Fatal rhinocerebral mucormycosis in diabetic patients: report of two cases

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Abstract

Mucormycosis is a potentially serious and quite rare fungal infection, caused by the *Saprophytic fungus*, of the order *Mucorales*, *Absidia*, *Mucor*, *Rhizomucor* and *Rhizopus*. These agents are commonly isolated from decomposing soil and plant material and remain dormant in healthy individuals in the respiratory and digestive tubes when inhaling or ingesting contaminated food. It becomes pathogenic when the individual gets immunocompromised and debilitated, progressing to an aggressive and often lethal clinical picture, which requires accurate diagnosis and prompt treatment. There are reports in the literature of its gastrointestinal, pulmonary, cutaneous, rhino-orbital-cerebral, endocardial and osteoarticular forms. Regardless of its location, treatment necessarily includes early clinical diagnosis, stabilization of systemic comorbidities and aggressive drug and surgical therapy, resulting in a mortality rate of up to 40% of cases. It is a relevant topic in tertiary care hospitals in terms of contamination, being a matter of concern if present in premature newborns and burn therapy units. The purpose of this article is to report a case of rhino-orbital-cerebral Mucormycosis acquired in the community by a decompensated diabetic patient who evolved with invasion of the hard palate, paranasal sinuses, orbits and cavernous sinus, spreading to the central nervous system and leading to thrombosis the cavernous sinus.

Introduction

Mucormycosis, also known as Zygomycosis, is characterized by an opportunistic, rare, and severe infection caused by fungal filaments belonging to the *Mucoraceae* family. Eleven genera and 27 species of *Mucorales* are associated with human infections, with *Rhizopus arrhizus* being the most common etiological agent (70% of cases) that causes Mucormycosis worldwide, followed by *Lichtheimia*, *Apophysomyces*, *Rhizomucor*, *Mucor* and species de *Cunninghamella* [1].

The infection by this fungus is considered an emerging disease, given the increasing number of patients who, for various reasons, have clinical and immunological impaired conditions such as unknown diabetes mellitus or non-compensated transplanted marrow patients or solid organs and immunosuppressed individuals [2]. Contamination can occur from environmental sources through the contaminated soil, plant decomposing and animal manure, with the main infection route, is inhalation, whilst admitting up the infection by skin continuity, contamination catheters, and puncture with contaminated needles in the hospital environment. The bad prognosis is the rule, which requires training for early diagnosis [2].

Case report 1

A female patient, 68, leukoderma, held extraction of maxillary canines 01 months of her final hospitalization. The patient evolved with recurrent sinusitis has been treated on an outpatient basis with antibiotic therapy and had no improvement. After the appearance of important clinical signs and the

evolution of a brain abscess (figure 1), she was admitted for infectious research, when a positive medical history for extremely decompensated diabetes mellitus was found.

On clinical examination, she was lucid, oriented, eupneic, responsive, reporting pain in the hard palate and face, in addition to having bilateral eyelid ptosis, bilateral amaurosis, ophthalmoplegia, and bilaterally fixed mydriatic pupils. The patient was followed up by the team of otolaryngology (ENT), ophthalmology, neurosurgery, and maxillofacial.

When mucormycosis was suspected and the brain abscess was checked, the following drugs were prescribed and administered: Vancomycin, Meropenem, and Amphotericin B. An incisional hard palate biopsy was performed to confirm the diagnosis and endoscopic sinusectomy to unclog the ostium. Due to the clinical and imaging signs, cavernous sinus thrombosis was considered and even after agglutination of the brain infection and craniotomy for drainage, the patient passed away.

Case report 2

A female patient, 42, leukoderma, was admitted with a headache, cellulite on the right maxilla and positive medical history for hypothyroidism, decompensated type 1 diabetes, using non-regular insulin.

The patient presented hemiplegia of the limbs on the left and paralysis in the hemiface on the right and also extensive oroantral communication in the posterior region of the right maxilla – affecting the entire hard palate and portion of the soft palate – and severe mobility in the teeth on the right side. There was also observed palpebral ptosis on the right, visual acuity and eye movement of the right eye without response, mydriatic and fixed right pupil. Upper dental elements on the right side with mobility.

