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Rhino-maxillary and orbital mucormycosis in a patient with acute myeloid leukaemia: a successful surgery and antifungal therapy combined approach

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ABSTRACT:

Mucormycosis is an aggressive opportunistic infection caused by fungi within the order Mucorales, which includes the genera *Rhizopus*, *Mucor*, and *Absidia*. Most of the reported cases involve immunocompromised patients and different clinical pictures have been observed. The most common form is the rhino-cerebral infection that manifests in the nasal mucosa and in the paranasal sinuses and may involve the ethmoid through the orbital vessels. Despite aggressive medical and surgical treatment, mortality in patients with mucormycosis can be as high as 65%. Here we report a clinical case of a patient with an acute leukaemia successfully treated with a combination of surgery and antifungal therapy.

Key words: *Rinomaxillary, Orbital, Mucormycosis, Surgery, Antifungal treatment.*

INTRODUCTION

Mucormycosis is an aggressive opportunistic infection caused by fungi within the order Mucorales, which includes the genera *Rhizopus*, *Mucor*, and *Absidia*. Most of the reported cases involve patients with immunocompromising illnesses, such as uncontrolled diabetes mellitus with ketoacidosis or hematologic malignancies. Different clinical presentations including gastrointestinal, pulmonary, cardiac, subcutaneous, rhino-maxillary, rhino-cerebro-orbital or disseminated infection have been observed. The most common form is the rhino-cerebral one that manifests in the nasal mucosa and in the paranasal sinuses and may involve the ethmoid through the orbital vessels.

CASE REPORT

In august 2007, a 68 years-old caucasian man with a history of rheumatoid arthritis and Parkinson disease, was diagnosed for M4 acute myeloid leukaemia (AML) according to the French-American-British (FAB) classification. He received chemotherapy until October 2007. In the same month, despite itraconazole prophylaxis, a severe inflammation started from nose and cheek with rapid evolution (Figure 1). CT and MRI scans were performed showing the necrosis of the entire right nasal/paranasal region with erosion of the nasal septum, of the whole hard palate, of the medial and anterior walls of the right maxillary sinus, of the premaxilla and of the right orbital floor

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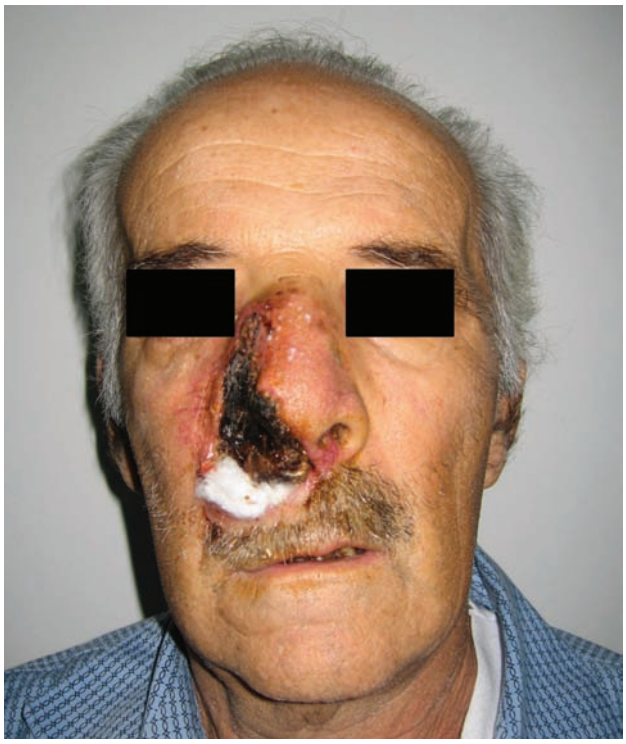

Figure 1. Clinical appearance of the disease showing a wide necrosis of the right rhyno-maxillary area.

(Figures 2). Histological and mycological tests were performed and a diagnosis of invasive rhino-maxillary and orbital mucormycosis due to *Rhizopus arrizus* was made. Antifungal therapy with liposomal amphotericin B (250 mg QD) was promptly started. The same month he underwent surgery at the Department of Maxillofacial Surgery with wide excision of necrotic tissue that involved the nose, the premaxilla, the right maxilla extended to the whole hard palate and the right orbital floor (Figure 3). Tracheostomy was performed too. Besides, a percutaneous endoscopic gastrostomy (PEG) was positioned to allow enteral nutrition. After surgery he was transferred to the Intensive Care unit where a spinal derivation for cerebro-spinal fluid fistula was temporarily placed.

