Managing acute invasive fungal sinusitis

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ABSTRACT

Acute invasive fungal sinusitis is the most aggressive form of fungal sinusitis and can be fatal, especially in patients who are immunosuppressed. Early diagnosis and intervention are crucial and potentially lifesaving, so primary care providers must maintain a high index of suspicion for this disease. Patients may need to be admitted to the hospital for IV antifungal therapy and surgical debridement.

Keywords: fungal sinusitis, acute invasive, immunocompromised, neutropenia, HIV, diabetes

H umans routinely inhale naturally occurring fungal spores into the sinuses and lungs. Although this is not a significant health risk for healthy patients, those who are immunocompromised are vulnerable to life-threatening diseases. The three types of invasive fungal sinusitis are chronic, granulomatous, and acute. Noninvasive fungal sinusitis typically occurs in immunocompetent patients and can be classified as allergic, saprophytic, or fungal ball (mycetoma). This article focuses on acute invasive fungal sinusitis, the most devastating form of fungal sinusitis, which occurs almost exclusively in immunocompromised patients with neutrophil dysfunction or neutropenia.1

Primary care providers must be aware of the signs and symptoms consistent with the development of acute invasive fungal sinusitis. Promptly discerning noninvasive disease from invasive disease is essential because the treatment and prognosis differ. Although acute invasive fungal sinusitis is rare, early detection can significantly reduce morbidity and mortality.

EPIDEMIOLOGY

Acute invasive fungal sinusitis is a rapidly progressive, potentially lethal form of fungal sinusitis that is rare in the general population and immunocompetent patients. Unfortunately, this disease is becoming increasingly common in immunosuppressed patients. Neutropenia is the most common predisposing factor.2 Patients with acute invasive fungal sinusitis may present with a medical history that includes hematologic malignancies, hematopoietic stem cell transplantation, solid organ transplantation, advanced HIV infection, or other forms of immunosuppression.3,4 In addition, patients with uncontrolled diabetes or those in diabetic ketoacidosis are at an increased risk. Historically, mortality ranged from 30% to 80%; however, more recent studies report mortality under 20%, which is attributed to earlier diagnosis and aggressive medical management.5

PATHOPHYSIOLOGY

The most frequently implicated organisms are species of Aspergillus and members of the class Zygomycetes (Mucorales and Rhizopus). Aspergillus is the most common cause of acute invasive fungal sinusitis. These fungi are commonly found in soil, dust, and decaying materials and produce airborne spores.6,7

Fungal colonization of the sinus cavities does not indicate infection. The status of the patient’s immune system plays an integral role in the various manifestations of acute invasive fungal sinusitis. In immunocompromised patients, after the fungal spores have been inhaled into the nose and parasinal sinuses, germination occurs and hyphae invade the blood vessels. This progresses to fungal thrombi formation and fibrin activation, resulting in tissue necrosis.5,8 The fungus spreads hematogenously to local structures such as the orbit, cranium, and oral cavity.3 This results in a dry gangrenous appearance of the affected tissues. Histopathology reveals evidence of fungal growth along the internal elastic lamina of blood vessels resulting in dissection away from the media, as well as hyphal growth into the vessel lumen causing endothelial dysfunction and thrombosis.8

In immunocompetent patients, neutrophils and macrophages kill and remove the Mucorales.9 Neutrophils damage fungal hyphae by extracellular mechanisms; macrophages kill intracellular spores by oxidative mechanisms.10 Corticosteroid therapy and diabetes impair the neutrophil and macrophages mechanisms of inhibiting spore germination, and are risk factors for acute fungal sinusitis.10

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RISK FACTORS
In addition to patients with weakened immune systems, patients with anatomic abnormalities of the nasal passageways are at an increased risk of infection because they have difficulty with nasal cavity drainage. Chronic exposure to fungal spores, iron overload, burns, and blood dyscrasias also are risk factors for acute fungal sinusitis. Piromchai and Thanaviratananich proposed that diabetes is the most common underlying risk factor for invasive fungal rhinosinusitis with orbital complications. Sinopulmonary risk factors include a weakened immune system; neutropenia; history of lung cavities, asthma, or cystic fibrosis; or long-term corticosteroid therapy.

CLINICAL MANIFESTATIONS AND COMPLICATIONS
Acute invasive fungal sinusitis can present with vague, overlapping features consistent with a variety of diseases; however, clinical manifestations commonly occur quite rapidly. Symptoms generally are nonspecific; however, the differential diagnosis should include acute invasive fungal sinusitis when an immunocompromised patient complains of facial pressure and swelling, nasal congestion, epistaxis or nasal eschar, fever, headache, proptosis, paresthesias, ophthalmoplegia, vision changes, seizures, or altered mental status. Sinopulmonary involvement may present with hemoptysis, wheezing, shortness of breath, or chest pain. Immunocompromised patients may remain afebrile.

