Combined Mucormycosis and Aspergillosis of the Rhinocerebral Region

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Abstract. Background: Opportunistic fungal infections are rare, life-threatening conditions and are a major cause of morbidity and mortality in immunocompromised hosts. Our experience in the management of a case of combined mucormycosis and aspergillosis of the rhinocerebral region is presented. Patients and Methods: The infection developed a few weeks after tooth extraction, massively involving facial structures. After diagnosis, the patient underwent prolonged combined systemic antifungal treatment. Once the local and general conditions had stabilized, an extensive surgical debridement was performed, followed by reconstruction with a pedicled myocutaneous flap. Results: This approach was curative with patient survival after 16 months. Conclusion: Early diagnosis, early anti-fungal treatment and early stabilization of the patients’ general condition are fundamental for patient survival. Surgery is necessary for fungal eradication, but must be performed according to the above conditions. Pedicled muscle flaps are considered the first reconstruction choice because of their excellent blood perfusion and resistance to fungal invasion.

Opportunistic fungal infections are rare, life-threatening conditions which are a major cause of morbidity and mortality in immunocompromised hosts.

Rhinocerebral mucormycosis is a rare opportunistic fungal infection, caused by fungi of the Mucoraceae family. The rarity of this disease leads to difficulties in diagnosis and delays can result in a poor prognosis (1). Oral manifestations are often the earliest signs of the rhinocerebral form (2).

Aspergillosis is the clinical syndrome caused by species of Aspergillus, most often A. Fumigatus.

Reports of combined mucormycosis and aspergillosis infections limited to the oro-rhinocerebral region are very rare (3).

This case report of a combined rhinocerebral fungal infection is of interest because it developed a few weeks after tooth extraction and massively involved facial structures, but did not progress to a fatal end.

Case Report

A 50-year-old woman was referred to an Oral Surgery Clinic in Rome, Italy, in July 2003, with local symptoms of periodontitis. Three weeks earlier, she had undergone a right first premolar tooth extraction under local anesthesia without complications. On the day of referral, the patient presented loss of consciousness and was transferred to the Emergency Department (ED) of the Policlinico Umberto 1st University Hospital. Physical examination revealed swelling and tenderness of the right cheek. The body temperature was 37.3 °C, blood pressure 140/100 mmHg and the pulse rate was 120 beats/min. The first blood tests revealed a hematocrit of 33.6%, a total white cell count of 8,800 Î¼L–1, glucose of 580 mg dL –1, pH 7.09, PO2 80 mmHg, PCO2 18 mmHg and bicarbonate 10 mmol L –1. Diagnosis of ketoacidotic diabetic coma was made. Insulin therapy was rapidly given, balancing the blood glucose level. Intravenous (i.v.) ceftriaxone was started. Three days later, the patient suffered a right cerebral ischemia, due to subtotal stenosis of the right inner carotid with consequent left face hemiplegia. The tenderness of the right cheek evolved, during the following 3 days, into an extensive necrotic lesion. Extensive ulceration and necrosis involved the orbital floor, the maxilla, the hard palate and alveolar process, resulting in exposed bone and exfoliation of the anterior teeth. The ulceration had undermined edges and a brownish-black base.

A computerized angio-transaxial-tomogram (angio-CT, Figure 1) and magnetic resonance imaging (MRI) showed an acute inflammatory process of the affected cerebral area due to ischemia (medium cerebral artery territory) with alteration of the hematoencephalic barrier. Variable
clouding of the paranasal sinuses and destruction of the anterior sphenoidal wall were also observed. One week later, the patient's general conditions remained stable, while the necrotic area enlarged, with right eye involvement and loss of vision.

Figure 1. Angio-CT imaging showing the acute inflammatory process of the right cerebral area.

Figure 2. Histological specimen, showing mucor hyphae surrounded by inflammatory cells (hematoxylin-eosin stain, 400x).

Figure 3. Aspergillus fumigatus culture (Sabouraud’s dextrose agar +/- chloramfenicol).
Biopsy specimens were taken from the sides of the necrotic lesion and sent for histological examination. The outstanding microscopic features were of an intense, acute and chronic inflammatory infiltration, including scattered broad, branching, aseptate fungal hyphae, suggestive of infection by Mucoraceae (Figure 2). Furthermore, a wound swab from the maxillary sinus was cultured evidencing conidia, associated with flower-like conidiophores, suggestive of Aspergillus

Figure 4. Clinical aspect at first consultation.

Figure 5. (A) Intra-operative view after extensive surgical debridement. (B) Intra-operative view after reconstruction with a pedicled myocutaneous pectoralis major flap. (C) Clinical aspect 2 weeks after operation. (D) Clinical aspect 16 months after operation.
fumigatus (Figure 3). The diagnosis of combined mucormycosis and aspergillosis of the rhinocerebral region was made 6 weeks after hospital admission.

Specific antifungal therapy was started, consisting of i.v. combined therapy of Voriconazole (6 mg/kg for 2 doses, followed by 4 mg/kg twice a day), Caspofungin (70 mg on day 1, followed by 50 mg/day once a day) and liposomal Amphotericin B (1.5 mg/kg/day once a day). At this stage, the patient was referred to us (Figure 4). We performed daily dressing changes, disinfecting with chlorhexidine and dressing with iodoform gauze. Aggressive surgical debridement was subordinated to local and general improvements.

