An Approach to Fulminant Invasive Fungal Rhinosinusitis in the Immunocompromised Host

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Objective: To examine the pathogenesis of fulminant invasive fungal rhinosinusitis to determine factors that may affect patient survival.

Methods: Retrospective chart review of 25 patients treated for invasive fungal rhinosinusitis over a 10-year period at an academic tertiary referral center. Evaluation of the medical and surgical records, radiographic studies, surgical pathology specimens, and culture results allowed for a multifactorial comparison between survivors and nonsurvivors. Survivors were patients who left the hospital with the invasive fungal disease stable or cured.

Results: Fungal invasion often occurs within the nasal cavity (92% of patients), most commonly at the middle turbinate (62% of patients receiving biopsy). Survivors had complete surgical resection more often than nonsurvivors (90% vs 0%), and were more likely to respond to granulocyte colony-stimulating factor than nonsurvivors (100% vs 0% of those treated).

Conclusions: Rigid nasal endoscopy with frozen section biopsy of suspicious nasal lesions and high-incidence areas (ie, middle turbinate) allows for the timely diagnosis of invasive fungal rhinosinusitis. Survival improves if the disease is limited to the nasal or sinus cavities, which may represent an earlier stage of disease. Favorable prognostic signs include the ability to achieve a complete surgical resection and a positive response to granulocyte colony-stimulating factor in the neutropenic patient.


Invasive fungal sinusitis is a well-described clinical entity characterized by the mucosal infiltration of mycotic organisms and angiocentric extension into orbital and intracranial structures. Invasive fungal disease of the nose is less frequently discussed especially as it relates to the pathogenesis of fungal sinusitis. A better understanding of the clinical and pathologic spectrum of invasive fungal disease in the sinonasal region may lend insight into the pathogenesis of this deadly disease. The population at risk for invasive fungal rhinosinusitis is growing with the increased prevalence of human immunodeficiency virus disease and the increased use of immunosuppressive therapies. Invasive fungal rhinosinusitis continues to be lethal in 50% to 80% of cases, which necessitates a better understanding of the pathogenesis of the disease to make a more timely diagnosis and institute a more effective treatment regimen.

This retrospective study of 25 patients with invasive fungal rhinosinusitis demonstrates progression from intranasal to sinus involvement with an associated increase in mortality. This finding supports the use of nasal endoscopic surveillance and directed mucosal biopsies for early diagnosis, which is correlated with a more favorable outcome. Based on the present findings, an algorithm is presented for managing patients at risk for invasive fungal rhinosinusitis.
MATERIALS AND METHODS

The medical and surgical records of 25 patients treated for invasive fungal rhinosinusitis at the Johns Hopkins Hospital, Baltimore, Md, from January 1, 1987, through June 30, 1997, were reviewed. Patients were selected from a computer search of autopsy reports, surgical pathology reports, and microbiology records of the past 10 years. Inclusion in the study required (1) histopathologic evidence of mucosal invasion by fungal organisms or (2) a destructive sinus or nasal lesion with a positive fungal culture. Fungal disease is determined to be invasive if histopathologic examination reveals (1) hyphal forms within the submucosa with or without angiocentric invasion and (2) tissue necrosis in the absence of a host inflammatory process. Of the 25 patients who met this criteria, 21 patients demonstrated invasive fungi on surgical pathology evaluation, while 4 patients had cultures of destructive lesions extending beyond the nasal cavity that yielded fungal organisms. Clinical information was obtained from a review of the hospital chart and electronic patient record and included discharge summaries, operative notes, radiologic reports, and laboratory and pathology reports. The anatomic distribution of invasive fungal disease was obtained from the (1) description of endoscopic findings, (2) histopathologic results of directed nasal biopsies, and (3) histopathologic findings in surgically resected specimens.

matologic deficiency (3 patients), and heavy systemic prednisone use in a patient with refractory asthma (1 patient). Three patients had more than 1 of the preceding disorders. Six of the 11 patients with hematologic malignant neoplasms had undergone bone marrow transplantation.