Perform a thorough head, neck, and pulmonary evaluation. Clinical signs of orbital involvement include periorbital edema, ophthalmoplegia, vision loss, proptosis, and impaired intraocular movements. Orbital complications include preseptal cellulitis, orbital cellulitis, subperiosteal abscess, orbital abscess, and vision loss. Perform nasal endoscopy to inspect the nasal mucosa for insensate areas, ulcers, pale nasal mucosa that may represent ischemia, and the presence of eschar (which is pathognomonic for acute invasive fungal sinusitis). Nasal mucosa may appear edematous and hypervascular secondary to acute inflammation. Alternately, it may appear pale and have minimal bleeding when biopsied due to ischemia.

Inspect the patient’s oral cavity for evidence of palatal ulceration, which can progress to bony necrosis and subsequent oronasal communication in later stages. Also perform a comprehensive neurologic assessment, including cranial nerve evaluation and mental status examinations, at bedside. Intracranial complications include epidural or subdural abscess, brain abscess, meningitis, encephalitis, and cavernous sinus thrombosis.

EVALUATION AND DIAGNOSIS
An urgent evaluation is recommended for patients with clinical suspicion of acute invasive fungal sinusitis. Depending on the extent of the disease, the patient may need consultations with an otolaryngologist, ophthalmologist, neurosurgeon, pulmonologist, and infectious disease specialist.

Delays in evaluation and treatment can be devastating for the patient. Primary care providers must identify early signs and symptoms of acute invasive fungal sinusitis and arrange immediate hospital admission for the patient. Workup by specialists should include clinical examination...
and possibly nasal endoscopy, tissue biopsies, nasal cultures, sputum culture, complete blood cell count with differential to evaluate absolute neutrophil count, and imaging studies.

Physical examination with biopsy remains the gold standard for diagnosis and pathologic evaluation is necessary for the diagnosis. Histopathologic evaluation will reveal fungi invading nasal tissue and hyphae formation within the nasal mucosa and blood vessels or bones present near the paranasal sinuses.11 Acute invasive fungal sinusitis most commonly begins as mucosal inflammation around the middle turbinate. This may be why the middle turbinate is the most frequently positive biopsy site, accounting for two-thirds of the cases.12 The otolaryngologist will take additional biopsies of any areas appearing to have ischemia, necrosis, eschar, or sloughing of tissues within the nasal or oral cavity.

Biopsied materials will be evaluated with potassium hydroxide 20% preparation, histopathologic, mycologic, and molecular evaluation to identify any fungi present.6 As reported by Tugsel and colleagues, initial culture of diseased tissue may be negative and histopathologic examination is essential for early diagnosis.13 Aspergillosis and mucormycosis appear similar with histopathologic evaluation, so tissue samples and cultures must be evaluated microscopically to differentiate them because their treatments differ.7 Tissue biopsy is critical not only in establishing a diagnosis but in directing appropriate therapy.5,12,14

Nasal endoscopy may not provide adequate visualization and imaging studies are a necessary supplementation. Imaging also plays an integral role in establishing the diagnosis, evaluating the extent of the disease, and guiding surgical planning for further biopsy and debridement.5 MRI and CT may be used to assess soft tissue and bony changes. Groppo and colleagues reported that MRI was more sensitive and had a higher negative predictive value in detecting early changes of acute invasive fungal sinusitis, although the specificity and negative predictive value were equal to that of CT.16 CT with contrast will demonstrate the degree of sinus involvement, areas of bony erosion, and any extension into adjacent structures. To completely evaluate the sinuses and surrounding structures, CT scans should be performed at intervals no greater than 3 mm in both the axial and coronal planes.17 Patients suffering from acute invasive fungal sinusitis with orbital complications may have CT findings of sinus wall erosions and hyperdense lesions.13 CT characteristics include unilateral opacification of multiple sinuses, often with focal bone erosion, soft-tissue thickening, and edema of the sinuses and lateral nasal wall mucosa, subtle infiltration of premaxillary fat, and orbital invasion.5,18 Involvement of the ethmoid or sphenoid sinuses and bony destruction are negative prognostic factors and increase the likelihood of extension to surrounding structures.5 Early in the disease process, acute invasive fungal sinusitis may have similar features to simple rhinosinusitis on imaging studies and it is imperative the provider considers the full medical evaluation and not focus on only one portion of the workup. Late-stage findings on imaging include osseous erosion and extrasinus extension. MRI studies must be used as the primary imaging source when intracranial or orbital invasion is suspected. MRI findings may include nonenhancing, hypointense turbinates (“black turbinate sign”), sinus opacification, air-fluid
levels, obliteration of the nasopharyngeal planes, variable intensity within the sinuses on T1- and T2-weighted images (more likely hypointense on T2), loss of contrast enhancement of the sinonasal mucosa and extraocular muscles, inflammatory changes in the extraocular fat and muscles, and leptomeningeal enhancement.\textsuperscript{5,19-21}

**DIFFERENTIAL DIAGNOSIS**

Early diagnosis of acute invasive fungal sinusitis is difficult because early signs and symptoms mimic those of viral or bacterial sinusitis. Nonfungal conditions to consider include complicated acute and chronic viral or bacterial rhinosinusitis, granulomatosis with polyangiitis (formerly Wegener granulomatosis), and malignancies. The most common sinonasal malignancies include squamous cell carcinoma and sinonasal non-Hodgkin lymphoma. Generally, malignancies do not follow the rapid onset similar to acute invasive fungal sinusitis. Cancers occurring in the nasosinus typically are persistent and worsen over many weeks to months, not hours to days as in the case of acute invasive fungal sinusitis. Granulomatosis with polyangiitis causes epistaxis, septal perforation, and multiple systemic complaints. A thorough history and physical examination will help rule out other possible causes.

