Fatal Attraction! Fungus and Man

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Abstract
Mucormycosis is a rapidly progressive disease with an acute course, and represents a classic nosocomial condition. The prognosis is usually poor, with high mortality rates that are influenced by the timeliness of diagnosis and, above all, by the underlying status of the patient. This fungal infection commonly occurs in diabetics, immunocompromised hosts, patients with leukemia, lymphoma, multiple myeloma, septicemia, hepatitis, cirrhosis, or renal failure, as well as patients receiving chemotherapy or steroids. Intravenous drug abusers are also at risk. Early detection and treatment are key elements for patient survival. This article describes a case of mucormycosis affecting the palate in an elderly patient with uncontrolled diabetes mellitus.

Introduction
Mucormycosis is an uncommon infection caused by saprophytic fungi of the Zygomycetes class, which comprises the orders Mucorales and Entomophthorales. This rare, opportunistic fungal infection shows a rapidly progressive and fulminant course, often with fatal outcome (1, 2). In 1800, Platauf described zygomycetes as pathogenic organisms causing disseminated disease in cancer patients. Members of the order Mucorales have most often been implicated as pathogens in human disease and include the genera Rhizopus, Mucor, Rhizomucor, Absidia, Apophysomyces, Saksenaea, Cunninghamella, Syncephalastrum and Corinomyces (3).

Rhinocerebral mucormycosis is the most recognized form of this disease, due to its severity, and oral manifestations are usually the first clinical signs (4). This invasive, opportunistic fungal infection is usually seen in immunocompromised patients, and particularly in the setting of diabetes or immune deficiency. Colonization of the nasal mucosa is assumed to involve inhalation of spores, allowing the fungus to spread via the paranasal sinuses into the palate, pharynx, and orbits, producing facial and orbital pain, paranasal sinusitis, sloughing of the hard palate, orbital cellulitis, ophthalmoplegia, proptosis and loss of vision. Fungal hyphae can invade the blood vessels and destroy cranial nerves.

Case Report
A 65-year-old man living in a farming community reported to the Department of Oral Medicine and Radio-diagnosis complaining of an 8-month history of inability to eat from the right side of the mouth. Medical history included dental intervention (incision and drainage) for a swelling on the right middle-third of the face 6 months earlier by a general medical practitioner, following which he lost his upper teeth spontaneously during the previous months. He was not aware of any investigative procedures or medications prescribed following his first dental visit. At the time of presentation, the patient was asymptomatic. He denied experiencing fevers, chills, rhinorrhea, sore throat, or visual
disturbances, and had no complaints of nausea, vomiting or diarrhea. The patient was unaware of his underlying medical condition and therefore his past medical history was non contributory.

General physical examination revealed a blood pressure of 140/100 mmHg, and other vital signs were normal. The patient remained conscious and cooperative throughout the examination. On extra-oral examination, solitary submandibular lymph nodes were palpable bilaterally, but were non-tender and freely mobile. A solitary fistula measuring approximately 2.0 × 2.5 cm in size was present on the right middle one third of the face, 2 cm below the right lower eyelid and above the zygoma. The fistula was asymptomatic and presented with a suppurating cavity (Fig. 1).

Intraoral examination revealed the denuded palate and the remaining buccal and palatal mucosa presented with slough, food debris and plaque. The mucosa of the posterior aspect of the maxilla was bulbous and enlarged, with rolled-out margins. The buccal cortical plates were completely destroyed/resorbed in the right posterior maxilla, showing evidence of communication with the extraoral fistula. The alveoli were devoid of teeth from the maxillary right second molar to the maxillary left second molar region. On palpation, the exposed palatal bone and alveoli were non-tender and mobile with scrapable, necrotic bone (Fig. 2).

The mandibular arch revealed a full complement of teeth covered with debris and calculus. Breach in the continuity of the epithelium were apparent at bilateral commissures of the mouth.

A provisional diagnosis of deep fungal infection was made based on the history and clinical presentation. Differential diagnoses of candidal or aspergillosis infections, rhinocerebral mucormycosis, and osteomyelitis were considered. The patient was assessed for predisposing factors, presenting signs and symptoms, number and sites of surgical debridement, and the possible outcome.