Prolonged steroid and antibiotic use was seen in this patient population. Thirteen patients (52%) had a course of prednisone-equivalent steroids of at least 2 weeks. All patients were receiving intravenous antibiotics at the time of diagnosis, and 20 (80%) were taking a multidrug (3 or more) regimen. Sixteen patients (64%) had been receiving intravenous antibiotics for more than 2 weeks.

The most common presenting symptoms included fever (16 [64%]), facial and periorbital pain and swelling (16 [64%]), nasal congestion and rhinorrhea (14 [56%]), and headache (13 [52%]). Less commonly, the patient presented with ophthalmologic complaints, including decreased visual acuity or ophthalmoplegia (7 [28%]). Many patients (22 [88%]) had 2 or more of these symptoms although 1 patient presented with fever alone, and (14 [56%]) had 3 or more of these symptoms.

Twenty-one of the 25 patients were evaluated with rigid nasal endoscopy. Mucosal abnormalities were most commonly noted on the middle turbinate (14 [67%]), followed by the septum (5 [24%]), the palate (4 [19%]), and the inferior turbinate (2 [9.5%]). Discoloration (16 [76%]) and crusts and/or granulation (11 [52%]) were more common than ulcerations (7 [33%]) (Figure 1).

The mucosal discoloration was inconsistent and was variously described as white or pale, gray, green, and black. Hematologic derangements were common at the time of diagnosis. Neutropenia, defined as a white blood cell count less than 0.50×10^9/L, was present in 14 (56%) patients including all of the patients with hematologic malignant neoplasms. The neutropenia was secondary to the use of cytotoxic chemotherapy with or without bone marrow transplantation. The median duration of neutropenia was 26 days with a range from 18 days to 6 months. Severe thrombocytopenia (platelet count <60×10^9/L) was present in 40% of patients. Two thirds of the patients were anemic (hematocrit <0.30), and of those patients, most (12 of 17) had a hematocrit below 0.27. Three of the 5 patients with AIDS had CD4 counts less than 0.05×10^9/L.

RADIOGRAPHIC AND PATHOLOGIC EVALUATION

The 25 patients in the study were all examined radiographically. Computed tomographic (CT) scan of the paranasal sinuses was the study of choice in 19 (76%) of the patients. One patient received magnetic resonance imaging (MRI) alone, while 5 received both MRI and CT scans. Evidence of invasion, such as erosion of bone or abscess beyond the confines of the sinonasal region, was noted in 11 (44%) of 25 patients (Figure 2). In the 5 patients who received both CT and MRI, 3 patients had additional findings on MRI that could not be visualized on CT, including visualization of inflammatory processes within the intracranial cavity.

The diagnosis of invasive fungal rhinosinusitis was confirmed by the histopathologic evaluation of biopsy specimens in the majority of patients (Figure 3). Invasive fungal organisms were observed in submucosal tissues in 84% (21/25) of patients. Histopathologic evidence of invasion was indeterminate in 3 patients, and no biopsy was performed in only 1 patient. These 4 patients were diagnosed as having invasive fungal rhinosinusitis when a culture or biopsy of a destructive nasal lesion yielded a fungal organism. Figure 4 is a schematic of the nasal cavity showing areas that underwent biopsy in the 21 patients with histologic evidence of dis-
ease. The figure includes the percentage of patients with mucosal invasion at a given site. The middle turbinate was almost 2 times more likely to have a positive biopsy than the next most common sites.

**THERAPEUTIC INTERVENTION**

Treatment of the patients consisted of a combination of antifungal drugs and surgical resection. Amphotericin B was the predominant antifungal chemotherapy in 21 (84%) of 25 patients. Sixteen patients (64%) received daily doses of 1 mg/kg or greater.

Surgical resection was performed in 24 (96%) of 25 patients. Local resection, which refers to transnasal endoscopic surgery, external ethmoidectomy, or Caldwell-Luc operation, was the only surgery performed in 16 patients (64%). Radical surgical resection, including medial maxillectomy, total maxillectomy with orbital exioneration, or craniofacial resection, was performed alone in 4 patients (16%). A combination of local resection followed by a more radical resection was performed in 4 patients (16%).

The operative report and postoperative notes were used to determine the completeness of the surgical resection. Of the 10 survivors, complete resection to viable, bleeding tissue margins was achieved in 9 patients. One of the survivors was clinically suspect for residual disease at the end of the surgical procedure. Ob-
new-onset anemia in November 1995, and an evalua-
tion, and radiologic findings.

vicious disease was left behind in 9 of 9 patients who died of the disease.

