Fungal Sinusitis in Healthy and Immunocompromised Individuals

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Clinical and microbiologic aspects of fungal sinusitis occurring in six patients are presented. Three of the six patients were immunosuppressed. Fatal disseminated fungal disease developed in two of those immunosuppressed. The three patients with normal immune function had fungal infections confined to the nasal sinuses. Aspergillus fumigatus and Aspergillus flavus were recovered from the immunosuppressed patients and Sporothrix schenckii, Alternaria species, and Pseudallescheria boydii were recovered from the immunocompetent patients. Surgical debridement was performed on all patients; however, anti-fungal therapy only was prescribed in patients who were at risk of progressive fungal disease. The microbiology laboratory aids in the diagnosis of fungal sinusitis by examining surgical biopsy material for fungal organisms and by culturing the material for recovery of the fungal pathogen. (Key words: Fungal sinusitis; Microscopic examination; Culture; Surgical debridement; Amphotericin B) Am J Clin Pathol 1984; 82: 597-601

FUNGAL INFECTION of the nasal sinuses may occur in immunocompromised and immune competent individuals. Disease in immune competent individuals usually is a localized infection of the nasal sinuses and can be managed successfully by surgical and medical treatment. However, in immunocompromised patients, disease usually results in disseminated fungal infection, which is refractory to any form of therapy.

Among the immunocompromised patient population, those who have leukemia or have renal or bone marrow transplant recipients are most frequently afflicted with fulminant fungal sinusitis. In these patients, Aspergillus fumigatus is the most common etiologic agent. Aspergillus flavus is less common, and Aspergillus niger, Aspergillus oryzae, and Aspergillus nidulans have been recovered only rarely. A. fumigatus is also the most common etiologic agent of fungal sinusitis in immune competent individuals. Other fungal species reported to cause disease in this patient group include A. flavus, A. niger, Sporothrix schenckii, Pseudallescheria boydii, Alternaria species, Paecilomyces species, Candida species, Basi- dobolus haptosporus, Stemphylium mucorsporidium, and Penicillium melinii. These fungi are common saprophytes, and infection is acquired by inhalation of fungal spores. These fungi may colonize the nasal sinuses without causing disease and are sometimes seen as laboratory contaminants. Therefore, interpretation of fungal cultures from material obtained from the nasal sinuses may be misleading and should be correlated with the clinical findings.

In this current review, six cases of fungal sinusitis are presented. They emphasize the importance of considering a fungal etiology of sinusitis in healthy and immunocompromised patients. The clinical and laboratory diagnosis and patient management of this disease are discussed.

Methods

This study is a retrospective analysis of six patients with fungal sinusitis at the Mayo Clinic from 1976 to 1982. To be included, patients must have fulfilled the following criteria: positive nasal sinus fungal cultures and biopsy specimens demonstrating invasion of the mucosa by fungal hyphae.

Microbiology

Necrotic and/or purulent material obtained during surgery was cultured for aerobic bacteria and fungi. Material was inoculated on a tryptic soy agar plate containing 5% sheep blood, chocolate agar plate, eosin-methylene blue agar plate, and colistin, nalidixic acid agar plate (CNA) for bacteria; and Sabouraud's dextrose agar, inhibitory mold agar, brain heart infusion agar with 10% sheep blood (BHI) with gentamicin and chloramphenicol, and BHI with gentamicin, chloramphenicol, and cycloheximide for fungi. Plates for aerobic bacterial culture were incubated at 35°C in a 3–5% CO₂ atmosphere. Plates for fungal culture were incubated at 30°C
in room air. The bacteria and fungi recovered were identified by standard methods.

Results

The six patients in this study were from 19 to 77 years old. Four were males and two were females (Table 1). Two patients had severe immunologic impairment (bone marrow transplantation and aplastic anemia), one patient received steroid therapy (15 mg/day prednisone), and three patients did not have any known immunologic impairment.

The diagnosis of fungal sinusitis was protracted in all patients. Diagnosis of the immunosuppressed patients (patients 1 and 2) was delayed up to one week due to intervening medical emergencies. The other four patients (patients 3–6) were diagnosed improperly initially as having either bacterial sinusitis (patients 3, 5, and 6) or Wegener’s granulomatosis (patient 4), thus delaying diagnosis 3 to 36 months.