He was then transferred to the Infectious Disease department on November 2007. On admission he was in poor general conditions and afebrile, he presented an extended surgical wound on the right side of the face. On the joints of wrists and fingers the typical deformations consistent with rheumatoid arthritis were present. Several teeth were missing due to surgery. Blood chemistry showed: WBC 5820 mm³ (65.8% polymorphonuclear leucocytes; 15.6% lymphocytes; 10.7% Eosinophils); erythrocytes 2850 mm³ haemoglobin 8,4 g/dL; hematocrit 24,5% platelets (PLT) 74000 mm³, the remaining laboratory tests were normal. Intravenous antibiotic therapy with piperacillin-tazobactam 4.5 g tid and ceftazidime 2 g tid, antifungal therapy with liposomal AMB (250 mg once a day), oral ropinirole (1.5 g three times a day) and levodopa plus carbidopa (100 + 25 mg once daily). Regular care of the facial wound was performed and a culture from the tracheostomy was positive for coagulase positive *Staphylococcus aureus* and *Stenotrophomonas maltophilia*. Intravenous teicoplanin 400 mg qd was added.

At the end of November 2007 the patient developed intense cough, physical examination and a chest x-ray were

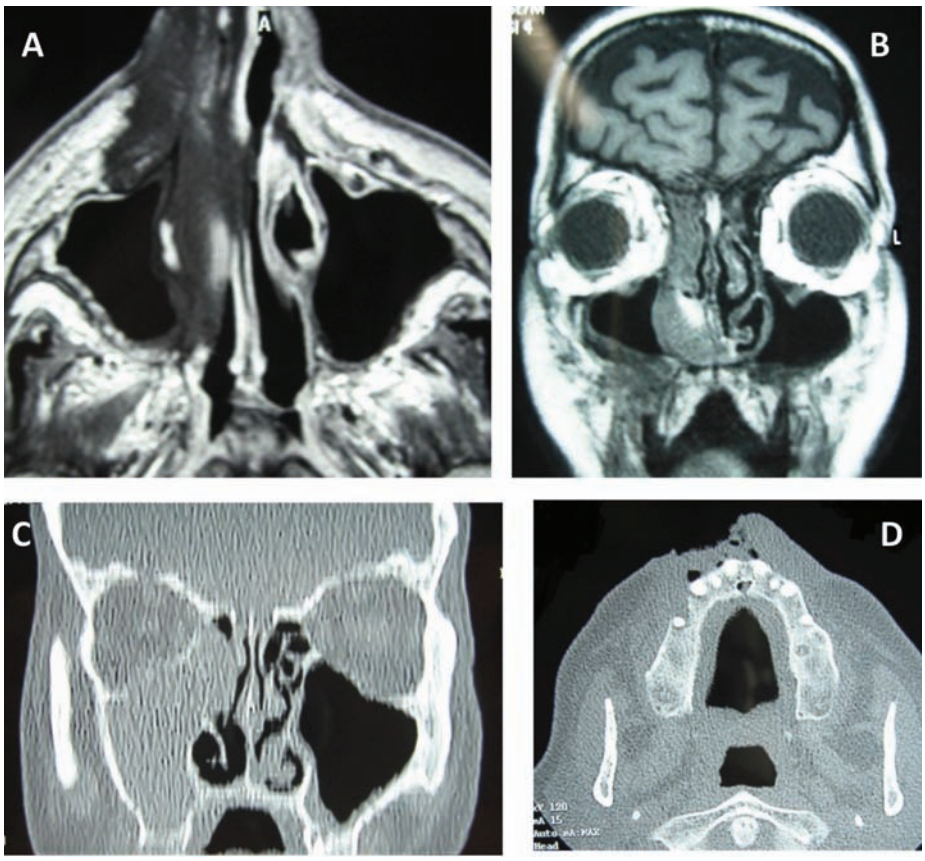

Figure 2. *A-B*, MRI scan shows necrosis of the entire right nasal/paranasal region. Also, erosion of the nasal septum and of the medial and anterior walls of the right maxillary sinus is visible. *C*, Coronal CT scan, performed few days after MRI exam, shows a progression of the disease with opacification of the entire right maxillary sinus and the ethmoid, with bony erosionofthe maxillary sinus medial wall, of the maxillary alveolar bone, of the hard palate and of the orbital floor. *D*, Axial CT scan shows destruction of the right maxillary alveolar bone and a wide ulcer of the nasal, paranasal and labial soft tissues.

