Rhinoorbital mucormycosis secondary to Rhizopus oryzae: A case report and literature review

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Abstract
Mucormycosis is a form of fulminant invasive fungal infection of the sinonasal tract that often extends to the orbit, brain, palate, and skin. It is caused by members of the order Mucorales, and it is considered to be the most fatal fungal infection known to man because it is rapidly disseminated by the blood vessels. It is most commonly associated with diabetic ketoacidosis, hematologic malignancies, acquired immunodeficiency syndrome, and immunosuppressive therapy. This rare opportunistic infection exists in many forms, the most common of which is rhinocerebral mucormycosis. Treatment includes aggressive surgical debridement of the necrotic tissue combined with systemic antifungal therapy. In this case report, we describe the successful management of rhinoorbital mucormycosis, a subtype of the rhinocerebral variety, secondary to Rhizopus oryzae that developed in a patient with lymphoma. We review the diagnostic work-up and discuss the literature with respect to the presentation, pathophysiology, management, and outcome of the disease.

Introduction
At least four forms of fungal infection of the sinonasal tract have been recognized. Two are noninvasive: allergic fungal rhinosinusitis and fungus ball (mycetoma). The other two are tissue-invasive: chronic invasive (indolent) fungal sinusitis and acute invasive (fulminant) fungal sinusitis.

One form of acute invasive sinusitis caused by fungi of the order Mucorales is known as mucormycosis.1 Mucormycosis is a rapidly progressive infection that usually develops in patients who are metabolically or immunologically compromised. Left untreated, it is rapidly fatal.

Mucormycosis classically involves the nasal mucosa with invasion of the sinuses, orbit, and brain.2 The causative organisms are members of the family Mucoraceae, which belongs to the order Mucorales of the class Zygomycetes. They are saprophytes commonly found in soil, decomposed vegetation, and in the healthy human respiratory and digestive tracts, and their distribution is worldwide.3

Mucormycosis can manifest as one of six different clinical syndromes; it appears in rhinocerebral, pulmonary, gastrointestinal, central nervous system, subcutaneous, and disseminated forms. Rhinocerebral mucormycosis (RCM) is the most common of these forms, and it is subdivided into three subtypes: rhinomaxillary, rhinoorbital, and rhinoorbitocerebral.4,5 The classification of RCM has no effect on patient care, however, because the mainstays of therapy are similar regardless of the site of extension. The keys to management are reversal of the underlying cause of immunocompromise, be it diabetic ketoacidosis or neutropenia, and appropriate antifungal therapy and surgical debridement of the involved tissues.3,7

Patients usually present with headache, rhinorrhea, or epistaxis along with black nasal or oral masses. Anesthesia precedes the development of the characteristic tissue necrosis.8 Progression can lead to orbital cellulitis, orbital apex syndrome, cavernous sinus thrombosis, and eventually fatal involvement of the central nervous system. The diagnosis is made histologically because it is invasion and tissue reaction rather than the mere presence of such ubiquitous fungi that characterizes the disease. Culture is used to identify the specific species.4

In this article, we describe a classic presentation of rhinoorbital mucormycosis. This case illustrates the importance of maintaining a high index of suspicion in making an early diagnosis.

Case report
A 51-year-old man presented to the hematology/oncology unit with fever and generalized lymphadenopathy of 1 month’s duration. He had been diagnosed with non-Hodgkin’s lymphoma that had transformed into acute
lymphoblastic leukemia, for which he was placed on a chemotherapeutic regimen. After 1 week of chemotherapy, the patient developed severe neutropenia with fever, mucositis, and generalized lassitude, which necessitated intravenous broad-spectrum antibiotic therapy as well as empiric antifungal treatment with fluconazole.

After a few days of this treatment in the medical ward, the patient began to exhibit recurrent mild left-sided nasal bleeding, left facial edema, excessive lacrimation from the left eye, and periorbital swelling. An ophthalmologist who was consulted noticed mild proptosis with edematous, congested conjunctiva and ophthalmoplegia; however, the eye fundus and vision were normal. A preliminary diagnosis of orbital cellulitis was made, and urgent computed tomography (CT) was requested. CT showed partial opacification of the left maxillary, ethmoid, and frontal sinuses with nasal mucosal swelling and an obvious extension of the inflammatory process to the inferomedial orbital wall, which displaced the globe anterolaterally (figure 1). But no clear collection or bony erosion was noticed, and the brain was intact. Further examination by an otolaryngologist revealed that the most striking feature of this disease was the presence of black necrotic tissue (eschar) in the left nasal cavity and a patchy black discoloration of the hard palate in two areas, each 5 mm in diameter, opposite the molars (figure 2). No ulceration was evident.

