Reviews

Forefront of Diagnosis and Treatment of Deep-steam Mycology in Korea- Rhinoorbitocerebral Zygomycosis

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Abstract

Mucor is a mold which exists in nature, but mucor infections of humans, even in immunocompromised hosts, are rare. Clinical manifestations of mucomycosis are nonspecific and diagnosis is based on microscopic examination and culture of biopsy specimens. Serologic test or molecular methods of speciation are used only as research tools.

We investigated medical records especially for underlying diseases, clinical findings, treatment, and prognosis of patients diagnosed with rhinocerebral mucormycosis retrospectively in the Asan Medical Center. The underlying diseases were diabetes mellitus in 8 patients, acute leukemia in 2, kidney transplantation in 2, and myelodysplastic syndrome in 1 of the total 13 patients. Six patients complained of nasal symptoms including stuffy nose, rhinorrhea, 5 patients complained of ophthalmic symptoms such as decreased visual acuity, diplopia, and ophthalmic pain and 2 of hard palate ulcer. The mortality was 23% (3/13; the two patients with kidney transplant, and one patient with acute leukemia).

In summary, mucomycosis should be considered in an uncontrolled DM and an immunocompromised host. The combined modality of early surgical debridement and antifungal agents was used for better treatment of rhinocerebral mucormycosis.

Key words : rhinocerebral, zygomycosis

INTRODUCTION

Zygomycosis (also known as mucomycosis) is an infection caused by saprophytic fungi of the class Zygomycetes, which are primarily opportunists that invade immunocompromised hosts and produce angioinvasive disease 1). Infections are acquired by inhalation or ingestion of Zygomycetes or by trauma-related exposure. Rhinocerebral and pulmonary manifestations are common types of infection 2).

The class Zygomycetes is subdivided into two orders, both containing human pathogens, the Mucorales and the Entomophthorales. Zygomycetes describes infections due to agents of the order Mucorales. Although the organisms of the order Entomophthorales cause specific syndromes distinct from those due to the Mucorales, they may also cause opportunistic pulmonary and disseminated infection similar to that of the latter. The zygomycetes are ubiquitous in soil and are commonly found in decaying organic matter such as fruit and bread 3). They grow rapidly on virtually any carbohydrate substrate and produce large numbers of hyphae, sporangiophores, and asexual sporangiospores that permit the organism to propagate into the environment. Many of the zygomycetes are able to grow at temperatures above 37°C. These properties of wide ecological distribution, rapid growth, and thermotolerance are of particular importance in developing human disease. Culture on Sabouraud dextrose agar yields large fluffy white, gray, or brownish colonies in 2 to 3 days that rapidly fill a medium container.

In the present study, our clinical experiences on rhinoorbitocerebral mucormycosis are described.

EPIDEMIOLOGY

Zygomycosis was first reported as a cause of human
disease in 1885\(^1\), and the organism now infects an
even broader and more heterogenous population. In
the past 20 years, there also has been an emergence of
this infection in the more classically defined immuno-
compromised risk groups, such as patients with hema-
tological malignancy, recipients of bone marrow trans-
plant, and recipients of a solid transplant\(^2\). However
Rodén et al. reported persons with no underlying con-
dition or diabetes represented >50% of all infected
patients\(^3\). Zygomycetes organisms are unique among
filamentous fungi because of their disproportionately
high capacity to cause devastating disease in persons
without underlying condition. Most commonly,
zygomycosis develops as a nosocomial infection affect-
ing a wide range of susceptible hosts\(^3\).

The patient group had comorbidities such as poorly
controlled diabetes mellitus, diabetic ketoacidosis,
 hematologic malignancy, solid organ transplantation,
and dysfunction of macrophages-monocytes (as seen
following prolonged corticosteroid use) (Table 1). Recep-
t of iron chelation therapy, profound neutropenia,
and disruption in mucosal membranes are also risk
factors for rhinoorbitocerebral mucormycosis\(^3\).

Deferoxamine mobilizes iron making it easily avail-
able for enhanced zygomycetes growth\(^3\). The drug
has been linked to the development of zygomycosis,
particularly in patients with chronic renal failure\(^4\).

