CASE REPORT
ALLERGY AND RHINOLOGY
DOI: 10.5152/B-ENT.2023.22942

Rhino-Sinusal Mucormycosis: About the Management of 2 Clinical Cases

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Cite this article as: Ancion A, Mai-Liên Poirrier A, Dessard L, et al. Rhino-sinusal mucormycosis: About the management of 2 clinical cases. B-ENT. 2023;19(3):180-183.

ABSTRACT

Mucormycosis is a fungal infection with a high mortality rate due to a fungus of the mucorales order, ubiquitous in our environment. It is an uncommon disease that occurs in severely immunocompromised patients, poorly controlled diabetics, or those on chronic immunosuppression or corticoid therapy. It can also develop in immunocompetent patients with cutaneous lesions, facilitating their installation. Symptomatology varies depending on its location (rhino-orbito-cerebral, cutaneous, pulmonary, disseminated, etc.). The cases reported describe the management of 2 patients who presented with rhino-sinusal mucormycosis infection 3 months apart in the same geographic area. The risk factors and the evolution of the pathology were different in these 2 patients. This text also includes an explanation of the pathophysiology, a summary of the different diagnostic techniques, and management recommendations.

Keywords: Mucormycosis, fungal sinusitis, mucorales

Introduction

Mucormycosis is an angioinvasive fungal infection caused by a pathogen agent of the mucorales order, omnipresent in our environment.[1,2] This is a rare disease occurring mostly in immunocompromised patients, decompensated diabetics, patients under prolonged corticosteroid treatment but also in immunocompetent subjects with cutaneous-mucosa lesions, facilitating the installation of this fungus.[1,2] Clinical presentation depends on the localization. In the order of frequency, we have rhino-orbito-cerebral (44%-49%), cutaneous (10%-19%), pulmonary (10%-11%), disseminated (6%-11%), and gastrointestinal (2%-11%) forms.[1-3] We present 2 cases of sinonasal mucormycosis who presented in our department 3 months apart.

Informed consent was obtained from patients described below.

Case Presentations

Case 1

A 47-year-old woman immunocompromised for 6 months following a kidney transplant had continuous bilateral facial pain and headache for 2 weeks with a nasal obstruction and clear rhinorrhea. Anterior rhinoscopy showed ulceration of the septal mucosa. The cone beam computed tomography (CBCT) revealed a left pansinusopathy and lysis of several rhinosinus regions (Figure 1). A magnetic resonance imaging (MRI) completed this examination and confirmed diffuse involvement of the left ethmoid, which was suggestive of mucosal necrosis compatible with mucormycosis (Figure 2A and 2B).

Treatment with liposomal amphotericin B (Amb-L) intravenously (10 mg/kg/day) was started, and the patient underwent surgery to debride the necrotic tissue and confirm the diagnosis on biopsy samples in the same procedure. Middle meatotomy,

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Received: March 25, 2022 **Accepted:** March 09, 2023 **Publication Date:** August 9, 2023
Available online at www.b-ent.be

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Figure 1. Cone beam computed tomography showing left pansinusopathy with complete left ethmoid frontal filling and lysis of the ethmoidal septations, partial lysis of the papyraceous lamina, and lysis of the anterior part of the left cribriform plate at the level of the olfactory cleft.

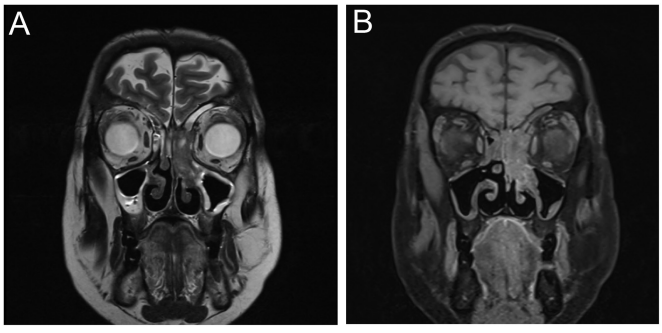

Figure 2. (A) Coronal T2 image: Magnetic resonance imaging showing infiltrative mucosal involvement of the left ethmoidal labyrinth, involving the left olfactory cleft and focally the left middle turbinate. Intraosseous extension lysing the left ethmoid sieve and lateral lamina, invading the left papyraceous lamina in its middle third. (B) Post-contrast coronal T1 image with fat saturation that highlight the left papyraceous lamina and olfactory cleft involvement.

middle turbinectomy, radical ethmoidectomy, and endoscopic sphenoidotomy were performed. Anatomopathology and bacteriology results confirmed the presence of degenerated mycotic hyphae in the necrotic material, consistent with a rhizopus microsporus (Figures 3 and 4).