OUTCOMES

Patients were grouped according to outcome. The patients were classified as disease (ie, invasive fungal rhinosinusitis) survivors, dead of disease, or dead of other causes. Survivors were patients treated for invasive fungal rhinosinusitis who left the hospital with the disease cured or stable. Outpatient follow-up ranged from 0 to 24 months with a median follow-up of 8 months. In the present series of 25 patients, there were 10 disease survivors, 9 who died of disease, and 6 patients who died of other causes.

Survivors and nonsurvivors were compared with respect to the location of the disease at presentation (Table 1). Patients with disease limited to or primarily involving the nasal cavity had a higher incidence of survival. Two of the 9 survivors were noted to have had invasive fungal disease limited to the nasal cavity. Eight of 9 patients who died of disease had disease that extended to the skull base at the time of diagnosis. The response to treatment of different outcome groups was also examined (Table 2). All disease survivors who were treated with granulocyte colony–stimulating factor (GCSF) responded to therapy (5 of 5 patients) with an increase in white blood cell count of greater than 0.50 X 10^9/L, whereas all 4 nonsurvivors treated with the drug did not respond. The 10 survivors all underwent surgical resection; 9 of the 10 received local resection alone. Six of the 10 survivors required 2 procedures for complete resection. Patients who died of disease were much more likely to require radical debridement (7 of 15) than survivors (1 of 10). Residual disease was more likely after surgery in nonsurvivors, and was present in 9 of 9 patients who died of disease, and 3 of 6 who died of other causes. Only 1 of the 10 survivors was suspected of having residual disease following surgical resection.

CASE EXAMPLES

Case 1

A 30-year-old woman with a history of non-Hodgkin lymphoma in remission since 1994 presented with new-onset anemia in November 1995, and an evalua-
tion revealed acute myelogenous leukemia. In January 1996, she received a course of chemotherapy, followed by neutropenia of 3 weeks duration. While neutro-
epnic, she developed nasal congestion and fever of unknown origin and was prescribed broad-spectrum intravenous antibiotics including amphotericin B (1.5 mg/kg per day). Granulocyte colony–stimulating factor was administered without an increase in the white blood cell count. The patient experienced increasing right-sided facial pain and epiphora in the right eye. A CT scan of the paranasal sinuses demonstrated opacification of the right maxillary sinus and bilateral frontal, ethmoid, and sphenoid sinuses without bone erosion.

On preliminary bedside examination by the otolar-
yngology–head and neck surgery service, the patient was noted to have some right-sided facial edema and tenderness, and anterior rhinoscopy demonstrated hyperemic nasal mucosa with thick yellow discharge. The middle turbinate was not visualized. In the absence of the classic black or pale mucosal changes of fungal sinusitis, nasal decongestants and expanded anaerobic coverage were recommended. After several days of symptomatic improvement, the patient experienced increasing fever and right-sided facial pain. Rigid nasal endoscopy demonstrated a pale right middle turbinate that did not bleed when a biopsy was performed. Histopathologic study of the frozen section biopsy specimen revealed invasive fungal forms, and a culture of the specimen yielded Aspergillus flavus.

Following preoperative red blood cell and platelet transfusions, the patient was taken to the operating room where necrotic black eschar of the right lateral nasal wall was found and biopsy specimens of the septum, naso-
pharynx, and left nasal cavity demonstrated histologic evidence of invasive fungal disease. A right medial maxillary and radical nasal debridement was performed via a Weber-Ferguson approach. The surgical margins were positive for persistent disease. The patient died 6 days later of massive cerebral infarction believed to be secondary to invasive fungal disease.
Comment

The increase in the prevalence of invasive fungal rhinosinusitis is thought to be secondary to the increasing numbers of immunocompromised hosts. Medical advances have prolonged the survival of patients with AIDS, hematologic malignant disease, and type 1 diabetes mellitus, which has in turn increased the population at risk for developing invasive fungal rhinosinusitis. Although the present study covers a period of 10 years, 19 of the 25 cases have occurred during the last 3 years. In addition, there appears to be a change in the underlying cause of immunocompromise in our series, with a rise in the number of patients with hematologic malignant neoplasms and AIDS and a decrease in the number of patients with diabetes. The mortality rate of invasive fungal rhinosinusitis remains 50% to 80% by some estimates, underscoring the need for a better system of diagnosis and patient management.

