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Rhinoorbitocerebral mucormycosis: A case report and literature review

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Abstract

Mucormycosis is a rare oportunistic infection typically described in diabetic patients with a ketoacidotic status, as well as neutropenic patients. The infection is caused by a group of saprophytic fungi of the class *Phycomicetes*, being the most frequent ones the *Rhizomucor, Rhizopus* and *Mucor.* Its hystological findings include vascular trombosis and tissue necrosis, predominantly in the rino-orbito-cerebral area.

Even though the frequency of presentation is very low, given its rapid evolution and severe consequences which include a high mortality rate, it is very important to be aware of the main features of the disease and treat it promptly. Although the diagnosis is based on the high clinical suspect, the computed tomography (CT) and the magnetic resonance image (MRI) plays an important role in determining the extension. The patients should receive treatment in a reference hospital so that a multidisciplinary approach is ensured.

In this sense, we present a case of rhino-orbito-cerebralmucormycosis in a diabetic patient, recently treated in our Department. A comprehensive review of the literature has been performed to update the physiopathology and diagnosis. Finally, we describe the different treatment options focusing in the surgical approach, as well as the medical treatment with amphotericine and posaconzole

Key words: *Mucormycosis, diabetes, ketoacidosis, inmunosupression, paranasal sinuses, Amphotericine B, extended maxillectomy, Rhizopus oryzae.*

Introduction

Mucormycosis (also known as zygomycosis or phycomycosis), was first described by Paulltauf in 1885 (1). Typically developed by poorly controlled diabetic patients, this opportunistic infection is characterized by a very acute onset. It produces vascular thrombosis and tissue necrosis and the most frequent form is the rhino-orbito-cerebral (2). It must be ruled out in every patient with risk factors (ketoacidotic patients and haematologic malignancies) and signs or symptoms affecting the nose, paranasal sinuses, orbit or central nervous system (CNS) (2,3). The prognosis is poor, with severe sequelae and high mortality even in patients with a prompt diagnosis and correct treatment.

Case Report

The patient was a 75 year-old male with diabetes mellitus (DM) treated with oral antidiabetics (metformin, glicipide), elevated blood pressure controlled by drug therapy, inhaler therapy for his chronic bronchitis (teophylline), and benign prostatic hypertrophy. He was attended in his local hospital for respiratory failure due to relapse of his pulmonary disease. He was prescribed prednisone and doxycycline. Five days later he developed unspecific discomfort in his left eye and poor glucemic control. The laboratory findings showed 12.600 WBC/mm3 (90% neutrophiles, 3% lymphocytes, 5% monocytes), blood glucose level 420 mg /dl, urea 18 mg/dl, creatinine 0.6 mg/dl, sodium 132 mmol/l, potassium 3.6 mmol/l, liver enzymes and coagulation values without alteration. The venous gasometry revealed acidosis (pH 7.23, HCO3 14 mmol/l). The urine test determined glucose greater than 1000 mg/ml, density greater than 1030, proteinuria 30 mg /dl and cetonic bodies greater than 80 mg/dl. He was evaluated by the ophthalmologist because of his left eye pain and chemosis, and acute conjunctivitis was diagnosed. Finally he was admitted to control the glucemia. Two days later, in spite of the regulated blood glucose levels and the correction of the acidosis, the ocular pain and chemosis worsened and proptosis and motility restriction of the affected eye developed. A serohematic suppuration from his left nostril appeared, and a complete necrosis of the left hemipalate was evident (Fig. 1). As mucormycosis was suspected, intravenous amphotericin B therapy (3 mg/ kg day) was established, and an incisional biopsy was taken under local anaesthesia. The histopathologic study was consistent with mucormycosis. The computed tomography (CT) study showed palatal involvement, left nasal fossa, left maxillary and ethmoid sinus and left orbit occupation (Fig. 2). The patient was then referred to La Paz University Hospital because of the extension of the infection. Eight days later, on arrival at our hospital, the patient showed complete left palate necrosis, serohematic suppuration with abundant necrotic tissue from his left nostril, severe left ocular involvement with reduced visual acuity, pupilar afferent defect and severe chemosis and ophtalmoplegia in his left eye. An emergency surgical resection was undertaken by the maxillofacial surgeon, neurosurgeon, ophthalmologist and ENT surgeon. A complete left maxillectomy with orbit exenteration extended to the infratemporal fossa was performed. The sphenoid and frontal sinuses were endoscopically examined and found to be free from disease. A small cephalorachidian liquid fistula was discovered and successfully treated intraoperatively with local flaps and dura mater sealers. The defect was packed with terramicine gauze, as the topical use of amphotericin B is banned in Spain. The postoperative period was uneventful, with good glucemic and renal control, and administration of 5 mg/ kg day of liposomal amphotericin. Several biopsies were performed, all of them negative for fungus. The MRI examinations showed no new fungus extension. After 37 days of intravenous treatment with amphotericin B, the patient was discharged and sent to his local hospital to continue the parenteral treatment. The final microbiologic exam performed in the National Microbiologic Center detected a Rhizopus Oryzae infection (Fig. 3)