Although the maxillary sinuses were involved most often (five of six patients), one patient had primary infection of the ethmoid sinus (patient 4) and one patient had infection involving both maxillary and ethmoid sinuses (patient 2). Sinus infection in the severely immunocompromised patients began in the maxillary sinus(es) and spread progressively to the adjacent sinuses and lungs. Infection in the immunocompetent individuals, which began in the maxillary sinus, remained confined.

Nasal congestion was the most common symptom beginning 1 week to 36 months before diagnosis. The initial symptom(s) in the severely immunosuppressed patients was nasal congestion, facial pain, and/or bloody nasal secretions. The immunocompetent and less severely compromised patients presented primarily with nasal congestion, and in descending occurrence unusual nasal secretions, facial pain, headache, and fever.

Conventional sinus roentgenograms demonstrated significant opacification of the involved sinuses in the six patients. Sinus tomograms were only required in two patients (patients 1 and 4) to better define nasal bone destruction.

Examination of the nasal sinuses during surgery showed either pus (patients 2 and 4) and/or necrotic cheese-like material (patients 1–6). Microscopic examination of histologic slides prepared from nasal mucosal biopsy material obtained from patients 1–6 showed invasion of the mucosa by fungal hyphae. The biopsy specimens obtained from patient 4 were negative for fungal elements on microscopic examination.

Fungi recovered from biopsy material included A. fumigatus (two cases), A. flavus (one case), S. schenckii (1 case), Alternaria (one case), and P. boydii (one case). Biopsy specimens obtained from the two immunosuppressed patients were positive for only Aspergillus species; however, both bacteria and fungi were recovered from biopsy specimens cultured from patients 3–6.

Two procedures were used for the surgical management of patients 1–6, a Caldwell-Luc antrostomy for debridement of necrotic material and a nasal-antral window to provide permanent drainage and ventilation. Patient 4 required more extensive surgical procedures and debridement due to the extensive bone destruction (Table 1). Surgical treatment and antibacterial therapy were sufficient for the recovery of patients 3, 5, and 6. Patient 4 required surgical debridement, antibacterial therapy and Amphotericin B therapy. Despite appropriate surgical and medical therapy, infection of the individuals who had severe immunologic impairment (Patients 1 and 2) proved fatal.

Discussion

Aspergillus species are reported as the major etiologic agents of fungal sinusitis, although many other fungi have been reported to cause disease. Alternaria species is the etiologic agent of one case of paranasal sinus infection in this report (patient 5). It previously has been associated with hypersensitivity pneumonitis but just recently has been demonstrated to be an opportunistic pathogen causing cutaneous disease, osteomyelitis, and cutaneous ulceration. 

Invasion by Alternaria in an apparently healthy host is rare; however, Shugar has reported a case of sinusitis and a destructive granulomatous process in the nasal cavity and ethmoid sinus. 

The clinical course was similar to aspergillosis of the paranasal sinuses that occurs as a chronic disease in a healthy individual.

We also report a case of S. schenckii paranasal sinus infection (patient 4). This fungus is more often the etiologic agent of a chronic infection characterized by a subcutaneous nodule or ulcer at the site of traumatic implantation. The lymphocutaneous form of infection is the most common clinical presentation; however, extracutaneous infections including pulmonary, articulart, osseus, and meningeal dissemination have been reported. 

A report of a diabetic with a primary ethmoid sinus lesion with secondary spread to the eye has been reported. 

Pseudallescheria boydii, most notable as an etiologic agent of mycetoma, has been associated with an increasing number of syndromes including the following: fungus ball, ototomycosis, keratitis, endophthalmitis, meningitis, prostatitis, joint infection, osteomyelitis, soft tissue infections, and disseminated disease. 