In follow-up by the maxillofacial surgery and ENT teams, the patient was admitted with complicated rhinosinusitis involving hemimaxilla and right orbit with possible osteomyelitis in the sinuses on the right and suspected cavernous sinus involvement. The plastic surgery team drained the abscess in the maxilla and after 15 days she had a hemorrhagic stroke with a subdural hematoma on the right. After 40 days of recovery from cerebritis, the hematoma regressed but persisted with significant sinusitis. Through the maxillofacial surgery team, the surgery was scheduled for debridement of the sinuses and right hemimaxillectomy to remove necrotic tissues (figure 2 and 3).

Even after drainage of the brain abscess and intensive treatment and monitoring by the ENT, ophthalmology, maxillofacial surgery, neurosurgery and medical clinic teams the patient died.

Discussion

Mucormycosis is inherently found in soil and decomposing plants [3]. The main pathogenesis form is hematogenous dissemination (angio-invasion) due to its adhering ability and invade the endothelium of blood vessels neighbors, allowing it to invade any organ system and represents the third fungal infection angioinvasive most common [4].

The disease can be present in the lung tissue, gastrointestinal, rhino-orbital-cerebral and distributed in the skin [5]. Rhinocerebral and pulmonary forms account for about 54% and 60% of cases respectively. The primary site of infection differs with the various genders included in the Mucorales order and the underlying systemic condition of the organism [1]. It is a rare condition that arises more commonly in people with compromised immunity, such as in transplanted solid organs, leukemia, lymphoma, myeloma, diabetes mellitus, extreme burns, kidney dysfunction, liver cirrhosis, antineoplastic chemotherapy, chronic corticosteroid use, or immunosuppressive treatment [6].

Nithyanandam et al. [7], describes a mortality rate of approximately 40% in diabetics with rhinocerebral mucormycosis and a similar survival rate for rhinocerebral disease in patients with hematological neoplasms [8]. Mucormycosis rarely develops in other cases of immunosuppression such as AIDS or in immunocompetent patients [9].

In rhino-orbital-cerebral mucormycosis, the most common complaints are purulent or bloody rhinorrhea (most of the time unilateral), fever, headache, and general malaise. Fever is variable and may be absent in up to half of cases [10]. When orbital involvement occurs, complaints are eyelid edema, diplopia and decreased visual acuity. On physical examination, unilateral or bilateral rhinorrhea, proptosis, chemosis, periorbital cellulitis, alteration of the intrinsic and extrinsic ocular motricity and amaurosis can be observed. Nasofibrolaryngoscopy can demonstrate necrotic lesions in the nasal mucosa [11].

If left untreated, the infection typically progresses from the ethmoid sinus to the orbit, causing loss of extraocular muscle activity and exophthalmos. It is very important to keep in mind that, if mucormycosis is suspected, initial and empiric therapy with pollinated antifungal should begin before the diagnosis is confirmed, rather than waiting for a long sequence of diagnostic tests to be completed [11].

Rhinocerebral presentation of Mucormycosis remains the most common clinical form of the disease, accounting for half of all cases [12]. About 70% of cases of rhinocerebral mucormycosis (occasionally referred to as craniofacial) are found in diabetic patients in ketoacidosis [13], but it also occurred in patients who received solid organ transplantation or those with prolonged neutropenia [14]. Rhinocerebral disease is a growing problem in patients undergoing hematopoietic stem cell transplantation [15] and in these cases, it has been widely associated with the use of steroids for graft-versus-host disease. The infection can spread to the central nervous system through the orbital apex, the involvement of bony walls of the paranasal sinuses, or the cribriform plate of the ethmoid [15].

Risk of death increases rapidly as the fungus penetrates the skull and reaches the main intracranial vasculature. The early surgical excision of the infected sinuses and proper debridement of the retro-orbital space, in this situation, might prevent the infection from spreading to the eye, therefore preventing its need for enucleation, resulting in an exceptionally high rate of cure for patients (around 85 %) [7]. To ensure that all necrotic tissue has been debrided and the infection has not advanced, periodic surgical exploration of the sinuses and orbit may be required [7].