The proper identification of the at-risk population is critical in making a timely diagnosis. The primary risk factor for invasive fungal rhinosinusitis is an immunocompromised state. Secondary predisposing factors identified in this study include prolonged steroid use and multiple (3 or more) intravenous antibiotics for periods greater than 2 weeks, which is in agreement with earlier studies.

A combination of 2 or more symptoms consisting of fever, nasal symptoms, facial pain or swelling, headache, and visual loss was the most common presentation of patients in this series. These findings are in agreement with Berlinger, who found that fever and one additional finding, such as sinus tenderness, facial edema, or rhinorrhea, was the usual presentation of invasive fungal rhinosinusitis. A combination of immunocompromised state and local symptoms should lead to a thorough rigid endoscopic nasal examination.

The most consistent physical finding in invasive fungal rhinosinusitis is a change in the appearance of the nasal mucosa on rigid nasal endoscopic examination, such as discoloration, granulation, or ulceration. The most common involved nasal structure with mucosal change seen on CT of 21 rigid endoscopic examinations. In addition, the middle turbinate was the most commonly involved nasal structure with mucosal change seen on CT scans of patients with invasive fungal rhinosinusitis.

Anterior rhinoscopy by speculum or otoscope, however, provides only a limited view of the middle turbinate and meatus. The patient described in case 1 appeared to have bacterial sinusitis and anterior rhinoscopy but was found to have pale necrotic nasal mucosa on a more thorough rigid endoscopic evaluation. The patient described in case 2 had a suggestive lesion discovered on rigid endoscopic examination, which allowed for early biopsy and diagnosis with timely intervention. Rigid nasal endoscopy, therefore, is believed to be essential in the examination of the high-risk patient, to note subtle visual changes in mucosal color or the presence of granulations or ulcerations. Additional features include decreased mucosal bleeding or tactile sensation. Endoscopic evaluation allows for directed biopsies of suggestive lesions or high-incidence areas (ie, the middle turbinate) in the clinic setting followed by permanent or frozen section histopathologic study or culture. Nasal biopsy should be preceded by correction of thrombocytopenia to a platelet count greater than 60 × 10^9/L and replacement of any needed coagulation factors. The threat of hemorrhage is further minimized by the use of cutting 2-mm cup forceps, which limits the size of the mucosal deficit, followed by silver nitrate cautery of the wound base. Absorbable gelatin sponge or cellulose packing may also be used. This approach would allow for an increased chance of diagnosing the disease at an earlier stage while it is confined to the nasal cavity, and is likely to have a positive impact on survival.

Computed tomography of the paranasal sinuses was the most commonly used imaging modality in this review. It is important to note that 3 patients had no evidence of significant sinusitis on CT, which stresses the observation that CT and MRI cannot take the place of careful intranasal examination and biopsy.

Wiatrak et al found that CT scans of patients with invasive fungal rhinosinusitis are nonspecific and do not correlate well with surgical and pathologic findings. The present study suggests that a CT scan, although not diagnostic of invasive fungal rhinosinusitis, does document the presence of sinusitis and defines bony architecture, and often provides evidence of invasive processes. In the 5 patients who...
had both CT and MRI scans, the MRI scan provided new information about the intracranial extent of disease in 3 patients. The ability of the CT scan to define bony architecture makes it the imaging study of choice in patients suspected of having invasive fungal sinonasal disease.\(^5\) The MRI scan may still have a role, especially in patients with evidence of intracranial involvement (stroke, seizure, and diplopia).