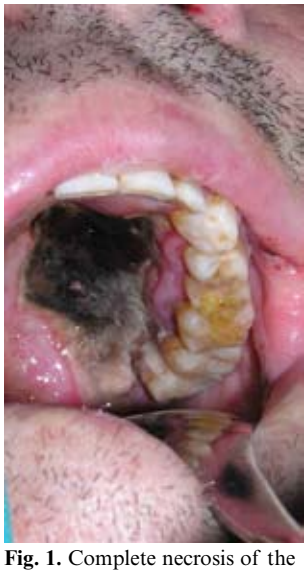

Fig. 1. Complete necrosis of the left hemipalate.

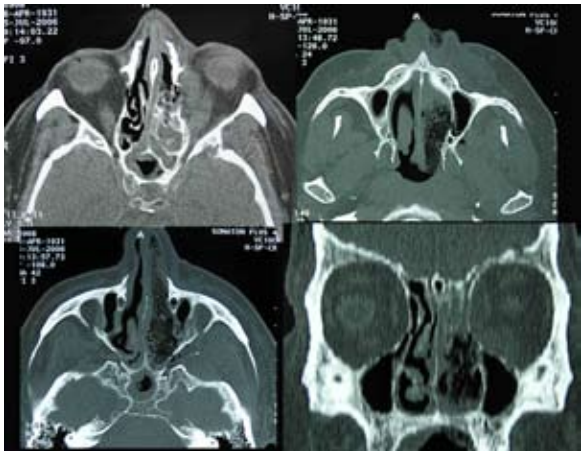

Fig. 2. The computed tomography (CT) study showed palatal involvement, left nasal fossa, left maxillary and ethmoid sinus and left orbit occupation

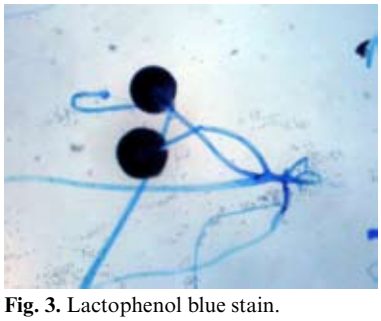

Fig. 3. Lactophenol blue stain.

The microsurgical reconstruction was delayed to ensure the patient was free from disease. An obturator was elaborated so the patient was able to eat and speak, enjoying a good quality of life and avoiding tissue scarring retraction. Unfortunately, before the reconstruction was performed, the patient presented a cardiac arrest and died.

Discussion

Mucormycosis is caused by fungi in the phycomycetos order, the main pathogens belong to the *Rhizomucor, Rhizopus, Absidia* and *Mucor* species, but we can find many different fungi (*Cunninghamella, Saksenaea, Syncephalastrum, Cokeromyces, Mortierella*).The few cases reported by the *Apophytomices* in the medical literature usually correspond to healthy individuals with traumatic inoculation. This fungus usually acts as an opportunistic pathogen. It is present in soil, decaying organic debris and bread moulds but only infects compromised subjects. The principal predisposing factors are diabetes mellitus (specially with acidosis) and hematologic malignances with neutropenia. It has been established that high glucose concentrations enhance fungus growth. Evenmore, cetoacidotic patient serum is not able to stop the fungus growth, maybe because it can not chelate the iron, and this iron excess is used by the fungus to produce rhizoferrin. As the cell responsible for the defence against fungus is the neutrophile, their alteration in number or function in hematologic malignancies leads to an increased risk of infection. Other identified risk factors are chronic steroid treatment, organ transplant, chemotherapy, chronic renal insufficiency, ferrum intoxication (desferoxamine treatment in dialyzed patients), burn patients. However, it is not frequent in immunodeficiency (HIV) patients as they suffer a lymphocitic immunity disorder. There are also cases related to tooth extraction, but it is not easy to determine if the extraction site was the entrance point for the infection or if the infection caused the toothache that led to the extraction. There are occasionally some cases without identified risk factors, usually related to *Apophytomices* in traumatic healthy patients.

We can divide this entity into 6 forms: rhino-orbito-cerebral, respiratory, gastrointestinal, cutaneous, widespread and mixed. The most frequent one is the rhino-orbito-cerebral, with or without CNS involvement, but almost always with ocular damage. No patient to patient spread has been reported, the dissemination occurs via inhalation of spores. In healthy subjects, these spores would be fagocitated by the polymorphonuclear leukocytes. On the other hand, in the risk patient the rapid growth in the nasal fosa is usually silent, with nasal obstruction and rhinorrea. Only in advanced disease with paranasal sinus, orbit or CNS involvement are the symptoms more specific. The necrotic eschar is very suggestive but it only appears in 20-40% of the patients, and is considered a bad prognosis sign.