Radiographic investigation comprising both conventional methods such as occlusal radiographs, orthopantomography, and paranasal sinus (PNS) views and 3 dimensional-computed tomography (3D-CT) was performed. The PNS view demonstrated destruction of the lateral wall and roof of the right maxillary antrum and perforation of the palate inferiorly (Fig. 3). 3D-CT comprising both axial and cross-sectional views of the maxilla and paranasal sinuses demonstrated sequestrated bone in the hard palate and maxillary region (Fig. 4). Irregular, asymmetrical, dense mucosal thickening was apparent in the right maxillary sinus with no evidence of intracranial involvement, although
the infraorbital floor on the right side was involved. Hematological investigation revealed Hemoglobin A1c level was 7.2%, random blood sugar level was 249 mg/dl and urine tested for ketone bodies was negative. Fasting blood sugar level the next day was 166 mg/dl. Routine serological investigations for human immunodeficiency virus antibody test yielded negative results, ruling out an immunocompromised state. The unknown diabetic status of the patient was brought under control, as it is one of the most important factors in deciding the prognosis. After obtaining consent from the patient and his physician, incisional biopsy and smear from the fragile alveolus and palatal mucosa was performed. Histopathological examination of a bone biopsy specimen using hematoxylin and eosin and Grocott methenamine silver stain showed both filamentous and budding non-septate and ribbon-like fungal hyphae with right- or obtuse-angle branching in fragments of necrotic tissue (Fig. 5). A definitive diagnosis of zygomycosis was established.
Immediate surgical management with adequate diabetic control was considered the best treatment option for this patient. He was placed on antifungal therapy with intravenous liposomal amphotericin B at a dose of 1 mg/kg/day (75 mg/day) and his renal function was constantly monitored. Partial maxillectomy (Fig. 6) and reconstruction of the orbital floor with a free flap from temporalis muscle was performed. A maxillary post-surgical obturator was fabricated to facilitate food intake. The patient was discharged with follow-up instructions. Further maxillofacial reconstruction and rehabilitation was planned, but the patient did not survive 6 months postoperatively. The cause of death could not be ascertained, since no post-mortem examination was performed.

Discussion

Mucormycosis is the third-most important invasive mycosis after candidiasis and aspergillosis, and is caused by fungi of the class Zygomycetes. The most important species based on frequency is *Rhizopus arrhizus* (oryzae). The incidence of mucormycosis is approximately 1.7 cases per 1,000,000 inhabitants per year (6). The main risk-factors for this pathology involve an immune compromised state, such as from hematological malignancy, bone marrow or peripheral blood stem cell transplantation, neutropenia, solid-organ transplantation, ketoacidosis, iatrogenic immunosuppression, use of corticosteroids and deferoxamine therapy for iron overload that may predispose patients to fungal infection. Other potential factors include disruption of mucocutaneous barriers by catheters or other devices, exposure to bandages contaminated by the fungi, or an atypical presentation of fulminant invasive non-identified zygomycetes following the use of unsterile instruments in the oral cavity. Mucormycosis in immunocompetent hosts is rare, and is often related to trauma (7-12). Mucorales invade deep tissues via inhalation of airborne spores, percutaneous inoculation, or ingestion. Colonization occurs in a high number of patients without causing invasion (8).

Mucormycosis manifests most commonly in the sinuses (39%), lungs (24%), skin (19%), brain (9%), and gastrointestinal tract (7%), in the form of disseminated disease (6%), and at other sites (6%) (6-9,11). With the exception of rhinocerebral and cutaneous mucormycosis, clinical diagnosis of mucormycosis is difficult, and often made at a late stage of the disease or post-mortem. Confirmation of the clinical form requires a combination of symptoms compatible with histological invasion of tissues. Histological examination reveals that both mononuclear and polymorphonuclear phagocytes in normal hosts kill mucorales through the generation of oxidative metabolites and defensins, which are cationic peptides (Table 1) (8,12). Clinical evidence demonstrates that these phagocytes represent the major host defense mechanism against mucormycosis (8).

Amphotericin B represents the first-choice pharmacotherapy (6). Vascular thrombosis may prevent systemic medication from reaching the fungus in necrotic tissue, so the importance of surgical debridement has been emphasized and is seen as responsible for the survival of 50% of

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<tr>
<th>Increased risk of mucormycosis in:</th>
<th>Reasons</th>
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<tr>
<td>Hyperglycemia</td>
<td>Impairs the ability of phagocytes to move toward and kill the organisms by both oxidative and non-oxidative mechanisms e.g: Severely immunocompromised neutropenic patients and those with phagocyte dysfunction</td>
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<tr>
<td>Ketoacidosis</td>
<td>Decreases movement of phagocytes towards the source of infection and their capacity for lysis by oxidative and non-oxidative mechanisms and also by the release of iron bound to protein.</td>
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<td>Patients treated with deferoxamine</td>
<td><em>Mucorales</em> uses this chelant as a siderophore to obtain more iron.</td>
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<td>Following traumatic inoculation</td>
<td>If inoculation is contaminated with water and soil or dental procedures in the oral and maxillofacial region are inadvertently contaminated.</td>
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patients by preventing spread of the disease to the central nervous system, as in this case. Small focal lesions can often be surgically excised before progressing to involve critical structures or disseminate (8).

Rehabilitation of a patient with oro-antral/oro-nasal communications requiring closure can be achieved surgically using free flaps or by constructing a prosthetic appliance (4).

Newer therapeutic modalities include use of hyperbaric oxygen, cytokines such as gamma interferons and granulocyte macrophage-stimulating factor. (6) Long-term Posaconazole has recently proven beneficial in diabetic patients with rhinocerebral mucormycosis (10).

Conclusion

Cases of mucormycosis in a diabetic patient are rare and may provide a diagnostic and therapeutic dilemma for clinicians unfamiliar with the clinical presentation. The rapidly progressive nature of the pathology can prove fatal. This geriatric patient’s medical and oral health issues were completely ignored. The cure and care of such patients depends on thorough medical examination, early diagnosis, and reversal of predisposing conditions, followed by systemic antifungal therapy and immediate control of underlying disease processes in order to combat this disease.

References