

Aggressive combination treatment for invasive fungal sinusitis in immunocompromised patients

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Abstract

*Invasive sinonasal fungal disease is a potentially fatal complication of chemotherapy-induced immunosuppression and neutropenia. We reviewed the outcomes of seven cancer patients who had been diagnosed with invasive fungal sinusitis; six patients had hematologic malignancies and one had breast cancer. At the time of their sinus diagnosis, all patients had been hospitalized and were receiving combination chemotherapy for their underlying malignancy. Impairment of their immune function was characterized by an absolute neutrophil count of less than 1,000/mm³. Aggressive management of their sinonasal fungal disease consisted of surgical debridement and systemic amphotericin B for all patients, and treatment with granulocyte colony-stimulating factor for two patients. Invasive *Aspergillus* infection was identified in six patients and invasive *Candida albicans* infection in one. Although the prognosis for these patients was poor and two patients died of the fungal infection, the aggressive treatment strategy resulted in long-term survival for the remaining five patients.*

Introduction

Even though invasive fungal disease is still relatively rare, its incidence might be higher now than in the past because of the increase in the number of immunosuppressed patients. The growing number of patients with acquired immunodeficiency syndrome, coupled with their improved survival, has increased the number of chronically immunosuppressed individuals. Meanwhile, advances in the use of chemotherapeutic agents have al-

lowed physicians to prescribe more aggressive therapy for cancer patients, and thus lengthen the duration of their immunosuppressed status.

Paranasal sinus mycoses were first reported by Mackenzie in 1893.¹ Since then, several varieties have been identified, including allergic, indolent, and invasive forms. *Aspergillus* spp are the most common isolates that affect the paranasal sinuses; they are either indolent or invasive.² The invasive form is more common in the immunocompromised host, which poses a life-threatening risk to the patient and presents a diagnostic and therapeutic challenge to the physician. Immunosuppressed patients are at risk for invasive fungal disease of the paranasal sinuses as a consequence of intensive chemotherapy, which results in prolonged periods of neutropenia. The current management strategy calls for a multimodality approach, including aggressive surgical debridement and the use of antifungal agents for all, and treatment with granulocyte colony-stimulating factor for selected patients.³

It is not yet understood which combination of these therapies constitutes optimal management. However, it is clear that success depends on early diagnosis, treatment, and restoration of the patient's neutrophil counts. Invasive fungal sinusitis progresses rapidly in immunocompromised patients, and its early signs and symptoms can be subtle.⁴ Consequently, a late diagnosis often results in death, and overall mortality rates approach 90%.⁵ Prompt diagnosis and aggressive treatment to restore the patient's immunologic competence provide the best opportunity for cure.⁶ In this article, we describe the outcomes of seven immunocompromised patients who developed invasive fungal sinusitis while they were hospitalized at our institution. We also review the literature in an effort to emphasize how subtle the presentation of this potentially fatal infection can be and to address the difficulties encountered in both diagnosing and treating it.

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Materials and methods

We undertook a retrospective review of computerized hospital records over a 5-year period (1991-1995) at the Memorial Sloan-Kettering Cancer Center. We found seven cases of invasive fungal sinusitis that developed in immunocompromised patients. The four male and three female patients ranged in age from 8 to 64 years (median: 23), and their duration of followup ranged from 9 to 26 months (median: 16). All patients had been receiving combination chemotherapy—six for hematologic malignancies and one for breast cancer. Three of the six patients with hematologic malignancies had acute lymphoblastic leukemia, while the other three had acute myelogenous leukemia. Four of the patients with hematologic malignancies had come to the Head and Neck Service after they had undergone chemotherapy to ablate their bone marrow, but before they underwent bone marrow transplantation. The other two patients had already undergone transplantation; one came in 3 weeks following an autologous bone marrow transplant, and the other came in 2 weeks after an allogeneic transplant. The latter patient had also experienced graft-versus-host disease, renal failure, and bacterial septicemia.

An otolaryngologic consultation was initiated because these patients continued to experience 1) a persistent fever despite broad-spectrum antimicrobial therapy and 2) signs or symptoms localized to the nose or sinuses during a period of neutropenia, particularly an absolute neutrophil count (ANC) of less than $1,000/\text{mm}^3$. All patients had been hospitalized at the time the diagnosis of fungal sinusitis was made. During the initial otolaryngologic consultation, a thorough head and neck examination was performed, which included a fiberoptic nasal examination. Computed tomography (CT), without contrast, of the paranasal sinuses was performed on each patient. All patients had been receiving prophylactic broad-spectrum antimicrobial therapy and systemic amphotericin B. Three patients also were receiving high-dose corticosteroids.