Within 24 hours, the patient underwent urgent endoscopic debridement of the eschar on the lateral nasal wall under local anesthesia. Debridement spared the viable nasal and sinus mucosa, which was congested and edematous. The orbit was not penetrated. The removed material was sent for fungal culture and histopathologic study (figure 3). Both studies confirmed the diagnosis of a fungal infection consistent with mucormycosis.

The next day, intravenous amphotericin B at 1.5 mg/kg/ day was started along with saline nasal irrigation. Within a few days, the patient’s fever, orbital cellulitis, proptosis, and palatal necrosis had almost resolved. Treatment was continued for 6 weeks followed by further courses of chemotherapy for the underlying lymphoma. At 24 weeks following the last antifungal treatment, the patient exhibited no evidence of further infection.

**Fungal culture.** Processing of the nasal specimen for mycology was carried out in the manner described by Taj-Aldeen et al.⁹ The necrotic tissue specimen isolated from the nose was examined for evidence of fungal invasion. The tissue was cut into small pieces in sterilized saline and then ground for 30 seconds in a sealed plastic bag placed in a Stomacher Lab Blender (model No. 80). A drop of the homogenate containing the small pieces of tissue was viewed in lactophenol cotton blue and in a 30% KOH solution and visualized under light microscopy at a magnification of 400. Branched, nonseptate, broad hyphae were evident in this preparation. The remainder of the homogenate was cultured onto two sets of three media: Sabouraud dextrose agar (SDA) plus 40 U/ml of streptomycin and 20 U/ml of penicillin (SDA + SP), SDA without antibiotics, and a brain-heart infusion plus 40 U/ml of streptomycin and 20 U/ml of penicillin. One set of plates was incubated at room temperature and the other at 37°C.

Fungal colonies appeared in 2 days. Examination of the fungus revealed a pure growth of *Rhizopus oryzae* Went and Prinsen Geerlings. The fungus was further subcultured on SDA + SP slants and stored in screw-capped tubes. The identification of *R oryzae* was confirmed by the Centraalbureau voor Schimmelcultures Fungal Biodiversity Center in Utrecht, The Netherlands. All investigations were performed under safety conditions (class II) in order to
minimize contamination with airborne germs. 

**Histopathology.** In addition to the routine hematoxylin and eosin (H&E) staining, the tissue sections were stained for fungal elements. Two histologic stains—periodic acid-Schiff (PAS) and Grocott-Gomori methenamine-silver stains—were used to visualize the tissue and the fungal pathogen. A careful microscopic examination of the debrided nasal mucosa on PAS staining demonstrated widespread tissue necrosis that was heavily infiltrated by broad, ribbon-like, nonseptate or barely septate hyphae, which were haphazardly branched or branched at right angles (figure 4, A). Histology of the tissue stained by Grocott-Gomori methenamine-silver revealed that the fungal hyphae had invaded the blood vessels, a characteristic feature of mucormycosis (figure 4, B).

**Discussion**
Mucormycosis has certainly earned its designation as the most acutely fatal fungal infection known to man. Mucormycosis is also known as *zygomycosis*, *hyphomycosis*, *phycomycosis*, and *fulminant fungal sinusitis*. The infection can involve the lungs, central nervous system, gastrointestinal tract, and skin, but it is probably best known for its rhinocerebral presentation, which usually originates in the nose and sinuses and eventually extends to the orbit and brain.11 Upper airway mucormycosis was first described in 1885 by Paltauf, who called it *mycosis mucorina*.12 In 1943, Gregory et al reported the more typical findings of advanced RCM in 3 patients with fatal diabetic ketoacidosis.13 Cure of the disease was first reported in 1955 by Harris.14 Mucormycosis refers to any fungal infection of the order Mucorales. Most pathogenic species are members of the family Mucoraceae, which includes the genera *Absidia*, *Mucor*, *Rhizomucor*, and *Rhizopus*. *R. oryzae* is the predominant pathogen, accounting for 60% of all forms of mucormycosis and 90% of all cases of RCM.10,15 Assessment of the exact causative species is limited by the lack of fungal culture information in most of the reported cases.2-7,16 Regardless of the causative agent, the clinical presentation and management are the same. Mycologic evaluation of the infected tissue specimen in our patient revealed the growth of *R. oryzae*. Although the responsible fungus...
can be isolated in the nose of healthy subjects, it can turn pathogenic in patients with immunologic or metabolic compromise. Among the recognizable risk factors for the development of RCM are poorly controlled diabetes, hematologic malignancies, acquired immunodeficiency syndrome, severe burns, renal diseases, malnutrition, iatrogenic immunosuppression after organ transplantation, and deferoxamine therapy. Few cases have been reported in patients who did not have a predisposing factor. At least two factors favored the diagnosis of RCM in our patient: hematologic malignancy in relapse and chemotherapy.

