Management and outcomes of three cases of rhinocerebral mucormycosis

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Mucormycosis is a rare opportunistic infection caused by fungi belonging to Mucorales order. The infection usually starts in the middle or inferior nasal meatus and then spreads to the paranasal sinuses and the orbit. Then it reaches the brain through the ethmoid and the orbit apex and can lead to lethargy, paralysis, and death. The majority of cases of rhinocerebral mucormycosis are diagnosed in patients with immunologic and metabolic disorders. Early diagnosis is fundamental, and so is medical therapy with amphotericin B along with surgical toilet of the compromised tissues. This article presents and discusses the management of 3 cases of rhinocerebral mucormycosis with different onsets, progressions, and outcomes. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:e69-e74)

Mucormycosis is a rare opportunistic infection caused by fungi belonging to the Mucorales order and the Mucoraceae family, which also includes Zygomyces, Absidia, Mucor, Rhizomucor, Rhizopus, Cunninghamella, and more rarely Apophysomyces and Saksenaea.1

These are usually saprophytic organisms found in nasal, paranasal, and oral mucosae and can be isolated from decaying vegetation.2 Mucormycosis was first described by Paultauf in 1885,1,3 and in 2005 Roden et al. reviewed 929 cases of zygomycosis reported in the international literature.4

The infection usually starts in the middle or inferior nasal meatus and then spreads to the paranasal sinuses and the orbit. Then it reaches the brain through the ethmoid and the orbit apex and can lead to lethargy, paralysis, and death.1,5,6 Rhinocerebral mucormycosis (RM) often begins with migraine, rhinorrhea, and growth of oral and nasal necrotic masses. A necrotic lesion is in fact found within the nasal or oral mucosa in ~80% of affected subjects. RM survival rates range from 21% to 70%. The overall survival rate for mucormycosis, including its other forms (gastrointestinal, lung, and disseminated), ranges from 6% to 73%.7

The majority of cases is diagnosed in patients with immunologic and metabolic disorders. In particular, RM is mostly observed in subjects who suffer from ketoacidotic diabetes, lymphoma, leukemia, myelodysplastic syndromes, prolonged corticosteroid therapies, acute renal failure, and severe burns.1,3,8 Paradoxically, the highest mortality rate is reported for healthy patients who do not suffer from diabetes.

Clinical manifestations include 6 different forms: rhinocerebral, lung, gastrointestinal, central nervous system, subcutaneous, and disseminated mucormycosis. RM is the most frequently observed, and it can be subdivided into rhinomaxillary and rhino-oculocerebral forms, the latter being characterized by a high mortality rate.9

Early diagnosis is fundamental, and so is medical therapy with amphotericin B along with surgical toilet of the compromised tissues.10,11

The purpose of the present article is to present and discuss 3 cases of RM with different onsets, progressions, and outcomes.

CASE REPORT 1

A 59-year-old female patient was referred with a right cheek swelling after a right upper third molar extraction performed 2 weeks earlier. The patient was partially sighted in the left eye since birth and was affected by noninsulin-dependent diabetes and arterial hypertension (both under treatment). The patient also showed total right eyelid ptosis, palsy of extrinsic and intrinsic muscles with medium mydriatic fixed pupil and hypoesthesia, palsy, and edema of the right half of the face.
Computerized tomography (CT) highlighted an inflammatory invasion of the right maxillary sinus and a thickening of the cheek soft tissues in the canine fossa area. No intraorbital fluid collections could be detected (Fig. 1).

Magnetic resonance imaging (MRI) revealed the presence of an irregular and peripheral enhancement of the right cheek soft tissues and involvement of the sphenoid sinus and the ethmoid. The patient had significant neutrophilia and hyperglycemia. Meropenem was administered immediately as well as insulin therapy.

Then an endoscopic right middle meatotomy was carried out. Nasal fossa had an atrophic mucosa covered with black-yellowish crusts mostly in the anteroinferior portion of the septum, the middle meatus, and the inferior meatus (Fig. 2). Direct examination of the maxillary sinus through the canine fossa revealed an unevenness of the bone plate and the presence of grayish layers which covered an atrophic mucosa surrounded by areas of hyperemia and bleeding mucosa.

The day after surgery, after a sudden syncopal episode and the onset of a left arm hypostenia, the patient was transferred to the emergency department and CT scan showed a recent ischemic area in the right paracapsular region and the presence of hypodense material within the ossicular chain. Clinically, the patient presented a high temperature and a gradual worsening of general and neurologic conditions.

Six days after surgery, a microbiologic diagnosis of mucormycosis of the maxillary sinus was obtained. Treatment with amphotericin B/lipid complex was started immediately, and the surgical intervention of emimaxillectomy and exenteratio orbitae was planned. Successive MRI highlighted an altered signal area in supratentorial site in correspondence with the lowest portion of ganglia base extension to the underlying mesencephalic-diencephalic area.