Like Aspergillus species, this fungus has a tropism for blood vessels and can appear similar to Aspergillus in histopathologic sections. Specific identification is necessary. Unlike Aspergillus and most other fungal species, P. boydii exhibits...
### Table 1. Data for Patients with Fungal Sinusitis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Underlying Disease and/or Immunosuppressive Therapy</th>
<th>Symptoms</th>
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<tr>
<td><strong>Patients with Severe Immunological Impairment</strong></td>
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<tr>
<td>1. 32-M</td>
<td>Acute lymphocytic leukemia, 8 months after bone marrow transplantation, graft vs. host disease, prednisone and immunuran X 6 months, WBC = 8,600/mm³</td>
<td>Nasal congestion, radiating right sided facial pain X 2 months</td>
<td>Opacified right maxillary sinus</td>
<td>Necrotic nasal mucosa containing septate fungal hyphae</td>
<td>Tissue from maxillary sinus: <em>Aspergillus fumigatus</em></td>
<td>Right Caldwell-Luc antrostomy; right nasal-antral window; amphotericin B</td>
<td>Erosion of posterior and lateral maxillary sinus and extension into infratemporal fossa; death within 1 month, no autopsy</td>
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<td>2. 19-F</td>
<td>Aplastic pancytopenia, fever (39.6°C), lymphadenopathy X 4 months, Prednisone X 2 weeks</td>
<td>Left sided nasal congestion, clear thick mucous discharge with blood X 1 week</td>
<td>Day 1—Opacified left maxillary sinus; Day 2—opacification both maxillary sinuses and ethmoids</td>
<td>Necrotic nasal mucosa, pus and light-colored cheesy material containing septate fungal hyphae</td>
<td>Washings: left side nasal: <em>Aspergillus flavus</em> Staphylococcus epidermidis, viridans Streptococcus, Left maxillary sinus: <em>Aspergillus flavus</em></td>
<td>Left antrostomy and washing, right antrostomy Antibiotics including amphotericin B</td>
<td>Death within days Invasive pulmonary aspergillosis</td>
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<td>3. 57-M</td>
<td>Prednisone (15 mg/day) X 18 months for undefined vasculitis</td>
<td>Nasal stuffiness and yellow discharge X 18 months, fever (38.5°C)</td>
<td>Opacified left maxillary sinus</td>
<td>Necrotic material containing septate fungal hyphae</td>
<td>Tissue from left maxillary sinus: <em>Aspergillus fumigatus</em> Staphylococcus aureus, Corynebacteria species, viridans Streptococcus, <em>Enterobacter aerogenes</em></td>
<td>Left Caldwell-Luc antrostomy, left nasal-antral window, nasal septal reconstruction, erythromycin</td>
<td>No recurrence X 2 years</td>
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| **Patients without Immunologic Impairment** | | | | | | | |
| 4. 68-M | COPD, moderately heavy alcohol consumption | Destructive lesion right cathal area, Right-sided nasal obstruction and painful facial swelling X 3 weeks | Sinus tomograms: Lesion in right ethmoid sinus with bone destruction | Necrosis of nasal mucosa and chronic inflammation Mucopyocele: chronic inflammation with focal granulomas | Tissue from ethmoid sinus: *Prop. acnes*, *Sporothrix schenckii* Tissue from cathal area skin: *Sporothrix schenckii* | Right lateral rhinotomy, ethmoidectomy, sphenoidotomy, Right naso-antral window Oxacillin Amphotericin B | No recurrence X 3 years |
| 5. 77-F | No concurrent disease | Left nasal congestion with blood tinged secretions X 6 months | Opacified left maxillary sinus | Brown cheese-like material with massive amounts of branching septate hyphae | Tissue from maxillary sinus: *Alternaria species*, Staphylococcus aureus | Erosion of sinus mucosa; death within days | No recurrence X 3 years |
| 6. 60 | No concurrent disease | Right nasal stuffiness and right sided headache X 3 years | Opacification right maxillary sinus | Greensish-yellow cheesy material, edematous mucosa containing septate fungal hyphae | Tissue from maxillary sinus: *Pseudallescheria boydii*, *Citrobacter freundii* | Right Caldwell-Luc antrostomy and naso-antral window, erythromycin | No recurrence X 2 years |
Invasive Aspergillus sinusitis only recently has been recognized as a clinical entity. Corticosteroids, cytotoxic drug therapy, and a variety of underlying systemic diseases may produce neutropenia, decreased phagocytic ability, and decreased cellular and humoral immune responses and predispose these immunologically compromised patients to fungal infections. Similar to the etiologic agents of zygomycosis, Aspergillus has a propensity to invade blood vessels, leading to thrombosis and ischemia. Immunocompromised patients may experience rapid dissemination to the lungs, liver, spleen, or brain. Prompt recognition of the etiologic agent, adequate surgery, and specific parenteral anti-fungal therapy is essential for survival in these patients.