Host defenses against zygomycetes include mono-
cyte/macrophages and neutrophils\(^5\), an increased risk
for developing zygomycosis appears to involve func-
tional and/or numerical deficiencies of these cells\(^6\).
Metabolic acidosis may be a key factor in predisposing
patients to zygomycosis, since it has been demonstrat-
ed that low serum pH diminished the phagocytic and
chemotactic ability of neutrophils\(^7\). In addition, inter-
actions between the transfer of iron molecules and fun-
gus have been described and may be important in
enhancing fungal growth by acidic serum\(^8\).

**CLINICAL MANIFESTATION**

Rhinoorbitocerebral disease is the most common
form of zygomycosis\(^9\). Also, this form of zygomycosis
is most often found in patients with diabetes mellitus,
particularly in the presence of acidosis, and in patients
with leukemia who have been neutropenic for long
periods and who have been receiving broad-spectrum
antibacterial drugs\(^10\). The infection originates in the
paranasal sinuses following inspiration of fungal spores
and may evolve rapidly extending to neighboring tis-
sue. The manifestations of the disease may reflect the
sequential involvement of the nose, sinus, eye, and
brain\(^10\). Rhinocerebral disease produces characteristic
clinical features consisting of low-grade fever, sinusitis,
unilateral facial swelling, black nasal or palatal eschar,
decreased vision, and ophthalmoplegia (Table 2)\(^11\).
Blackened eschar is an indicator of rapidly advancing,
invasive disease with a poor prognosis (Fig. 1)\(^11\).

Once established in the paranasal sinuses, the infec-
tion can easily spread to and enter an orbit via the
nasolacrimal duct and medial orbit\(^10\). Factors con-
tributing to the ease of spread include the thinness of
the lamina papyracea, congenital dehiscences often
present along the medial wall, and the perforation of
the medial wall by arteries and veins. Spreading to the
brain may occur via the orbital apex, orbital vessels, or
via the cribiform plate\(^11\). Cerebral abscess as a compli-
cation of zygomycosis involving the nose and eye can

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**Table 1. Ages and comorbidities of thirteen mucormycosis patients (A patient can have multiple underlying diseases)**

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled diabetes mellitus</td>
<td>8 patients (69%)</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>2 patients (15%)</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>2 patients (15%)</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>1 patient (8%)</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>1 patient (8%)</td>
</tr>
</tbody>
</table>

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**Table 2. Clinical presentation of thirteen rhinocerebral mucormycosis patients**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal obstruction, rhinorrhea, post nasal drip, sinusitis</td>
<td>6 patients (46%)</td>
</tr>
<tr>
<td>Eye symptoms</td>
<td>5 patients (38%)</td>
</tr>
<tr>
<td>Ophthalmic pain, diplopia, decrease of visual acuity</td>
<td>2 patients (15%)</td>
</tr>
</tbody>
</table>

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**Fig. 1. Blackened eschar on the face of a patient with rhinocerebral mucormycosis.**
also occur. Cavernous sinus and internal carotid artery thrombosis are additional complications that reflect the vascular tropism of the fungus.

**DIAGNOSIS**

Plain orbit or sinus radiography are frequently nonspecific. CT provides a sensitive indicator of the extent of orbital involvement. Some investigators favor the use of MRI, given the susceptibility of vascular and other soft tissue structures to fungal invasions (Fig. 2). Because of the rapidity of invasive infection, CT or MRI should be performed at frequent intervals to monitor disease extension and response therapy.

Diagnosis depends on demonstration of the organism in the tissue of a biopsy specimen. Swab of a discharge or abnormal tissue is not appropriate and often results in erroneous information. A fresh tissue preparation using 10% to 20% potassium hydroxide provides a rapid diagnosis. Microscopically, the fungus is usually easily identified in necrotic tissue on hematoxylin-eosin stained sections, appearing as large, non-septate hyphae that tend to branch at right angles. Special stain such as periodic acid-Schiff or Gomori methenamine silver is often helpful in identifying the hyphae (Fig. 3).

The predominant histologic findings are ischemia or hemorrhagic necrosis. The fungi have a predilection for internal elastic lamina of blood vessels; thus, arterial thrombosis ensues, and later, invasion of veins and lymphatics leads to further thrombosis, edema, and hemorrhagic necrosis.

