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Successful treatment of rhino-facial mucormycosis in a diabetic patient

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ABSTRACT

Mucormycosis is a rapidly progressing and lethal infection caused by fungi of the order mucorales. The disease occurs mostly in patients with uncontrolled diabetes or other predisposing systemic conditions. We report a case of rhinofacial mucormycosis in a 39-year-old diabetic patient. The diagnosis was established by clinical examination, imaging, and confirmed by mycological examination. *Rhizopus arrhizus* was isolated. He was successfully treated with amphotericin B, surgical resection, diabetes control and hyperbaric oxygen therapy.

1. Introduction

Mucormycosis is a rapidly progressing and lethal fungal infection which involves the nose and paranasal sinuses and the neck regions [1]. It is caused by angiotropic fungi of the order mucorales, particularly among patients with uncontrolled diabetes or other predisposing systemic conditions [1,2]. It manifests as rhinoorbital, pulmonary, gastrointestinal, cutaneous or disseminated form [1]. A high index of suspicion for mucomycosis based on appropriate risk stratification and improved laboratory diagnosis are important to improving survival [1,3]. We report a case of rhinofacial mucormycosis in a 39-year-old patient with emphasise on early diagnosis and urgent treatment.

2. Case

39-year-old patient with a history of untreated diabetes and gout treated with Allopurinol. He complains of purulent rhinorrhea and a feeling of right nasal obstruction for 20 days with the appearance of a right jugular swelling extended to the right eye 7 days ago. The patient was initially treated with antibiotic and corticosteroid in ambulatory without any improvement.

The examination found a temperature of 38,5 °C. Examination of the face notes a painless jugular swelling with edema of the lower eyelid. At the anterior rhinoscopy, presence of a purulent rhinorea in the middle meatus with sero-hematic fluid issue in the right nasal fossa; at the examination of the oral cavity presence of a bulge of the palate of the right side with fistula allowing to emerge pus and bad oral state. An emergency sinus CT scan and MRI were requested (Figs. 1 and 2). It concluded to a pansinusitis with a subperiosteal collection of 7 mm at the posterior wall of the right maxillary sinus extending to the retropterygoid space. The patient was hospitalized on day 0 and treated by cefotaxim 6000 mg per day, metronidazole 1500 mg per day and fosfoycin 1200 mg per day with washes of the nasal cavity. In view of the necrotic aspect of the CT scan and the fistula of the plague, a mycological sample was done, having concluded at the direct examination to the presence of mycelial filaments of mucorales (Fig. 3). The diagnosis of rhinofacial mucormycosis was made. On day +1, the patient was treated by amphotericin B at a dose of 1 mg per kg per day (total of 60 mg per day), with dexamethasone 4 mg per day and cetirizine 10 mg per day with monitoring of renal function and ionogram; also, he received ordinary insulin. Day +2, surgical treatment was done, initial surgery consisted on bilateral average endoscopic meatotomy with exeresis of necrotic tissue. Day +4, the patient showed intolerance to amphotericin B with fever at 41 °C. Amphotericin B was stopped then resumed day +6 at a dose of 0.7mg per kg (total of 42 mg) every other day.

The culture showed expansive, fluffy and white colonies initially becoming gray to blackish gray by aging after 6 days at 27 °C (Fig. 4). Phenotypic methods identified *Rhizopus arrhizus*. Indeed, different incubation temperatures were used showing good growth at 27 °C and 37 °C and no growth at 50 °C. Microscopic examination of the colonies showed developed rhizoids, sporangiophores as 1–2.5 mm long and dark brown to black sporangium 120–250 µm in diameter (Fig. 5).

Day +7 the patient underwent surgery: trepanation of the anterior

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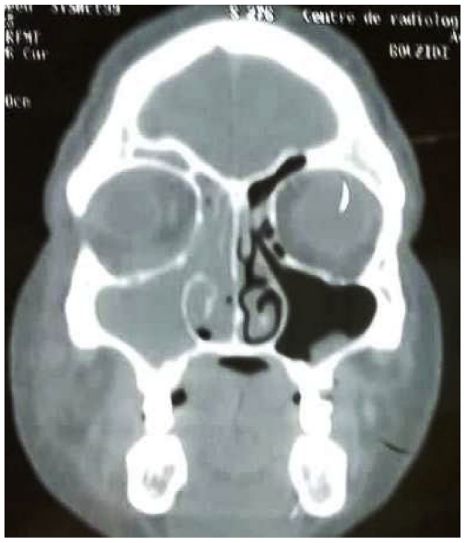

Fig. 1. CT scan with coronal-section of facial mass showing complete filling of the right maxillary sinus extended to the nasal fossa, ethmoidal sinus and frontal sinus.

