates. It is the most lethal form of fungal sinusitis, with a reported mortality rate of 50 to 80% (Waitzman and Birt, 1994). Patients with invasive fungal sinusitis are in overall poor physical health as a result of their underlying condition or treatment, and are expected to have a higher mortality rate and poorer prognosis. Symptoms include fever, nasal congestion, facial pain or numbness, epistaxis and serosanguineous nasal discharge, proptosis, maxillofacial soft-tissue swelling, headache, visual disturbances, mental status changes, seizures, neurologic deficits, and coma. It is clinically characterized by sinusitis, a painless necrotic nasal septal ulcer (eschar), and rapid orbital and intracranial spread. Aggressive bone destruction of the sinus walls occurs rapidly, and intraorbital, intracranial, and maxillofacial extension inflammation is common. A non-contrast computed tomography (CT) demonstrates the involved paranasal sinus and nasal cavity. MR imaging is excellent for evaluating intracranial and intraorbital extension of the disease. (Parikh et al., 2004; Aribandi et al., 2007).

Hematogenous dissemination and angioinvasion are frequent. Intracranial extension of the disease from the sphenoid sinus leads to carotid artery invasion or even cavernous sinus thrombosis, or to a pseudoaneurysm with resulting fatal cerebral hemorrhage and cerebral infarction. There is fulminant progression over a few days to several weeks, in which fungal organisms invade the mucosa, submucosa, blood vessels, and bony walls of the nasal cavity and paranasal sinuses. Patients who do not recover from their neutropenia seem to have a poor prognosis regardless of adjunctive therapeutic measures treat (DelGaudio et al., 2003; Aribandi et al., 2007). Historically, the organisms most frequently encountered in this disease are *Mucor*, *Aspergillus* and *Rhizopus*. On the other hand, invasive dematiaceous fungal sinusitis is an uncommon and aggressive disease in immunocompromised individuals (Taxy et al., 2009; Derber et al., 2010).

Treatment must be quickly provided, and requires aggressive surgical debridement and intravenous antifungal therapy, such as Amphotericin B. Acute invasive fungal sinusitis can be successfully treated with a combination of endonasal surgical debridement. An endonasal approach is more suitable for patients diagnosed in the early stages of the disease, and provides a minimal traumatic option for patients in poor health. Open surgery should be preferred in the presence of palatinal, intraorbital extension, or intracerebral involvement. Reversing the underlying disease process and immunosuppression is as important as surgical and antifungal treatments (Kasapoglu et al., 2010). The prognosis is poor without a correction of the underlying predisposing immunocompromise. Significant complications of invasive fungal infection may occur after medical remission. Patients should be followed long-term, until a resolution of crusting and remucosalization of the sinuses and the cessation of bony sequestration (Otto and Delgaudio 2006).

## MUCORMYCOSIS

Mucormycosis is a rare but potentially aggressive and fatal fungal infection of the order Mucorales in the class Zygomycetes (Deboni et al., 2006). Mucormycosis is seen in patients with chronic conditions, particularly uncontrolled diabetes mellitus and hematologic malignancies, renal failure, patients with extensive burn injuries, prolonged corticosteroid use, and deferoxamine treatment, because these patients are immuno-compromised. Patients have also been reported to have mucormycosis (Hadzri et al., 2009; deShazo et al., 1997, Bodenstein et al., 1993). *Rhizopus*, *Mucor*, and

*Lichtheimia* species are the most common members of the order Mucorales that cause mucormycosis, accounting for 70 to 80% of all cases (Gomes et al., 2011). Clinically, it manifests as pulmonary, cutaneous, soft tissue, disseminated, and gastrointestinal infections, but rhinocerebral mucormycosis is the most common presentation (Sugar 1992). Rhinocerebral mucormycosis is a rare but potentially aggressive, and it must be considered in the differential diagnosis of any severe acute headache, facial pain, edema, paresthesia, paralysis, orbital cellulites, or sinusitis, not only in immunocompromised patients but also in the absence of any underlying disease. It is characterized by sinusitis and a painless, necrotic black palatal or nasal septum eschar. The disease should be recognized and treated immediately (Sridhara et al., 2005). The diagnosis is confirmed histologically by demonstrating tissue invasion and subsequent tissue reaction to the fungi. Due to the rapid invasion, orbital exenteration was often indicated and local extension to the orbits. With the advent of new therapeutic regimes, however, the treatment strategy now involves rapid diagnosis, reversal, and stabilization of underlying medical conditions, with systemic antifungals and appropriate surgical debridement used only as needed (Hadzri et al., 2009; Peterson et al., 1997). Successful treatment requires tissue débridement and injection of Amphotericin B, which has been proven to be the only efficacious antifungal. It is administered parenterally at 1.0 to 1.5 mg/kg of the body weight/day, to a total dose of 2.5 to 4.0 g (Strasser, 1997). An Amphotericin B treatment, however, is limited by its renal and systemic toxic effects. Earlier recognition of the disease, medical attention specific to the patient's needs (example, withdrawal of prednisone, aggressive insulin control, initiation of dialysis, and earlier administration of Amphotericin B), and surgical debridement may improve patient outcome (Ferguson, 2007).