**Differential diagnosis**

Infection with *Aspergillus* is most likely to be confused with the rhinocerebral zygomycosis. The only method of differentiating between the two diseases is by examination of tissue or culture of a biopsy specimen. Certain aggressive orbital tumors can produce some of the findings of rhinocerebral zygomycosis, but the rapid pace of zygomycosis, the presence of fever, and the evidence of necrosis all favor a fungal cause. Cavernous sinus thrombosis that is caused by extension of staphylococcal lesions of the face can resemble rhinocerebral zygomycosis.

**TREATMENT**

Antifungal therapy for zygomycosis should be considered an essential and equally important part of a
combined therapeutic approach also involving surgical debridement of all devitalized tissue and reversal of the underlying predisposing condition. Amphotericin B is the drug of choice of zygomycosis. It is highly protein bound (>90%) and poorly dialyzable. Approximately 66% of plasma concentrations have been detected in the aqueous humor. Concentrations in the cerebral spinal fluid seldom exceed 25% of those in the plasma. Amphotericin B should be administered promptly at full dosages typically ranging from 1 to 1.5 mg/kg/day, daily high dose therapy to the full therapeutic level is essential. It should be continued for as long as possible in order to control the infection and facilitate surgical debridement. Duration of therapy is not clearly defined but prolonged treatment until symptoms are resolved seems prudent. Lipid complex amphotericin B is a formulation designed to be less nephrotoxic than conventional amphotericin B. Because drugs complexed with lipid vehicles have a longer residence time in the vasculature, they are able to localize and reach greater concentrations in tissues with increased capillary permeability (i.e., infection and inflammation) compared with regions of normal tissue, which are essentially impermeable to lipid-complexed drugs. Azoles can not be recommended as first-line therapy for this condition. Recent in vitro studies of posaconazole suggest that patients with refractory zygomycosis may benefit from intervention with this second generation triazole[2]. The usage of posaconazole in treatment of zygomycosis should be considered investigational and conducted following an approved protocol. Extensive surgical debridement to remove necrotic tissue and establish sinus drainage is essential and multiple debridements are often necessary for cure; frozen sections have been shown to be useful[2]. Because the vaso-occlusive characteristic of zygomycosis diminishes the delivery of intravenous amphotericin B, irrigation and packing of the surgical site with amphotericin B solution (5 mg/100 ml sterile water) has been advocated to improve delivery to poorly perfused infected and/or necrotic tissue[2]. Hyperbaric oxygen has been used as an adjunct to aggressive surgical debridement, amphotericin B therapy, and control of any underlying predisposing conditions. Hyperbaric oxygen therapy for zygomycosis should consist of exposure to 100% oxygen for 90 minutes to 2 hours at pressures from 20 to 25 atmosphere with 1 or 2 exposures daily for a total of 40 treatments[2]. Reported toxicities of hyperbaric oxygen include teratogenicity and, rarely, pulmonary or central nervous system side effects[2]. Several reports using either G-CSF or GM-CSF as adjuvant therapy for zygomycosis have been published[2]. In general, these reports have demonstrated favorable outcomes. In vitro data on an enhancing fungicidal effect on murine macrophages by interferon-gamma has shown some clinical correlation[2]. However, despite the potential benefits, the use of these modalities as adjuvant therapy for zygomycosis is thus far investigational, and should be evaluated on an individual patient basis. The authors considered the better outcome would be based on

1. Management of the underlying predisposition
2. Aggressive surgical debridement
3. Antifungal therapy, with early initiation and high drug doses.

PREVENTION

There are neither proven regimens for prevention of zygomycosis nor a vaccination for the disease. Appropriate environmental control measures, careful metabolic control of the underlying condition, and judicious use of deferoxamine and corticosteroids are important factors in preventing zygomycosis. High-efficiency particulate filters (HEPA) used in hospital rooms for patients with profound immunosuppression have been shown to reduce the risks of aspergillosis and zygomycosis.

However, there are still a couple of issues to be solved in the future such as: comparison of the roles of the various antifungal agents – the treatment of choice is one aspect to be solved. The optimal duration of therapy for mucormycosis is not known precisely. Epidemiological changes in the case of voriconazole prophylaxis in hemopoietic stem cell transplantation has been reported.

In summary, mucormycosis should be considered in an uncontrolled DM, and in an immunocompromised host such as organ transplantation and hematologic malignancy.

The combined modality of early surgical debridement and antifungal agents should be used for better treatment of rhinocerebral mucormycosis.

References

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