In otherwise healthy and immunocompromised patients, immediate microscopic examination of surgical specimens is useful for rapidly detecting fungi. Examination of frozen sections of tissue by an experienced surgical pathologist can provide important information for the physician and the microbiologist. Potassium hydroxide preparations can be made to identify and observe fungal hyphae in nasal–sinus biopsy specimens. Two rapid staining methods, the modified methylene blue stain (Macher AM, Gerxh SM, Gill VJ. Abstr. Ann. Meet. 22nd Interscience Conf. on Antimicrob. Agents and Chemotherapy, 1982, No. 582) and Calcofluor white fluorochrome staining technique (Hageage GJ Jr, Harrington BJ. Abstr. Ann. Meet. 21st Interscience Conf. on Antimicrob. Agents and Chemotherapy. 1981, No. 269), have been developed and have been reported to increase the sensitivity of direct examination of specimens for fungi. The methylene blue stain is a 5-minute procedure that directly stains fungal hyphae or yeast cells a deep azure blue. Calcofluor white (Polyscience, Inc.) staining requires 15 minutes. The fluorochrome stain binds to R 1-4 and R 1-3 polysaccharides in the fungal cell wall, resulting in fluorescence when viewed on a microscope with an ultraviolet light source. A methenamine silver stain that requires approximately two hours of staining time also has been used to detect fungi in tissue. Although the time to diagnosis is perhaps not as crucial in the healthy patient, the aforementioned procedures aid in establishing the diagnosis expeditiously and lead to early therapy in the critically ill, immunocompromised patients.

Permanent histologic sections prepared from nasal biopsy material establishes tissue invasion and is required for the diagnosis of fungal sinusitis. Hematoxylin and eosin is used to detect inflammatory changes and stains most fungal hyphae. Periodic acid-Schiff and Gomori methenamine silver stains adequately stain most fungal hyphae; however, zygomycetes may not be seen because of poor staining characteristics.

The clinical diagnosis of fungal sinusitis begins with suspicion of an infection, a thorough examination of the head and neck region, including the nose and sinuses and sinus roentgenograms. If bone destruction or osteomyelitis is suspected, sinus tomograms are required. Any question of intracranial extension is investigated by CT scans. Pulmonary dissemination is investigated by chest roentgenograms and diagnosed by transbronchial biopsy or open lung biopsy.

Serology is not helpful for the diagnosis of fungal sinusitis in immunocompromised or immunocompetent patients. Antibodies may be present in patients with disseminated aspergillosis, but the usefulness of this test is questionable.

Surgical treatment for either immunocompromised or immunocompetent individuals consists of surgical debridement of devitalized tissue and drainage and ventilation of diseased sinuses. The exact nature of the surgical procedure is dependent on the location and extent of disease. Caldwell-Luc antrostomies, ethmoidectomies, and sphenoid sinusostomies are the procedures used most commonly. In patients with extensive bone involvement, a lateral rhinotomy may be necessary for wider exposure, access, and debridement. Reoperation and additional debridement procedures may be necessary, depending on the clinical response to combined surgical and medical therapy.

Amphotericin B is the suggested therapy for Aspergillus sinusitis and disseminated disease in the immunocompromised patient. No concensus exists concerning the total amount of amphotericin B or the duration of treatment in this patient group. Combination therapy with 5-fluorocytosine has been reported to have been of variable success in treating disseminated aspergillosis. It is thought that leukopenia and thrombocytopenia are more common in patients treated with combination therapy than amphotericin B or 5-fluorocytosine alone.

It generally is agreed that amphotericin B be used alone if the bone marrow is aplastic or normal marrow is being induced.

The use of anti-fungal therapy for the treatment of fungal sinusitis in the immunocompetent patient is a more complex issue. Jahrdsdoerfer and associates suggest that many patients with noninvasive sinusitis (specifically Aspergillus) have been cured only by surgical excision and ventilation, although this is not true of all patients. In our group of patients, the individuals with uncomplicated sinusitis (patients 3, 5, and 6) did not receive anti-fungal therapy after surgical debridement and ven-
tilation procedures were performed. None of the patients relapsed after surgical therapy.

Fungal sinusitis is debilitating in otherwise healthy patients, however, infection is usually fatal in immunocompromised patients. The progressive dissemination of infection in immunocompromised patients demands rapid diagnostic tests and aggressive therapy if these patients are to survive. Sinus roentgenograms and examination of the nose and sinuses raises suspicion of the infection and aids in determining appropriate surgical procedures. Direct examination of surgical biopsy material for fungal hyphae can provide rapid confirmatory diagnostic information to the physician.

References