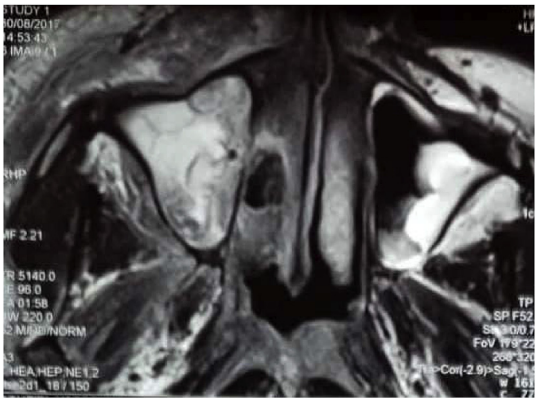

Fig. 2. MRI of the facial mass in axial section showing a total liquid filling of the right maxillary sinus with thickening in the mucous membrane.

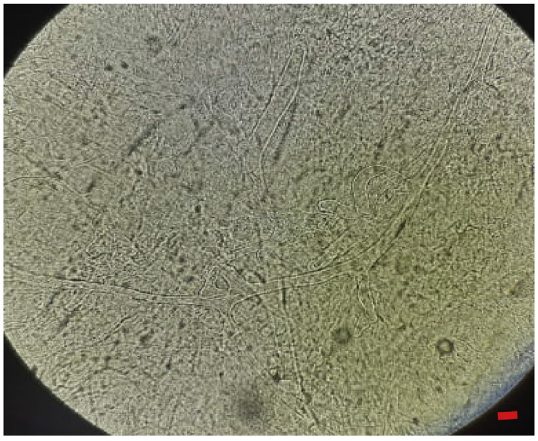

Fig. 3. Direct examination of the biopsy showing aseptate hyphae of mucorales with right-angle branching. **Scale bar** = 10 μm.

wall of the maxillary sinus was done with an evacuation of necrosis and pus every other day (day +7, day +9, day +11, day +13 …) until improvement of the local state on day +29 (Fig. 6) with good healing and appearance of neovascularization. Medical and surgical treatment was consolidated by hyperbaric oxygen therapy (HBOT) with a dose of 2.5 atm per session, 5 sessions per week. On day +30, 28 cures of Amphotericin B were totalized and 24 sessions of HBOT, the evolution was favorable with no recurrence within 2 years of follow-up.

3. Discussion

Mucormycosis is a serious relatively uncommon invasive fungal infection and one of the most aggressive and lethal invasive mycoses [1,4]. The fungi mainly affect patients with predisposing factors including uncontrolled diabetes [1,4–8] as was the case with our patient. The others predisposing factors are bone narrow or organ graft, malignancies such as lymphoma and leukemia, immunosuppressive therapy, renal failure [1,4,6]. Contamination is often through inhalation of fungal spores than ingestion or transcutaneous inoculation after breach of the skin barrier [2,6]. The pathogenicity of the fungal agent derives from its high affinity for vascular walls, leading to thrombosis and ischemic necrosis. Propagation is by contiguity or hematogenic [6,8].

The mucormycoses are usually grouped according to clinical presentation and anatomic predilection into 1 of 6 syndromes, although some overlap: sinusitis (rhino-facial, rhino-orbital or rhinocerebral), pulmonary, cutaneous, gastrointestinal, disseminated and other uncommon presentations, such as peritonitis (especially in the setting of peritoneal dialysis), tracheitis, mediastinitis, renal abscess, osteomyelitis, myocarditis, endocarditis, otitis externa, keratitis and isolated brain abscess in intravenous drug users [2,3,5].