The orbit extension occurs via the nasolacrimal duct, medial wall dehiscences or the anterior and posterior ethmoid orifices. The CNS is affected through the orbit apex, the orbit vessels or the cribiform plate. The fungus adheres to the internal elastic lamina of the blood vessels, leading to ischemia and necrosis. Perineural spread through the trigeminal branches has also been described.

Cavernous sinus thrombosis may be due to a complicated mucormycosis or to a bacterial septic thrombosis, the former being more acute. The CNS injury is produced by direct extension or internal carotid artery thrombosis.

This infection must be suspected in every patient with risk factors and signs or symptoms referring to nasal fosa, paranasal sinuses, orbit and CNS, even with inespecific disturbance. The diagnosis is confirmed by the histologic and microbiologic studies, obtained either by open biopsy or fine needle aspiration (FNA) . In the event of negative biopsy in a case of high clinical suspicion, the biopsy should be repeated to include deeper tissues and larger vessels to identify the fungus in the lumen. Hematoxilin-eosin, periodic acid-Schiff (PAS) and Gomori silver stains are usually employed. The optic microscopy shows large nonsepted hyphae that tend to branch at right angles. However, the *Aspergyllus* shows septated hyphae with a more acute branching pattern. Fungus culture is difficult and requires selective media. The extension study is based on CT and magnetic resonance image (MRI) studies, determining the involvement of sinuses, orbits and CNS. It must be taken into account that bone erosion is a late sign. The MRI gives a better visualization of the CNS, perineural invasion and vascular obstruction. It is the preferred choice because of the coincident use of nephrotoxic drugs and the presence of compromised renal function.

These patients should always be managed in a third level hospital, as they need evaluation and treatment by a multidisciplinary team (maxillofacial surgeon, ENT specialist, ophthalmologist, neurosurgeon, intensive care unit, infectious disease department and endocrinology service). It is essential to correct the acidosis status, to regulate the blood glucose levels, rehydrate the patient and correct the electrolithic disbalance. Immunosuppressor therapy as well as corticosteroids should be immediately discontinued and treatment with amphotericin B should be commenced.

Amphotericin B binds to the cellular membrane sterols, altering their permeability. Its numerous side effects condition an initial low dose with progressive increase if well tolerated. The most frequent ones include chills, fever ,backache, chest pain, dyspnea, bronchospasm, tachycardia, hypotension, rash, nausea and vomiting, abdominal pain, diarrhea, phlebitis…Some authors recommend premedication with diphenhydramine, petidine, paracetamol and Cortisone to avoid these side effects. Nowadays, we use liposomal amphotericin B, that although more expensive has less renal toxicity, fewer adverse effects, and a better

solubility in the CNS. Hence the dose can be safely increased. The initial dose is 1 mg /kg day, which can be increased to 3 or even 5 mg /kg day. The 5 mg dose has not shown better results than the 3 mg dose in patients with aspergyllus infections but is the dose of choice reported by many authors in mucor infections. Furthermore, some physicians recommend 15 mg /kg day. Renal function as well as potassium and magnesium must be rigorously monitored during the treatment, that usually lasts for 3 to 7 months.

Surgical treatment is always necessary, with extended resection until bleeding tissue is found. Efforts to save the ocular globe with conservative resections usually lead to a delayed enucleation and worsening of the patient. We must ensure the paranasal sinus drainage. It is quite frequent to perform repeated resections of small residual fungus foci from the margins of the wound during the postoperative period; in these cases, the frozen section analysis is extremely useful. There is agreement in the use of amphotericin irrigation of the surgical field, as well as the amphotericin embedded gauze. The aim is to ensure the drug biodisponibility in the surgical field, where the vascularitation is compromised because of the thrombosis. Surgical reconstruction is usually deferred until the infection is completely resolved.

The fungistatic and angiogenic effects of hyperbaric oxygen could enhance the effect of amphotericin B and improve the vascularization. Its value is not well established but it is thought to improve prognosis in CNS cases, with the use of 100% oxygen for 90 to 180 minutes at pressures from 2 to 2.5 atmospheres with 1 or 2 exposures daily for a total of 40 treatments.

The use of other drugs has been reported, such as the combination of rifampicin and amphotericin. In the US, posaconazole is employed in amphotericin resistance or intolerance, with good results. It can be administered orally, and is well tolerated with a high response rate. We can also find promising results with the use of granulocyte-monocyte colony stimulating factor in patients with hematologic diseases.

The follow up is based on clinical examinations as well as weekly MRI. Some authors recommend repeated biopsies. In the last 50 years, the prognosis has improved dramatically, with a mortality rate of 85% in 1960 that has now decreased to 30-35% . The most important prognosis factor is delayed diagnosis and treatment. Functional and aesthetic sequelae are to be expected in the rhinocerebral forms.

Conclusion

A prompt diagnosis is crucial to improve the survival and reduce the sequela of patients with rhinoorbitocerebral mucormycosis. The treatment must focus in correcting the general status, appropiate antimicrobian treatment and surgical resection. The gold standard of the medical treatment is amphotericin B, although the new antifungic generation is obtaining promising results with fewer adverse effects.

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