The diagnosis is based on the association between mycological analysis, histopathology and clinical signs [16]. Treatment development relies on the speed of diagnosis [17] and the implementation of surgery and antifungal therapy [18]. From an imagery point of view, CT scan is the most commonly available diagnostic aid, yet, bone loss is also seen late in the course of infection and other tissue necrosis has already occurred.

Magnetic resonance imaging (MRI) is a very useful technique for detecting potential intradural and intracranial extensions. Perineural presence can be shown by a contrast-enhanced MRI [19]. After all, it is very possible for patients at an early stage of the disease to have regular imaging scans, which reinforces that a surgical procedure with early biopsies, if there is clinical suspicion, is necessary for a correct diagnosis. Histological diagnosis of mucormycosis is supported by the finding of non-septate or small septate hyphae and these changes are different from that found, for example, in the stain of *Aspergillus*, the hyphae of which are narrower and often septate. The genus and species of the organism can be determined by growing the infected tissue in its own environment. Nevertheless, microorganisms are rarely isolated in blood, cerebrospinal fluid or sputum cultures [20].

The treatment of Mucormycosis is focused on multimodal therapy: application of antifungal drugs, regulation of predisposing factors (diabetes, immunosuppressive agents) and surgical debridement to eliminate infected and necrotic tissue [21].

The most widely used drug is Amphotericin B, classic or liposomal, in high daily doses (5 mg/kg/day) and may include an additional antifungal agent, such as Caspofungin, for 6 to 8 weeks [14]. Posaconazole (800 mg/day) is used in a reduction therapy and can be used in combination with Amphotericin B, as this medication is highly active against some species of Mucorales. Hyperbaric oxygen can be used as adjuvant therapy, but its benefit is not yet well established [21].

The responsiveness of the species to drug treatment may differ considerably such that the patient receiving Amphotericin B alone is inadequate during the diagnosis time. Minutes and hours matter, and if clinical suspicion is high, work can continue immediately, even if the patient is clinically healthy because late diagnosis is correlated with adverse outcomes [22]. Treatment success depends directly on efficacy, speed of diagnosis [17], and a combined approach between the surgical procedure and antifungal therapy [18].

Surgery (debridement) is necessary and urgent due to an immense amount of tissue necrosis arising during mucormycosis, which cannot be stopped by the death of the organism [23]. Given the fast-growing nature of rhinocerebral mucormycosis and the substantial rise in mortality as the infection reaches the brain, diabetic patients with headaches and vision changes are candidates for early assessment with imaging and nasal endoscopy to rule out mucormycosis. Radiographic findings are below clinical progression in this disease and a negative imaging study does not provide a justification for postponing more aggressive diagnostic maneuvers (endoscopy with biopsy) if the clinical suspicion is high [23].

In cases where the suspicion of Mucormycosis is high, blind biopsies of the sinus mucosa and/or thickened extraocular muscles are required for a conclusive diagnosis and the endoscopic approach is the most suitable [24].

The nature of the underlying disease and the reversibility of immune dysfunction are also important determinants of survival. Poor prognosis factors are: (a) delay in starting treatment, (b) intracranial involvement (hemiplegia and hemiparesis), (c) palatal or orbital, as well as (d) bilateral involvement of the sinuses and (e) facial necrosis [25]. Cerebral involvement is characterized by changes in the state of consciousness, which can cause seizures and/or hemiplegia. If occurs invasion of the cavernous sinus, fungal aneurysms of the internal carotid artery are common and generally fatal [19].

Mucormycosis is a rare opportunistic infection with an adverse prognosis. Very commonly, it affects those with a compromised immune system. Prevention involves environmental control, avoiding or minimizing direct contact with fungal propagules present in plants, flowers and domestic dust, and correct management of systemic impairments already present in the health of the patient.

Disclosures And Declarations

Consent to publish

We certify that the submission is an original work and is not under review at any other publication. All authors have seen and agree with the contents of the manuscript.

Conflict of interest statement

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Role of funding source

There is no financial interest to report.

Ethical approval

All procedures followed were in accordance with the ethical standards required by the institution. Informed consent was obtained from all patients for being included in the study.

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Figures

Figure 1

Axial section on computerized tomography (CT) showing intracranial abscess

Figure 2

Extensive necrotic wound

Figure 3

Excised hemi-maxillary and necrotic