Three months after hospital admission, the patient’s general and local condition had improved. Facial hemiplegia resolved, leaving just a decreased sensibility of the left face. At this stage, the patient’s condition was considered stable enough to allow surgery. Surgical debridement was then performed under general anaesthesia. Necrotic bony sequestra and devitalized soft tissue were excised, with removal of the right maxilla and sinus, orbital floor with exenteratio orbitae, nasal bones, the lateral side of the ethmoid bone, vomer, right hard palate, alveolar process and anterior wall of the sphenoid bone (Figure 5A).

Considering fungal affinity to blood vessels, free flaps were not considered for reconstruction. A myocutaneous pectoralis major pedicled flap was performed. The flap was elevated and turned over the defect. The skin island restored palatal continuity, the muscle body filled the defect cavity, and a skin graft covered the muscle deep surface to restore tegument continuity (Figure 5B).

In the postoperative period, fungal infection had a relapse; fungi attached massively to the flap, and slowly deteriorated part of it, leaving an open cavity (Figure 5C). Daily dressing changes were performed and i.v. antifungal treatment continued. One month postoperatively, the patient’s local condition had improved and the general condition remained stable. At this point, the patient opted for voluntary discharge, continuing i.v. antifungals for 2 more weeks and daily dressing changes with home care.

Sixteen months after hospital discharge, the patient was alive, fully oriented and could speak intelligibly. Locally, the pedicled flap had partially deteriorated. The right face presented a cavity from the oropharynx and the posterior sphenoid wall to the right orbit. The cavity was covered by mucosal epithelium. No evidence of active disease was present (Figure 5D).

Reconstruction options were reconsidered at this stage, but the patient refused them.

Discussion

We report the case of a rare combined infection of mucormycosis and aspergillosis in a patient with latent diabetes mellitus. The diagnosis was established when causative organisms were disclosed by histology and specific culturing techniques.

The fungi responsible for mucormycosis are opportunistic pathogens, becoming particularly lethal in debilitated patients (4, 5). Fungal hyphae have a predilection for growth into arteries, lymphatics and nerves (6) Vascular invasion of the hyphae produces a fibrin reaction and the development of mucor thrombi, which occlude vessels, producing ischemia and infarction. The infarction produces the black, necrotic eschars in the nasal and oral cavities and on the face that are characteristic of mucormycosis (7).

Vascular occlusion also produces an acidoctic tissue that is ideal for fungal growth and that is protected from the i.v. administration of antifungal agents (6). The infection spreads rapidly to the adjacent sinuses and orbit and then continues into the cranium via direct extension through the ethmoid bone or orbital vessels. Mucorales can also cause cavernous sinus or carotid artery thrombosis and progress to involve the orbita and cranium in just a few days (7). The diagnosis of rhinocerebral mucormycosis is made on the evidence of the characteristic hyphae on biopsy of necrotic ulcers in the nasal or oral cavities (6). Treatment includes early diagnosis, i.v. antifungals, control of underlying conditions and radical surgical debridement. Debridement of the nasal cavity and sinuses is essential and may include enucleation and intracerebral debridement (8). Hyperbaric therapy has proved to be effective in increasing survival rate (9).

Aspergillosis is a well known fungal infection. Invasive aspergillosis of the rhino-orbital region manifests initially in the sino-nasal localization and may spread to the palate or alveolar process, appearing as yellow to black necrotic ulcers (10). Delayed diagnosis and treatment may result in massive tissue destruction and, eventually, death. Aspergillosis very rarely affects healthy individuals, but more commonly patients with poorly-controlled diabetes, immunodeficiency or leukemia.

This case report of combined mucormycosis and aspergillosis of the rhinocerebral region is of interest for its rarity. Maiorano et al. described a case of combined infection in a patient affected by Castleman disease (3). Reviewing the literature and on the basis of our experience, we consider early diagnosis, early antifungal treatment, early control of disease and early improvement of the patient’s general condition fundamental for survival and morbidity. Definitive surgical treatment must be performed only after these requirements have been met. Surgery plays a key role in fungal eradication, but cannot be performed if the general condition (glucose homeostasis, immunological status, etc.) is not restored. We consider pedicled muscle flaps the first reconstruction choice for this condition, because of their excellent blood perfusion and for their properties which
allow antifungal agents and self-defense molecules to be transported to the site of infection after debridement. We do not recommend free flaps for first stage reconstruction due to the fungal affinity for blood vessels, associated with rapid invasion of unprotected vessel anastomoses and flap failure. In this case report, a pectoralis major flap, with its uninjured pedicle protected by the muscle, resisted fungal invasion, was only partially deteriorated and promoted fungal eradication. We think that flap sacrifice is acceptable for patient survival. Free flaps may play a role in delayed reconstruction.

In conclusion, following a multimodality and multistep treatment, this case report of combined mucormycosis and aspergillosis of the rhinocerebral region did not progress to a fatal end and the patient experienced long-term survival.

References


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