Sinusitis occurs more frequently in patients with poorly controlled diabetes [2,5,9]. Prolonged fever is seen in most patients. Rhino-facial mucormycosis gives initial signs such as facial pain, nasal congestion and rhinorrhea, which are poorly specific [6]. Then appears necrotic eschars in the nasal cavity, the palate as was the case for our patient, or even the face [2]. Nevertheless, they are present in only 50% of patients. Contiguous extension to the orbit may lead to preseptal or orbital cellulitis, subperiosteal and orbital abscess, with resultant eyelid edema, chemosis, ptosis, proptosis, ophthalmoplegia, and loss of vision. Intracranial complications include epidural and subdural abscess, cavernous and, less frequently, sagittal sinus thrombosis, but frank meningitis is rarely observed [2,3,9].

Computed tomography (CT) is a useful radiological examination to appreciate the extent of the disease and to follow its evolution under treatment [5,9]. In diabetic patients with rhino-facial mucormycosis, cranial CT or MRI is strongly recommended to determine if sinusitis is present. In our case, CT and MRI of the facial mass were urgently requested in the face of the strong clinical suspicion of mucormycosis. If sinusitis is diagnosed, endoscopy with biopsy is strongly recommended to diagnose mucormycosis [9]. In view of the rapid progress of mucormycosis, weekly CT scans are strongly recommended, particularly in unstable patients [2,3,9].

Histopathological examination of the biopsy may present difficulties diagnosis in case of fragmentation of the fungal elements. In addition, mucorales filaments can be difficult to distinguish from those of *Aspergillus* and those cut transversely may be mistaken for yeasts or spores [2]. However, in typical presentation, the mucorales hyphae are broad (3–25 mm), thin-walled, non-septate or pauci-septate, with non-dichotomous, irregular branching, occasionally at right angles. The Mucorales do not stain as deeply with specialized fungal stains, such as Gomorimethenamine silver (GMS) or periodic acid-Schiff stain (PAS), but they can often be detected in tissue sections stained with hematoxylin and eosin (HE). Costaining with HE intensifies GMS staining of hyphae, potentially providing a unique clue for identification of Mucorales. Calcofluor white, Blankofluor, or Uvitex may enhance detection of hyphae and improve the discrimination between septate and aseptate molds. The diagnosis of mucormycosis has been made only on histopathological examination in several Tunisian studies [10].

The most frequently reported pathogens in mucormycosis are

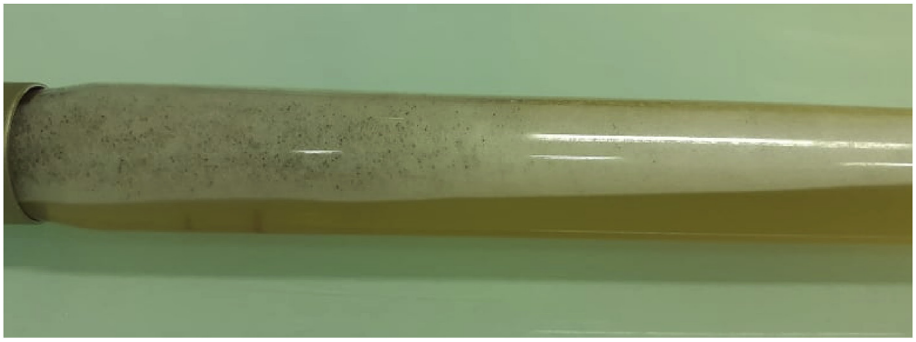

Fig. 4. Macroscopic morphology of *Rhizopus arrhizus* on medium Sabouraud chloramphenicol without actidione after 6 days of incubation at 27 °C.