Once the diagnosis of invasive fungal sinonasal disease is established, treatment should be instituted immediately. Most authors agree that a combination of surgical débridement and high-dose amphotericin B gives the best chance for survival.\(^1\) Our series, of the 10 survivors underwent resection to clear bleeding margins. Some have argued that surgery for invasive fungal rhinosinusitis increases mortality among neutropenic patients or is at best nonefficacious.\(^6\) This viewpoint is based on the observation that neutropenic patients cannot be cured without resolution of the underlying neutropenia.\(^10\) Our study supports the conclusion that survival is ultimately dependent on bone marrow recovery. In particular, patients who respond to GCSF are more likely to have a favorable outcome. Two possible explanations for this observation include (1) the presence of a response to GCSF indicates a more favorable bone marrow functional status, or (2) the increase in white blood cell count resulting from GCSF plays an active role in disease recovery. The first explanation is supported by the tendency of GCSF responders to have more contained and resectable disease than GCSF nonresponders. Patients who recover bone marrow function, however, are still at risk of dying of the disease.\(^14\) Although the resolution of neutropenia is critical for survival, early aggressive surgical débridement slows the progression of the disease, allowing time for bone marrow recovery, and prevents disease progression following the resolution of neutropenia.

Most reports have found that high-dose (>1.5 mg/kg per day) amphotericin B is required for adequate control of invasive fungal rhinosinusitis.\(^6\) A full course of amphotericin B involves a total dose of 2 g or greater.\(^5\) Early use of amphotericin B has not been shown to be predictive of a better outcome. One report found an initial 85% response rate to amphotericin B; however, 61% of responders went on to die of invasive aspergillosis.\(^14\) Others doubt the efficacy of amphotericin B entirely.\(^8\) The use of amphotericin B does not provide a clear advantage in the present study. Amphotericin B may play a role in the prevention of systemic dissemination, although this is unclear at this time. Liposomal amphotericin B can be given at higher dosages than standard amphotericin B, but is less effective on a milligram-per-kilogram basis and is more expensive than standard amphotericin B.\(^8\) Its use should be reserved for patients with renal disease or patients whose kidneys cannot tolerate standard dosages of conventional amphotericin B.

An algorithm for identifying and treating patients with invasive fungal rhinosinusitis is presented in Figure 5. High-risk groups should be identified, rigid nasal endoscopy performed, and selected frozen section biopsies of the middle turbinate and suggestive areas performed. Once a diagnosis is established, surgery is used to achieve complete débridement, while amphotericin B may be of use in preventing fungemia. Attempts to recover bone marrow function with growth factors (ie, GCSF) may be helpful. Close follow-up with frequent rigid nasal endoscopy is necessary so that disease relapse or progression can be identified and treated early.

The pathogenesis of invasive fungal rhinosinusitis is still unclear. The present series suggests that in most cases invasive fungal disease begins within the nasal cavity and then invades deeper structures (sinuses, orbit, cranial vault) as the disease progresses. The middle turbinate is exposed to the greatest volume of nasal airflow and is the major nasal air filter, which may increase the likelihood of fungal seeding of this site. Mucosal disruption, damage to the mucociliary system, and changes in the normal mucosal flora are common at the middle turbinate and meatus secondary to bacterial sinusitis, allergy, drying secondary to oxygen via nasal cannula, and mechanical damage (nasogastric tube). Damage to the middle turbinate may allow fungi to initiate the invasive process. We, therefore, favor the term invasive fungal rhinosinusitis over invasive fungal sinusitis to emphasize the important role of the nasal cavity in the pathophysiology of the disease. The role of the nasal cavity and middle turbinate is emphasized to prevent overlooking invasive disease in a patient who has intranasal but no sinus disease (ie, negative CT).

Strategies aimed at the prevention of invasive fungal rhinosinusitis would be helpful since the incidence

Figure 5. Algorithm for the diagnosis and management of invasive fungal rhinosinusitis. AIDS indicates acquired immunodeficiency syndrome; WBC, white blood cell; CT, computed tomographic; and GCSF, granulocyte colony-stimulating factor.
of the disorder is expected to rise. A prospective trial of the role of rigid nasal endoscopy and radiography before and during chemotherapy or bone marrow transplantation would help in the development of strategies to prevent and more effectively manage cases of sinonasal fungal disease. Early evaluation with rigid endoscopy and frozen section biopsy of the middle turbinate should be strongly considered in the high-risk population. Complete surgical resection and the reversal of neutropenia appear to be critical elements in achieving a successful outcome in patients with invasive fungal disease.

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