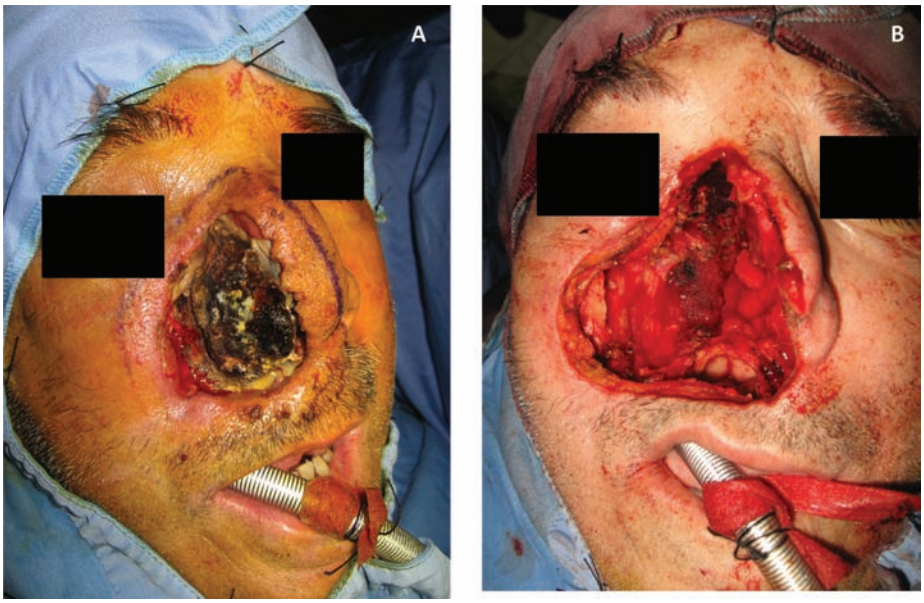

Figure 3. *A*, Intraoperative view: it is evident the wide ulcer of the right side of the face. *B*, Intraoperative view after wide surgical resection of the necrotic tissue that involved the nose, the septum and bilateral inferior turbinates, the premaxilla, the right maxilla, the whole hard palate and the right orbital floor.

consistent with basal pneumonia with pleural effusion. Antibiotic therapy was switched to iv meropenem 1 gr tid and tigecycline 100 mg qd. Control chest x-rays test after 14 days showed a resolution of the pulmonary consolidation but an increase of the pleural effusion in the right lung. Therefore, a thoracentesis was performed and allowed us to exclude an infectious pleuritis. A chest x-rays after a week showed a reduction of the pleural effusion. After ten days a CT scan substantially confirmed these results. A new control of blood chemistry at the end of December 2007 showed WBC 2700 mm^3; Polymorphonuclear leucocytes 1200 mm^3 HGB 9.1 g/dL; PLT 105000 mm^3. Haematological evaluation performed in the same period excluded a recurrence of the leukemia. Maxillofacial surgical consults were performed regularly and showed that the mucosal tissues inside the wound were normal and cultural tests performed showed no presence of fungal infection. Liposomal AMB was switched to oral posaconazole 400 mg bid.

In the same period, a prosthetic palate was modelled and allowed the patient to restart gradually a proper feeding even if PEG was maintained.

In mid January 2008 blood tests showed WBC 4320 mm^3, polymorphonuclear leucocytes 54.6%; PLT 144000 mm^3; erythrocytes 3870 mm^3; haemoglobin 8,9 g/dL. Facial TC scan performed on February 2008 did not reveal any lesion but a mucosal thickness of the left sinus, thoracic, abdominal and pelvic CT scan were normal (Figure 4 *A*). In early February 2008 histological and microbiological tests were negative for fungal infection. In mid February patient's general conditions were stable, enteral nutrition was discontinued and new haematological tests confirmed the complete morphological remission of AML (Figure 4 B). Thus, he was discharged with oral posaconazole 400 mg bid as maintenance therapy and anti-Parkinson's and antibiotic prophylactic therapy without recurrence of the mycosis.