**FIGURE 3.** Intracranial extension of angioinvasive fungal disease carries a high morbidity and is best detected with MRI. A coronal T1-weighted postcontrast fat-suppressed image (A) shows that the right cavernous sinus is abnormally distended with a paucity of internal enhancement consistent with cavernous sinus thrombosis (arrow). The expected flow void of the right internal carotid artery is no longer visible. A noncontrast time-of-flight head MRA (B) confirms occlusion of the right internal carotid artery (white ellipse) secondary to angioinvasive fungal sinusitis, thereby placing the patient at high risk for septic emboli and infarcts. Because of the close proximity to the paranasal sinuses, fungal sinusitis can directly invade the inferior frontal and anterior temporal lobes. Axial T2 FLAIR sequence (C) exhibits mild edema in the anterior right temporal lobe at the site of fungal invasion (arrowhead).
SPECIAL TOPICS IN INFECTIOUS DISEASES

TREATMENT

Patient survival depends on early detection of the disease, followed by aggressive medical intervention and surgery if indicated. \(^2\) Treatment includes tight regulation of blood glucose, management of diabetic ketoacidosis, reversal of the underlying immunocompromised state when possible, antifungal medications, and urgent surgical intervention if appropriate.

Though a variety of antifungal drugs exist and newer ones are being introduced regularly, the usual response rates of various drugs vary from 40% to 60%. \(^2\) The most common antifungal medications used for acute invasive fungal sinusitis are amphotericin B, voriconazole, and posaconazole. IV amphotericin B is the drug of choice for initial therapy. Posaconazole is a triazole antifungal and the first member of this class to have comparable in vitro activity to amphotericin B against most zygomycosis. \(^9\) When acute invasive fungal sinusitis is suspected, empiric IV antifungal therapy should be initiated. The result from histopathology will further guide medical management.

Although amphotericin B is considered the gold standard for systemic treatment, its unfavorable adverse reactions are well known. Various formulations have been developed in an effort to decrease these adverse reactions. The lipid formulation can be delivered at a higher dose with fewer adverse reactions, specifically nephrotoxicity. The specialist involved will determine the course of drug therapy; however, therapy should be continued until acute invasive fungal sinusitis appears to be resolving clinically, as well as radiographically. Patients who remain immunocompromised may require lifelong therapy.

Surgical intervention involves aggressive debridement of all involved tissues to prevent the spread of necrosis and reduce fungal load. \(^2\) When determined necessary, urgent surgical intervention can reduce mortality. Surgery may become extensive and typically requires multiple trips to the OR for debridement. Specialists will perform long-term surgical and medical management.

Although surgical debridement and antifungal therapy are important to control the disease, the main factor that determines outcome is the recovery of the patient’s neutrophil count. \(^5\) Adjuvant therapies include hyperbaric oxygen treatment, interferon-\(\gamma\), and granulocyte-macrophage colony-stimulating factor.

PROGNOSIS

Patients who are diagnosed and treated early, when fungal load is low, have the best outcomes. \(^7\) In a retrospective review by DelGaudio and Clemson, a multidisciplinary intervention program including hematology, otolaryngology, and neuroradiology was better able to identify acute invasive fungal sinusitis at an early stage; mortality decreased from 78.6% to 7.1% in the group with collaborative intervention. \(^2\)

PREVENTION

Immunocompromised patients should routinely be told to follow neutropenic precautions, such as avoiding damp areas, soil, gardening, yard work, and other activities that would increase their risk of inhaling large amounts of mold. \(^2\) Patients with uncontrolled diabetes require close monitoring and follow-up. Medical management with a diabetes specialist may be warranted to achieve optimal glycemic control.

Educating patients about the early signs and symptoms of acute invasive fungal sinusitis can help in early diagnosis. Patients with neutropenia, those undergoing stem cell transplantation, and patients with hematologic cancers can undergo antifungal prophylaxis. Daily posaconazole therapy has been shown to reduce the incidence of invasive fungal infections and attributable mortality in allogenic stem cell recipients with severe graft versus host disease, and reduced overall mortality in patients with acute myelogenous leukemia or myelodysplastic syndrome. \(^21\) In a recent study, patients at high risk of invasive fungal infections who received empirical antifungal coverage against zygomycetes had a superior survival rate compared with those who did not receive this therapy. \(^24\)

CONCLUSION

Acute invasive fungal sinusitis can be a difficult and challenging disease for medical providers to identify and treat. Early diagnosis, aggressive surgical and medical involvement, and medical management are key to a favorable outcome. Primary care providers may be the first contact for patients with symptoms of acute invasive fungal sinusitis, and should be alert for this condition, especially in immunocompromised patients with a clinical presentation out of proportion to their symptoms. \(\text{JAAPA}\)

REFERENCES