As a treatment for their sinonasal disease, all patients underwent surgical debridement of necrotic tissue, which was directed by preoperative CT and intraoperative findings. Six of the seven patients also underwent a second-look procedure and further debridement as indicated to ensure that all fungal elements were removed. Biopsy specimens were sent for histopathology and culture. Patients were also given systemic amphotericin B (1 mg/kg/day) for a minimum of 5 weeks after their surgery.

Results

At the time of the otolaryngologic evaluation, all patients had been neutropenic (ANC: $<1,000/\text{mm}^3$) for 7 to 21 days (mean: 14), and all were febrile. Other localizing signs and symptoms were subtle (table 1). Physical findings at the initial examination are listed in table 2. Following the

Table 1. Initial signs and symptoms in the seven patients

Signs/symptoms	No. patients (%)
Fever	7 (100)
Neutropenia	7 (100)
Edema of the facial soft tissue	6 (86)
Nasal obstruction	4 (57)
Sinus pain	3 (43)
Nasal discharge	3 (43)

Table 2. Initial physical findings in the seven patients

Signs/symptoms	No. patients (%)
Facial or sinus tenderness	5 (71)
Crusting of the nasal mucosa	3 (43)
Necrotic or dusky nasal mucosa	3 (43)
Septal ulceration	3 (43)
Perforated nasal septum	1 (14)

initial examination, two patients progressed to unilateral ophthalmoplegia, loss of vision, and chemosis, and one patient developed ulceration of the soft palate.

Preoperative CT detected nondescript inflammation of the maxillary sinus in five patients, bone destruction in the nasal spine and septum in three, ethmoid sinus in three, and sphenoid sinus in one. None of the patients had frontal sinus involvement. Two patients eventually died of their fungal infection, and both of them had evidence of bone destruction and fungal extension into the facial soft tissue on the preoperative CT.

All patients had been treated with radical debridement and systemic amphotericin B. The length of time between the onset of their sinus symptoms and the initial surgical intervention ranged from 2 to 7 days (median: 4). The initial surgical procedure included nasal endoscopy and a complete debridement of necrotic material down to healthy, bleeding tissue in all patients. Maxillary antrostomy was performed on five patients, intranasal ethmoidectomy on two, sphenoidotomy and a Caldwell-Luc procedure with external ethmoidectomy on one, and orbital exenteration with a subtotal maxillectomy on one.

Preoperatively, patients had been transfused with platelets as necessary until their platelet count exceeded $50,000/\text{mm}^3$. Postoperatively, a nasal packing impregnated with mupirocin ointment was applied for 24 to 48 hours. There were no surgical complications. Six of the seven patients were re-examined under anesthesia and underwent a limited secondary debridement. The length of time between the first and second surgeries ranged from 5 to 12 days (median: 7.5).

Histology identified invasive *Aspergillus* in the specimens of six patients and invasive *Candida albicans* in one. Of the six patients who had *Aspergillus* spp, four had *A flavus*, one had *A fumigatus*, and one had *A clavatus*. Direct microscopy of the tissue in 10% potassium hydroxide identified the septate hyphae in all *Aspergillus* spp.

Currently, four patients are still alive and exhibit no evidence of fungal disease. Two patients died as a result of progression of the fungal infection and concomitant pulmonary involvement. The third fatality was the result of multisystem organ failure 2 years after the patient had undergone a subtotal maxillectomy and orbital exenteration; this patient had no evidence of recurrent aspergillosis at the time of death. All five long-term survivors experienced a recovery of their ANCs to more than 1,000/mm³.

Discussion

In 1980, McGill et al described four patients (three with acute leukemia and one with aplastic anemia) who had an aggressive form of paranasal aspergillosis, which they termed *fulminant, invasive fungal sinusitis*.⁷ Since then, other authors—including Berkow et al,⁸ Romett and Newman,⁹ Colman,¹⁰ and Choi et al¹¹—have reported on the aggressive and lethal nature of invasive fungal sinusitis (table 3). Although the lungs are the most common site of infection in the immunocompromised host, the paranasal sinuses and the brain are the next most common.¹²

Many immunosuppressed patients become febrile at some point during their illness, and it is important to consider invasive fungal sinusitis when evaluating them. Invasive fungal disease can progress rapidly, even in the face of aggressive medical and surgical treatment. *Aspergillus* was the only invasive organism reported in the other series (table 3),⁸⁻¹¹ and it was the most common organism seen in our study. Other authors have reported that mucormycosis, candidiasis, and other opportunistic fungal infections were the cause of invasive disease in immunocompromised patients.¹³ Despite the fact that invasive fungal disease is relatively rare, it is significant because of its rapidly progressive and lethal nature.¹⁴