The day before planned intervention, the patient underwent a significant worsening of her neurologic conditions with headache and rigor nucalis. Liquor examination was negative for the presence of Aspergillus but showed an increased cellularity. A few hours later, the patient lost consciousness and entered into a coma. Cerebral angiography showed occlusion of the right internal carotid. CT described an atypical subarachnoid hemorrhage. After a significant desaturation episode, the patient presented dyspnea, sudden worsening of respiratory exchanges, and cardiocirculatory failure, which led to death 1 month after admission.

CASE REPORT 2
A 22-year-old man was referred to the Division of Maxillofacial Surgery, University of Turin, Turin, Italy, for the assessment of small ulcerative lesions on the hard palate mucosa and tongue dorsum. The patient presented with fever. Medical history included a recent liver transplantation after a motor vehicle accident trauma.

Bronchoscopic aspiration was carried out with the successive positive finding for A. fumigatus and Rhizomucor. MRI showed bilateral sinus involvement, with prevalence of the right side, as well as involvement of the frontal and ethmoid sinus (Fig. 3). Therefore, caspofungin and amphotericin B were administered.

Six days after the onset of oral and pharyngeal symptoms, a harder lesion of 2 cm diameter appeared in correspondence with the lingual V. Small superficial ulcers could be found (Fig. 4). Furthermore, a palate median ulcer of 2 cm diameter with a suspicion of bone erosion was found (Fig. 5). Cultural examination was performed with the consequent diagnosis of mucormycosis. Immunosuppressive therapy was suspended, and the patient underwent surgical intervention. Multiple biopsies were taken in both maxillary sinuses, and resection of palatal and lingual lesions were performed. Microbiologic examination excluded mycotic involvement in both sinuses. Therapy with high-dose amphotericin B was continued. Ten days after surgery, a palatal obturator was designed to allow oral alimentation. Strict follow-up was maintained. Four
months later, the patient complained of drug-resistant evening fever, dysphagia, and odinophagia. Clinical intraoral examination showed the presence of various 1–5-mm large white lesions on the surface of the posterior pharyngeal wall and right tonsillar bed. A biopsy was performed, and a histopathologic diagnosis of B-cell hepatitis B virus–related lymphoma was obtained. Mucormycosis recurrence was excluded. The patient underwent therapy for the lymphoma and was disease free at the time of writing.

CASE REPORT 3

A 49-year-old patient affected by chronic lymphoid leukemia (with cervical, sovraclavicular, axillary, and paraaortic...
lymphadenopathies) which was diagnosed 8 months earlier and under treatment was referred to the Division of Maxillofacial Surgery, University of Turin, because CT had showed bilateral involvement of the maxillary sinuses, which contained inflammatory tissue; the posterior portion of the ethmoid bone and the sphenoid sinus were also involved and seemed to be undergoing erosion. MRI also showed infiltration of the orbital fatty tissues and of the extrinsic muscles, thus causing a significant exophtalmia; the right cheek and the prevertebral soft tissues were involved too. Moreover, MR showed possible meningeal infiltration in the anterior cranial fossa (Fig. 6).

Multiple biopsies and cultural examination were performed. Histopathologic and microbiologic examination diagnosed mucormycosis. Therapy with amphotericin B was started rapidly, and the patient underwent a partial maxillectomy. Then allogenic bone marrow transplantation was performed with immunosuppressive therapy.

A new MRI of the maxillofacial region was carried out with the finding of involvement of orbit, ethmoid, dura mater in the temporal region, parapharyngeal spaces, and subcutaneous tissues of the zygomatic region. A combined neurosurgical-maxillofacial revision with partial maxillectomy, ethmoidectomy, exenteratio orbitae, and revision of anterior cranial fossa was proposed to the patient, who refused treatment.

Seven months later, the immunosuppressed patient developed a severe septic shock with concomitant pericardial,
pleural, and peritoneal effusion. A sensorial deficit of the right leg occurred, immediately followed by the sensorial deficit of the left leg. The progression of myelitis and mucormycosis appeared to be irreversible. Some days later the patient died.

This study was exempt from Institutional Review Board approval as a case report. We followed Helsinki declaration guidelines.

DISCUSSION

Mucormycosis is an opportunistic fungal infection that rarely affects healthy adults.4,12-26 Fungi undergo spore formation, which allows access to the human oral and nasal mucosa through inhalation.1,13 In healthy individuals, spores are easily cleared by phagocytosis, but in immunocompromised patients, germination and hyphae formation can occur.13-19 Factors that lead to invasion include noncompensated diabetes mellitus, hematologic disorders, severe burns, immunosuppression, and immunodeficiency. In some cases, systemic administration of steroids and chronic rhinosinusitis have been considered as predisposing factors. A glucose-rich environment and an acid pH may promote fungal invasion, because they directly affect macrophage affinity and efficiency.