Main Points

- Mucormycosis is a rare infection with a high mortality rate.
- In case of rhino-sinus involvement, the symptomatology is poor and atypical.
- Multidisciplinary management by ear, nose, and throat (ENT) specialists, neurosurgeons, pathologists, infectiologists, microbiologists, and radiologists is imperative in order to improve the prognosis.
- The treatment of mucormycosis is based on 3 elements: antifungal medication, surgical management, and correction of risk factors where possible

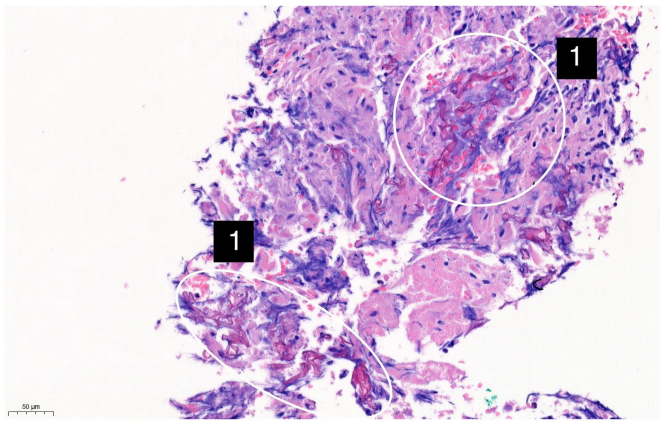

Figure 3. Extemporaneous anatomopathology: Hematoxylin-eosin stain showing fragments of ulcerated sinus mucosa associated with necrosis and inflammatory infiltrate. 1: mycotic filaments.

After 7 days of treatment, AmB-L was replaced by isavuconazole (ISZ) as the patient's renal function was deteriorating. A follow-up nasofibroscopy showed a partially necrotic lesion in the ethmoidal roof. An operation was performed 13 days after the first one. Ethmoidal roof bony dehiscence without dural breach was visualized without cerebrospinal rhinorrhea (Figure 5). The MRI performed the next day showed persistent mycotic involvement of the crista galli, with no apparent transdural extension. After 13 days of ISZ treatment, AmB-L was reintroduced at a dose of 5 mg/kg/day due to resistance to this treatment for 4 weeks. There was no further progression of mucormycosis thereafter clinically or on follow-up CT scans and renography. The treatment was stopped after 5 months. The clinical, endoscopic, and biological evolution remains good at the moment, although we are more than 7 months from the end of the treatment.

Case 2

A 51-year-old female patient presented with frontal and occipital headaches since a week. She complained of nasal congestion, hyposmia, and mild photophobia. Her medical history included poorly controlled diabetes and a lumbar stenosis treated with Medrol 16 mg 3×/day for over a year. Nasal endoscopy showed mucopurulent secretions from the left sphenoidal ostium into the cavum. The CT scan showed left sphenoidal sinusitis (Figure 6).

After 6 days in hospital, she underwent endoscopic sinus surgery which revealed a necrotic aspect of the entire vomer extending to the lower part of the sphenoidal sinuses. Middle meatotomy, ethmoidectomy, and sphenoidectomy were performed. Treatment with AmB-L was started. Pathological anatomy showed mucormycosis-like mycelial filaments and microbiology showed *Rhizopus arrhizus*.

On day 16, she required revision surgery during which almost total nasalization and a large portion of the bony palate was resected. A few days later, she presented with an atypical lung infection. On the 30th day, after an improvement of her general condition, she underwent a new surgical debridement (Figure 7). The patient presented with new respiratory failure, but refused transfer to intensive care and requested discontinuation of treatment after 49 days of AmB-L and died at day 50.

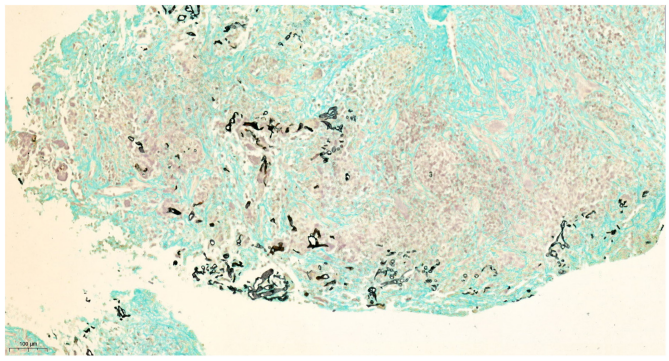

Figure 4. Extemporaneous anatomopathology: Special Gomori-Grocott stain showing necrotic areas with degenerated hyphae (stained black with special stains).