RCM begins with colonization of the nasal mucosa by airborne spores. In normal hosts, a phagocytic response to colonization prevents infection. In immunocompromised hosts, on the other hand, the response is suboptimal and germination ensues. Mucorales hyphae have a predilection for growth into arteries and the lymphatic system. These fungi also invade the nerves, fatty tissues, and bones; muscles are usually spared. Angioinvasion by the hyphae produces a fibrin reaction and the development of “mucor thrombi,” which occlude the arteries and lead to ischemia, infarction, and consequent formation of the black necrotic eschar of the skin and mucosa that is characteristic of RCM. Vascular occlusion prevents systemic antifungal agents from reaching their targets, and ischemia favors the development of acidotic tissue, which is ideal for fungal growth. The infection spreads rapidly to adjacent sinuses and the orbit and continues into the cranium via the ethmoid bone or orbital vessels. In our patient, the orbital manifestation occurred at almost the same time as did the nasal symptoms, yet the patient did not experience intracranial spread; hence, “rhinoorbital” mucormycosis was the most acceptable terminology.

Fever is the most common early symptom (44% of cases), followed by nasal ulceration or necrosis, periorbital or facial swelling, and decreased vision, each of which occurs in approximately 33% of cases. Ultimately, 80% of patients develop a necrotic lesion on either the nasal or oral mucosa. In addition to proptosis, our patient developed all of these signs and symptoms at about the same time. Other less frequent features include facial pain or numbness, nasal congestion or discharge, headache, ophthalmoplegia, anesthesia over the cheek, and cranial polyneuropathy, which may be consistent with orbital apex syndrome.

When the clinical picture includes the presence of sinusitis with black discoloration in the nose and palate in addition to a predisposing factor, a diagnosis of RCM should be highly suspected. Even so, a tissue biopsy is necessary to confirm the diagnosis. Invasive hyphae can be seen as ribbon-like, 10- to 20-microns-wide, haphazardly branched organisms with little or no septation. The fungus can be seen on H&E, PAS, and Grocott-Gomori methenamine-silver staining, and it is easily differentiated from *Aspergillus* organisms, which have a thinner wall, characteristic regular septation, and brush-like branching. In our patient, PAS and Grocott-Gomori methenamine-silver staining readily demonstrated the fungus.

Blood vessel invasion with thrombosis is a peculiar feature of RCM, and it contributes to its necrotic, ischemic appearance. Inflammatory response is variable and depends on the host’s immune status. Edema and necrosis with accumulation of neutrophils, plasma cells, and giant cells are usually seen. Direct nasal smear examination and culture for fungus help to identify the specific species (e.g., *R. oryzae*), but a lack of fungal growth does not exclude the disease.

Radiographic findings are helpful in assessing the different stages of the disease rather than in making a definitive diagnosis because the radiographic features may be indistinguishable from those of simple rhinosinusitis. In fact, during the early stages of RCM, imaging features may even be normal. It is only late in the progression of the disease that bony erosion will appear. In our patient, various degrees of mucosal thickening within the nose and sinuses were noticeable and the appearance of orbital extension was similar to that seen in bacterial orbital cellulitis, yet the bony framework was intact.

The treatment of RCM involves a combination of surgical and medical modalities plus correction of the underlying medical problem if possible. The timing of surgery is very crucial; surgery should be instituted without delay once the condition is diagnosed. Several surgical procedures have been described in the literature. They range from the simple to the complex—debridement of the necrotic mucosa; Caldwell-Luc surgery; medial maxillectomy, ethmoidectomy, and sphenoidotomy; and radical maxillectomy with orbital exenteration. Both endoscopic and open approaches have been described, in both single and multiple stages.

The standard medical therapy for RCM is amphotericin B in a dose of 1.0 to 1.5 mg/kg/day for a period of several weeks to several months, depending on the clinical response and the degree of the drug’s side effects, especially nephrotoxicity. Less toxic forms of amphotericin B—such as liposomal amphotericin B, colloidal dispersion amphotericin B, and amphotericin B lipid complex—may be more safe. In our patient, early debridement of the eschar followed by intravenous amphotericin B within 24 hours appeared to be very effective in controlling RCM, while chemotherapy simultaneously controlled the lymphoma. Other promising therapeutic modalities worth mention include hyperbaric oxygen therapy and nasally nebulized amphotericin B.

The prognosis of RCM appears to depend primarily on two factors: early diagnosis and resolution of the predisposing condition. Survival has been positively correlated with the time of diagnosis and initiation of treatment.
References