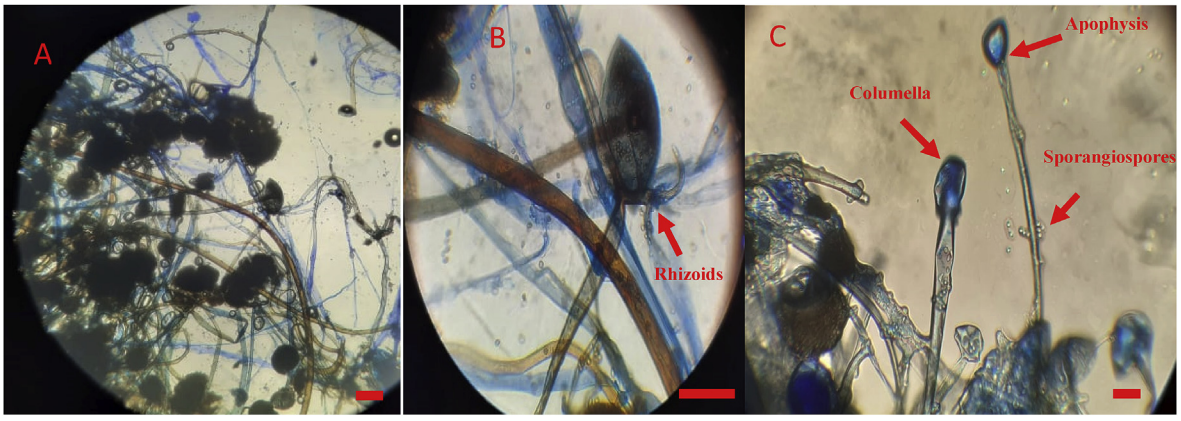

Fig. 5. Morphological characteristics of *rhizopus arrhizus:* **A:** long and brown sporangiophore, dark sporangium; **B:** presence of developed rhizoids, umbrella aspect of the ruptured sporangium; **C:** short apophysis, columella and sporangiospores. **Scale Bar:** A = 150 µm, B = 100 µm; C = 50 µm. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

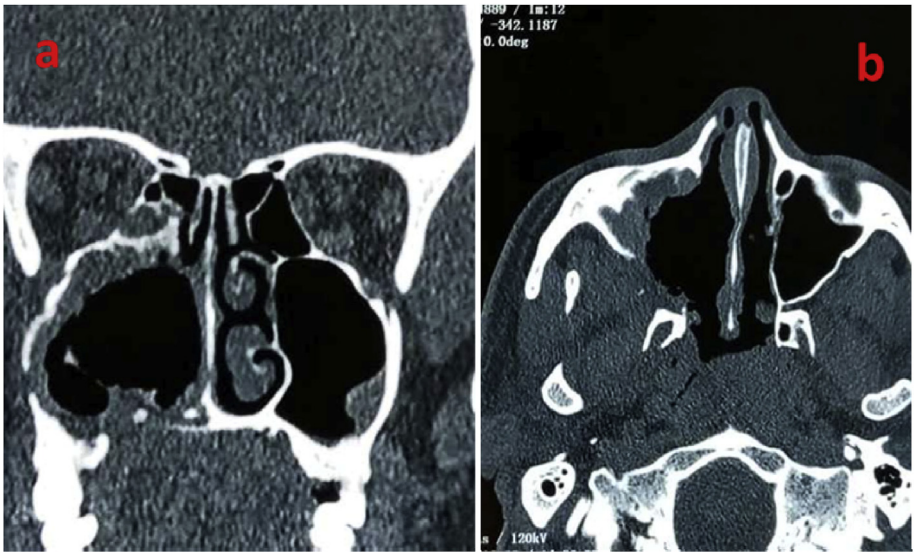

Fig. 6. CT scan of control (after surgery) in coronal (a) and axial (b) sections showing good pneumatisation of the sinuses with lysis of the right maxillary sinus floor.

Rhizopus spp, *Mucor* spp, and *Lichtheimia* spp (formerly of the genera *Absidia* and *Mycocladus*), followed by *Rhizomucor* spp, *Cunninghamella* spp, *Apophysomyces* spp, and *Saksenaea* spp.

Etiology of mucormycosis varies considerably in different countries. In Europe *Rhizopus* spp. (34%), *Mucor* spp. (19%), and *Lichtheimia* spp. (19%) were most commonly identified in patients with mucormycosis [11]. *Lichtheimia* spp were identified as the major cause of mucormycosis in a single hospital in Spain [12]. In India, although *Rhizopus* species are the most common cause of the disease, *Apophysomyces elegans, A. variabilis* and *Rhizopus homothallicus* are emerging species and uncommon agents such as *Mucor irregularis* and *Thamnostylum lucknowense* are also being reported [13,14]. Another new species of *Apophysomyces*, namely, *A. mexicanus*, has been reported from Mexico [15]. In Tunisia, all studies where mycological identification was done, reported *Rhizopus arrhizus* species [5,16]. This geographical variation emphasises the need to know local epidemiology.