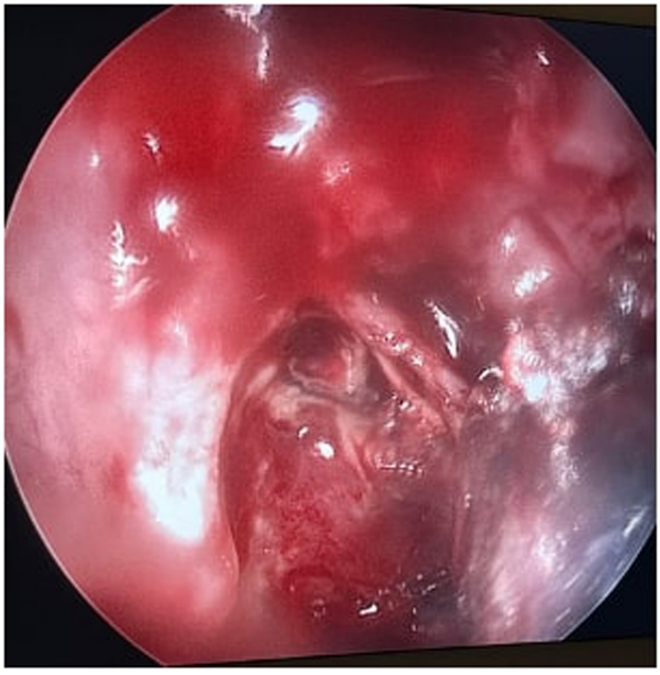

Figure 5. Anterior nasal endoscopy image showing ethmoidal artery dehiscence with an adjacent medial millimetric area of meningeal dehiscence without dural-meridian effraction.

Figure 6. Computed tomography scan showing a specific filling of the left sphenoidal sinus.

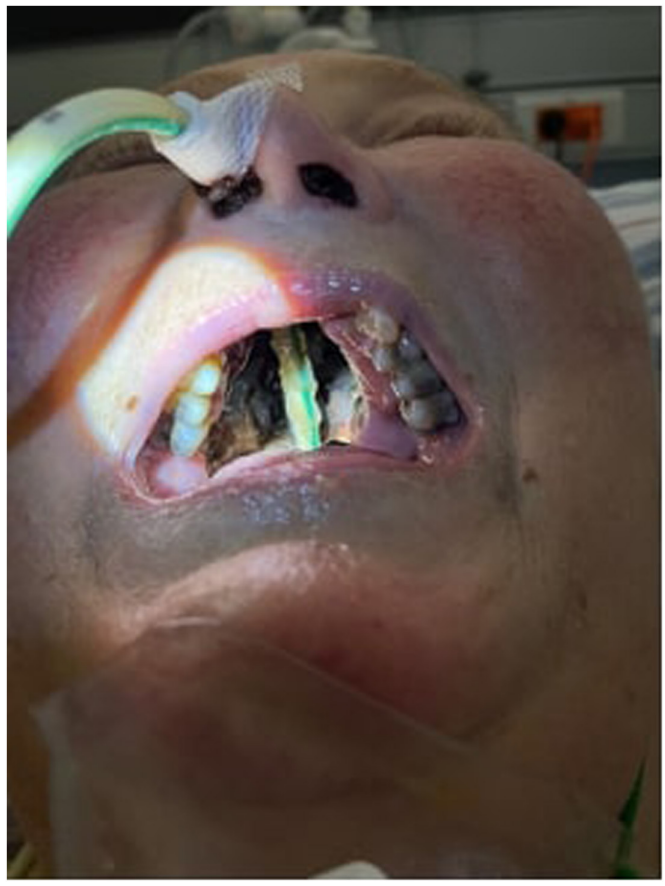

Figure 7. Endobuccal view of the surgical resection.