Fungus is typically capable of vessel invasion. The elastic lamina always appears infiltrated, and this feature is associated with ischemia, formation of thrombi, and tissue necrosis, all of which contribute to fungus growth. Mucormycosis that involves the nose and the paranasal sinus generally begins with signs and symptoms of an acute bacterial rhinosinusitis. When it hits the orbit, it causes cellulitis, proptosis, ophthalmoplegry, and eventually blindness. If the infection spreads beyond the first site of infection, then the central nervous system can be reached. Usually in these cases there are signs of bone destruction in CT scans.

Laboratory examinations do not play a specific role. Definitive diagnosis is based on direct examination of the involved tissues. Histopathologically, diagnosis is based on direct observation of hyphae whose diameter vary from 6 to 50 μm.1 Differential diagnosis with Aspergillus fumigatus must be taken into consideration. Differences include microscopic characteristics and evolution.14

In the majority of cases macrophages are capable of confining spores, but if their activity is not sufficient, proliferation occurs.15 In immunocompromised patients, hyphae invade arteries and can cause thrombosis, ischemia, and gangrena sicca. Through blood, infection can spread to other organs, particularly the brain and lungs. Rhinocerebral form is more frequent in patients with uncontrolled diabetes.1,3,8,16 High sideremia and hyperacidosis facilitate fungine growth.15 In the absence of predisposing factors, mucormycosis is an extremely rare disease.11-13 No interhuman contagion was demonstrated.14

Mucormycosis was considered to be fatal until the 1960s, when amphotericin B was introduced as a treatment. Amphotericin B is a fungistatic rather than fungicidal agent, which contributes to the lengthiness of treatment. This also underscores the need to correct the patient’s underlying medical condition as quickly as possible.20 The patients who were treated with amphotericin B were 4 times more likely to survive than patients not treated with the medication.20

The drawback to the use of amphotericin B is its nephrotoxicity. A new, more effective, and less toxic form of the drug has been developed. A liposomal encapsulated form of the drug, called liposomal amphotericin B, enhances the intracellular delivery of the drug to phagocytes and fungi and decreases its renal delivery.21,22 The development of this drug carrier system has increased the therapeutic index of amphotericin B >20-fold.20 Not enough data were available in the present study to make a definitive statement on the effectiveness of liposomal amphotericin B on patient survival.

Mortality among diabetic patients seems to be lower than patients that present other causes of immunosuppression. A significative group of patients present orbital involvement. This group is characterized by a high mortality. In fact, orbital involvement represents an advanced stage of the disease and above all a direct route for intracranial extension. Mortality rate among patients with orbital involvement is 33%, compared with 14% among other patients.1-26

Recent studies emphasized the importance of an aggressive surgical treatment that may involve exenteratio orbitae, partial or total maxillectomy, partial rhinectomy, and other techniques. Exclusively medically treated patients usually present a less favorable prognosis in relation to severity and aggressiveness of the disease. Timing of surgery does not seem to play a fundamental role in prognosis; most patients are initially treated with drugs and surgically treated within a week from diagnosis if it is possible. Surgical timing is strictly related to the medical treatment response and the general conditions of the patient. Hyperbaric oxygen therapy was proposed as adjuvant treatment, but its role was not precisely defined. Finally, the most relevant factors that may influence outcome seem to be early diagnosis and resolution of predisposing factors.1,25,26

Case report 1 was challenging as far as differential diagnosis. In fact, symptoms could erroneously indicate an odontogenic abscess or orbital cellulitis. However, amaurosis, ptosis, and II, III, IV, V, and VII cranial nerve deficits were absolutely atypical. The early diag-
nosis of mucormycosis with immediately following medical treatment was not successful, because of the rapid and dramatic worsening of general conditions which did not allow a second planned surgical treatment. Intracranial and carotid involvement with subsequent ischemic irreversible lesions led the patient to death in a month.

The peculiarities of case report 2 were its extremely favorable course and the rare tongue localization. In fact, the patient could have benefited from the early diagnosis, immediate starting of medical treatment, and radical and prompt surgical intervention. As for localization, we expected that sinus involvement in imaging was due to mucormycosis, but it was instead due to inflammatory material. We think that such a favorable course could be related to the general conditions of the patient.

Finally, the most relevant feature of case report 3 was the extremely slow evolution of mucormycosis in a patient that presented severe immunosuppression and an orbitocerebral involvement. In fact, despite the antifungal treatment, an initial conservative surgical intervention, and the refused radical surgery, a worsening evolution of patient’s condition was progressive and stretched to 7 months before death.

CONCLUSIONS

Rhinocerebral mucormycosis is a fulminating type of invasive mycotic acute sinusitis that can be encountered mostly in immunocompromised patients. Prognosis can be improved with early diagnosis, modern imaging techniques, and therapy progress, both surgical and pharmacologic. Finally, it is fundamental to correct every underlying or related metabolic alteration.

REFERENCES


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