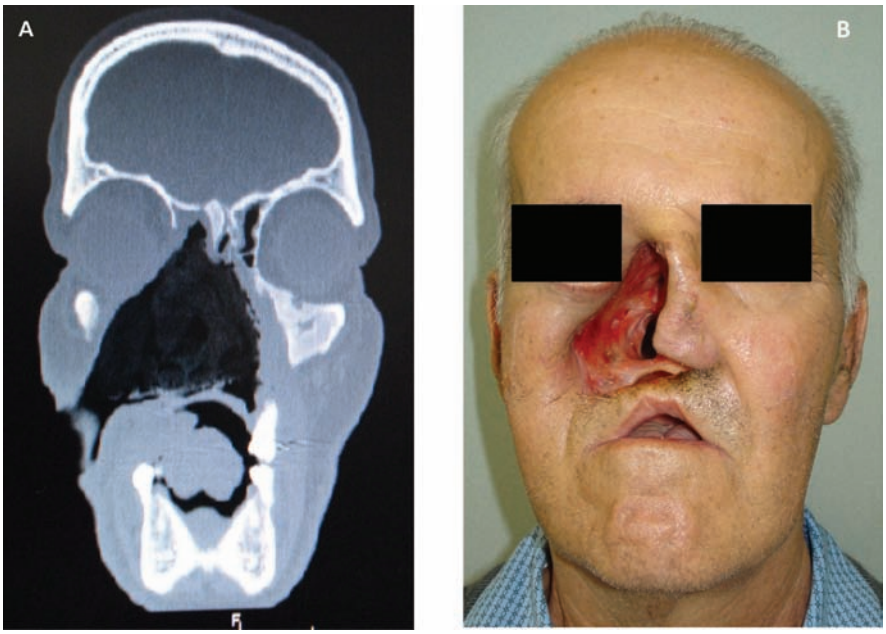

Figure 4. *A*, Postoperative CT scan showing the large surgical defect. *B*, Frontal view of the patient 4 months after surgery.

DISCUSSION

Mucor was first described by Paltauf in 1885. Taxonomically, the fungus belongs to the order Mucorales. The organisms causing mucormycosis are *Rhizopus* species, *Mucor* species, *Lichtheimia* species (former *Absidia* species), *Cunninghamella* species, *Rhizomucor* species, *Syncephalastrum* species, *Saksenaea* species, and *Apophysomyces* species[1]. These fungi are ubiquitous saprophytes found throughout nature. They are broad (5-50 um), non-septated hyphae with right-angle branching, which characteristically involve the blood vessels, causing thrombosis and ischemia[1].

Overall, rhino-cerebral (55%) and pulmonary (30%) mucormycosis are the most common clinical forms encountered, followed by gastrointestinal tract and cutaneous forms[2]. Disseminated mucormycosis accounts for 9% of cases[3].

Rhino-cerebral mucormycosis was first described in 1957 by Baker and since then several cases had been reported in literature. However, the disease remains a rare, infrequent and challenging diagnosis for clinicians. Rhino-cerebral mucormycosis is associated with immunocompromised patient state, hemochromatosis, desferrioxamine therapy, malignancy, diabetes mellitus with or without ketoacidosis, organ transplantation, severe burns, trauma and prolonged corticosteroid therapy[4]. Despite aggressive medical and surgical treatment, mortality in patients with mucormycosis can be as high as 65%[5,6]. Amphotericin B (AMB) formulations have remained the mainstay of treatment for mucormycosis in combination with early surgical debridement and reversal of immunosuppression[7]. Recent studies showed that posaconazole, a novel triazole agent, has in vitro activity against Mucorales[8]. However, among febrile patients with neutropenia or those with invasive fungal infection, posaconazole administered at a dosage of 400 mg orally twice daily resulted in serum levels <1 μg/mL, with considerable variability[9-11]. Therefore, pharmacokinetic and pharmacodynamic data raise concerns about the reliability of achieving adequate in vivo levels of oral posaconazole to treat mucormycosis[7]. Other azoles including fluconazole, voriconazole, and itraconazole do not have sufficient activity against mucormycosis[7].

Treatment of mucormycosis includes antifungal agents and surgical resection; better outcomes have been noted when a combination of antifungal agents and surgical resection is used[7]. Amphotericin B deoxycholate is the drug of choice[12] and its lipid formulations allows higher doses for prolonged periods of time with substantially less renal toxicity[12].

Recently, posaconazole has been used as a salvage therapy against Mucorales[13]. A prospective, matched case-control study showed AMB to be superior to posaconazole[14] to be superior to posaconazole[14]. Furthermore, AMB was shown to be superior or equally effective to posaconazole in neutropenic mice infected with *Mucor circinelloides*[15,16]. No data are available to date on a switch strategy to posaconazole after induction and successful therapy with liposomal AMB.

CONCLUSIONS

Our case showed that in the presence of severe rhino-maxillary and orbital mucormycosis a combined approach including surgery and antifungal therapy is preferable. Switching from liposomal amphotericin B to oral posaconazole has been effective as a maintenance therapy and allowed out-patient management with an improvement of the quality of life.

This approach could be of even greater interest with the recent introduction of posaconzole oral tablets that would certainly optimize patient's adherence.

Conflict of interest

The authors declare no conflict of interest regarding the manuscript.

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