Discussion

Physiopathological Mechanisms

Mucormycosis is mainly transmitted by inhalation but also by ingestion or direct contact.[4] There are different species responsible for mucormycosis, depending on the geographical location.[2,4] The mycelial filaments have a vascular tropism favoring hematogenous diffusion and angioinvasion by these filaments. The spores adhere to and destroy endothelial cells, causing ischemic lesions leading to extensive tissue necrosis by vascular thrombosis.[5] In immunocompromised patients, neutropenia (especially if deep and prolonged) reduces the efficiency of neutrophil elimination of mucosal filaments, and phagocytosis by macrophages is impaired.[6] In acidosis in unbalanced diabetics, the iron bonds of transferrin are disrupted, which increases the amount of free iron and increases fungal growth.[5] For these reasons, this condition occurs almost exclusively in compromised patients.[7,8] Prolonged systemic corticosteroid therapy, used notably for the treatment of COVID-19 infections, has been described to promote mucormycosis.[9] The symptomatology depends on the infection site. In rhino-cerebral infection, it is often poor and atypical, leading to delays in diagnosis. The most common symptoms are fever, rhinorrhea, headache, and nasal congestion.[10]

Diagnosis

The mucormycosis diagnosis can be complex and should not delay management. It is made by several different methods. The first step is imaging, with CT scan and MRI. Nasal endoscopy with biopsies and bacteriological sampling is essential.[11,12]

As this condition progresses quite rapidly, it is advisable to monitor its evolution by weekly scans.[11] Anatomopathology allows the visualization of mucosal hyphae by direct microscopy. The specimen should be stained with hematoxylin and eosin, periodic acid Shiff or Gomori-Grocott. The mucosal hyphae are 6-16 µm wide, non-septate, and have irregular branching at 90° angles.[11] Immunohistochemical methods using monoclonal antibodies and polymerase chain reaction on fresh or paraffin-embedded material are also used. They are highly specific but sensitivity is variable.[4,11] As for microbiology, the culture is carried out in Sabouraud's medium at 37°C, growth takes at least 24-48 hours and macroscopically reveals mucosal colonies with a flaky texture whose color varies according to the species: yellow for Mucor, brown for Apophysomyces, and gray for Lichteimia and Rhizomucor.[4,13]

Management

The mucormycosis treatment is based on 3 elements: antifungal medication, surgical management, and correction of risk factors where possible.[6,11,14] The first-line drug treatment is AmB-L at a dose of 5-10 mg/kg/day. The dose should be maximal from day 1, and a gradual increase is not recommended. The main side effect is renal toxicity. In this case, the first option is to decrease to 5 mg/kg/day. If there is no improvement in renal function, the second line can be switched to ISZ (p.o. or i.v. 3 × 200 mg d1-d2 then 1 × 200 mg from d3) or posaconazole (PSZ, p.o. or i.v. 2 × 300 mg d1 then 1 × 300 mg from d2).[5,6,11,14] In cases of extensive and rapidly progressive disease, AmB-L can be combined with ISZ or PSZ.[11] In case of failure of AmB-L treatment, salvage treatment with ISZ and PSZ is indicated.[11] There is still no clear consensus on the duration of treatment, but it is recommended to continue treatment at least until resolution of symptoms and stabilization of imaging. Surgical treatment by debridement to healthy margins should always be performed and as often as necessary as it improves prognosis.[5,6,11,14] However, the patient's general condition does not always allow surgery.[6,14]

Prognostic

The mortality rate varies from 40% to 80% and depends on the patient's conditions and comorbidities as well as the site of infection.[11] The 2 clinical cases illustrate 2 very different evolutions of the same pathology. It is therefore interesting to put forward explanatory hypotheses on this subject. We can envisage several possibilities: first, a different aggressiveness according to the type of mucor, second, the speed of medical and surgical management which conditions the prognosis, and third, the difference in the initial general state of the patients. A multidisciplinary involvement of ENT specialists, neurosurgeons, anatomopathologists, infectiologists, microbiologists, and radiologists is imperative. This unusual pathology requires rapid and coordinated management by the different specialists in order to improve its prognosis.

Informed Consent: Informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.R., A.A.; Design – A.A., F.R.; Supervision – AL.P., F.R., Ph.L.; Materials – A.A., N.D., G.R., U.D., P.L., L.D., A.B.; Data Collection and/or Processing – A.A., F.R.; Analysis and/or Interpretation – F.R., G.R., U.D., N.D., AL.P., P.L., A.B.; Literature Review – A.A., F.R., L.D.; Writing – A.A., F.R.; Critical Review – F.R., G.R., U.D., P.L., A.B.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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