## ASPERGILLOSIS

Invasive aspergillosis is the most common fungal infection among immunocompromised neutropenic patients (Silva et al., 2010). Aspergillosis of the paranasal sinuses is infrequent and usually involves the species *Aspergillus fumigatus* and *Aspergillus flavus*. The maxillary sinus is the most commonly affected sinus. Invasive cranio-orbital aspergillosis originating in the sphenoid sinus is rare and mostly occurs in immune-compromised patients with poor outcomes (Akhaddar et al., 2008). Aspergillosis of the nose and paranasal sinuses is known to cause ocular pain, ophthalmoplegia, proptosis, optic neuropathy, orbital apex, and cavernous sinus syndromes (Brown et al., 1994). In immune-competent hosts, invasive sinus aspergillosis carries high morbidity and mortality rates. Craniocerebral aspergillosis of sinonasal origin has been reported mainly in immunocompromised patients with high mortality, and has been described very infrequently in immunocom-petent hosts. Neurological complications are the result of invasive forms occurring in most cases for diabetic or immunocompromised patients. To improve outcomes, the diagnosis must be recognized early, before the organism can invade the central nervous system or vascular structures (Clancy et al., 1998; Siddiqui et al., 2004; Devèze et al., 2005). Management of both fulminant and chronic invasive aspergillosis requires surgical resection and systemic antifungal treatment. Amphotericin B remains the principal antifungal treatment, but its use is complicated by nausea, anemia, fevers, and renal failure. Itraconazole is a promising oral antifungal agent that has been well tolerated, and seems effective against *Aspergillus.* In the management of infection, aggressive surgical resection of the infected areas is of utmost importance (Denning and Stevens, 1990; Brown et al., 1994).

## ZYGOMYCOSIS

Zygomycosis is a rare, opportunistic infection of fungi belonging to the class of Zygomycetes; clinical manifestations may vary but the most fulminant one is the rhinocerebral form, which usually occurs in diabetic and immunocompromised patients and, increasingly, is reported in hematological patients. In transplant recipients, a high index of suspicion and cumulating risk factors for zygomycosis are required (Georgala et al., 2006; Uçkay et al., 2007). The most usual presentations are rhinocerebral, gastrointestinal, pulmonary, and cutaneous; other localizations, such as in the brain and kidneys, are seldom described. Rhinocerebral zygomycosis is a common presentation and almost always associated with hyperglycemia and metabolic acidosis (Roden et al., 2005). The onset of the disease is acute: a stuffy nose, fever, purulent nasal droppings, headache, and tender sinuses. All sinuses may be involved; the infection progresses by local infarction and can spread to the orbits, brain, skin and large blood vessels (Georgala et al., 2006).

The successful management of zygomycosis is based on three major elements: early surgical treatment, appro-priate antifungal therapy, and resolution of the underlying condition. Amphotericin B remains the gold standard in the treatment of zygomycosis. Combining surgery and early diagnosis is mandatory to improve survival rates (Roden et al., 2005; Kontoyiannis et al., 2000). Hyperbaric oxygen treatments have been an appropriate addition to standard surgical and antifungal therapies, particularly for rhinocerebral disease. Unfortunately, there has not been any extensive experience with this treat-ment modality. In a retrospective analysis of the cases seen in a medical center, the addition of hyperbaric oxygen treatments improved patient survival (Ribes et al.,

2000).

## CONCLUSION

Fungi have been increasingly recognized as important pathogens in severe acute and chronic sinusitis in immunocompromised hosts. Earlier recognition of the disease, medical attention specific to the patient's needs is required. Significant complications of invasive fungal infection may be seen after medical remission. Patients should be followed in the long-term, until remucosalization of the sinuses, resolution of crusting, and the cessation of bony sequestration has occurred.

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