Mycological diagnosis is important to confirm mucormycosis in the immediate on a positive direct examination. The latter, read urgently

after adding drops of KOH or lactophenol, shows mycelial filaments of mucorales easily identifiable. Direct microscopy with fluorescent brighteners or silver stains (Gomori-Grocott) is strongly recommended because it may increase sensitivity in cases of low fungal density [9,17].

Otherwise, the culture of specimens is strongly recommended for genus and species identification, and for antifungal susceptibility testing. Homogenisation of tissue should be avoided before culturing because it may cause loss of viability of the mucorales [5,9,17]. The culture is made on the medium of Sabouraud glucose containing antibiotics (chloramphenicol, gentamicin) without cycloheximide. The recommended incubation temperatures are 25 °C and 37 °C for a minimum of 5 days for optimize growth.

Phenotypic identification requires strong expertise in taxonomy based on macroscopic, microscopic, physiological characteristics, optimal growth temperature (most mucorales are thermophilic and tolerate up to 40 °C). The maximum growth temperature was 45 °C for *Rhizopus arrhizus* and until 52 °C for *Rhizopus microsporus.* Macroscopic examination shows flaky colonies of varying color: white (*Saksenaea*) to yellow (*Mucor*), brown (*Apophysomyces)* or gray (*Lichtheimia, Rhizopus, Rhizomucor)*. Observation of culture using a binocular magnifier allows to estimate the height of the mycelium and the branching of the sporangiophore which vary according to different genus of mucoralean fungi. Microscopic examination is based on observation morphological characteristics: sporangiophore branching, the sporangium (shape, color, size), the presence or absence of apophysis, coulumella, rhizoids, chlamydospores and sporangiospores [17].

Molecular identification for direct detection lacks of standardization [9,17]. However, molecular identification by PCR sequencing from colonies is useful when phenotypic identification is not concluant. In most trials, DNA genes ribosomal (18S, 28S, 5.8S) and ITS1 regions (internal transcribed spacer) and ITS2 were chosen as targets. Various PCR techniques such as conventional PCR, real-time PCR, PCR high-resolution melt analysis (HRMA), RFLP-PCR have been tested [3,17,18].

Antifungal susceptibility testing is recommended to adapt the treatment but it lacks of standardization. The European confederation of medical mycology recommended the use of technique **E-test** [9].

The management of mucormycosis is multimodal, including reversal of underlying risk factors, administration of antifungal agents, surgical intervention and various adjunctive therapies. Timely and adequately dosed antifungal therapy is necessary. Only two antifungals are currently available with reliable activity against most agents of mucormycosis amphotericin B (and the lipid formulations) and posaconazole.

In general, the treatment duration ranged from one week to three years with mean duration approximately 6 months. Isavuconazole and posaconazole may be administrated as maintenance therapy [3,9,19].

Associating surgical debridement, repeated according to evolution, to medical treatment is indispensable due to poor antifungal diffusion within necrotic tissue; it also reduces fungal load. Resection should be as complete as possible, until obtaining healthy margins. In our case surgery was done one day/2 consisting of washes, cleaning of the sinuses and nasal cavities and debridement of all necrotic lesions.

Hyperbaric oxygen therapy and cytokines (interferon gamma, GM-CSF) as adjuvants to medical treatment are under assessment. Hyperbaric oxygen therapy has a fungistatic effect and allows revascularization of ischemic tissue [20]. In our team we are used to apply HBOT in front of any invasive and necrotic cellulitis such as the case of our patient.

The functional and vital prognosis of mucormycosis is severe. Our patient benefited from a fast and adapted care which favoured the good outcome. In fact, the mortality rate remains high despite therapeutic progress and ranges from 30% to 80% [4]. The evolution depends essentially on the delay of diagnosis. Treatment, initiated urgently, associated antifungal therapy, surgical resection and control of risk factors. Herein, HBOT has proved its effectiveness in the treatment of mucormycosis.

Declaration of competing interest

There are no conflicts of interest for any authors.

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