Aspergillus is a ubiquitous, spore-forming fungus in the environment that can be inhaled and reach the mucous membranes of the nose and paranasal sinuses. Its exact

mechanisms are unclear, but the environmental load of the fungus and certain host conditions appear to be associated with its invasiveness and disease progression. Immunodeficiency and local tissue conditions, such as allergic mucosal hypertrophy and chronic bacterial sinusitis, can create an obstruction of the ostiomeatal unit and provide favorable conditions that allow the fungus to proliferate and invade.¹⁵ Fungal sinusitis is characterized by invasion of the organism into the vascular endothelium, which leads to subsequent tissue ischemia and necrosis. Fungal extension from the paranasal sinuses into adjacent structures such as the orbit and the intracranial cavity can occur with direct local extension or hematogenous spread.¹⁶ This is an ominous event.

Bone erosion is not always seen on CT, but it is not necessary for the development of intracranial or intraocular complications, because the fungus can extend along vascular channels. Ocular sequelae can include diplopia as a result of involvement of the extraocular muscles, as well as proptosis, chemosis, and loss of vision. Neurologic sequelae can include meningitis, brain abscess, and cavernous sinus thrombosis.¹⁷

The single most important risk factor for the development of invasive fungal sinusitis in the immunosuppressed patient is prolonged neutropenia.⁴ As we observed in this study, recovery of the ANC is of paramount importance for the patient's survival. A successful outcome is contingent on both the recovery of the immune function and early medical and surgical intervention. A neutropenic patient with a persistent fever of unknown origin despite broad-spectrum antibiotic therapy is at risk for fungal sinusitis. Such a patient should be placed on systemic amphotericin B and undergo an immediate otolaryngologic evaluation and CT scan of the paranasal sinuses. Local findings such as sinus tenderness, soft tissue swelling, and nasal discharge can focus the evaluation. Signs and symptoms of intracranial or orbital extension appear late and are an ominous finding.

Once the diagnosis of invasive fungal sinusitis is suspected and an otolaryngologic evaluation is obtained, anterior rhinoscopy can be performed to detect any necrosis or ulceration in the mucosa. CT is the best means to assess soft tissue extension and bony erosion, and it should be performed prior to surgery and again afterward

Table 3. Findings in previous reports of invasive paranasal sinus disease

Author(s)	Number patients	Number immunosuppressed	Number survivors	Causative organism
Berkow et al ⁸	5	5	0	<i>Aspergillus</i> spp
Romett and Newman ⁹	1	unknown	1	<i>Aspergillus</i> spp
Colman ¹⁰	5	5	1	<i>Aspergillus</i> spp
Choi et al ¹¹	3	3	3	<i>Aspergillus</i> spp

as a followup measure. Magnetic resonance imaging (MRI), with or without gadolinium, is better at defining intracranial extension, particularly cavernous sinus involvement.¹⁸ Zinreich et al reported that a decrease in signal intensity on T1- and a marked decrease in signal intensity on T2-weighted MRIs is characteristic of fungal disease.¹⁹ Although CT and MRI can suggest fungal disease and might alert the physician, a definitive diagnosis can be made only after histologic confirmation of the operative specimens. Examination under anesthesia by nasal endoscopy allows for the early detection and prompt debridement of invasive nasal fungal sinusitis and the institution of antifungal treatment. The choice of surgical approach depends on the site and extent of the involvement. The choice of options is guided by preoperative CT, and options vary considerably.

Although the combination of aggressive surgical debridement and amphotericin B therapy is the cornerstone of treatment, it is not without risk. Debridement carries the risk of bleeding in a thrombocytopenic population, as well as the risk of inadvertent damage to the orbit, lacri-

mal system, dura, and brain, which can lead to a loss of vision, epiphora, cerebrospinal fluid leakage, and meningitis. Patients who receive amphotericin B must be monitored closely because of the drug's dose-related renal toxicity.⁹ All approaches have inherent risks, but when dealing with such a fatal disease, aggressive therapy is justifiable and has been associated with better outcomes.²⁰

The most important factor in the long-term success is the recovery of the patient's immune system. Some authors have suggested administering a white blood cell transfusion to control infection in a patient with invasive fungal sinonasal disease, and there are some data that suggest its efficacy.²¹ Its use makes sense intuitively, given the central role that neutropenia plays in predisposing patients to invasive sinonasal fungal disease. Although the use of white blood cell transfusions in this setting has not been studied in a controlled fashion, it might hold promise if it is instituted early rather than as a last resort. Finally, the use of granulocyte colony-stimulating factor and other means of stimulating bone marrow recovery might also play a role in the future.

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