CASE REPORT

Rhinocerebral mucormycosis: literature review apropos of a rare entity

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SUMMARY

Mucormycosis is a rare fungal infection that affects immunocompromised patients, and the rhinoorbitocerebral presentation is the most common clinical form of the disease, often associated with diabetes mellitusThe treatment is complex and involves amphotericin B and surgery. Studies show increasing success without or with minimal surgeries. The authors present the case of a diabetic woman with a 1-month history of intranasal and right periorbital pain associated with progressive deficit of various cranial nerves, sudden amaurosis and homolateral ptosis. *Rhizopus oryzae* species was identified in pus in the nasal mucosa. She was treated with antifungal therapy and minimal surgical debridement with success. The authors decided on publication because of the rarity of this entity, alerting for the need of a high suspicion index for the diagnosis, which should be made as early as possible due to the high mortality rate, as well as presenting data about the increasing discussion of therapeutic strategies, with some new approaches that prioritise minimal surgeries.

BACKGROUND

The class of zygomycetes is divided into two orders: Mucorales and Entomophthorales. The order Mucorales is responsible for an acute angioinvasive infection, called mucormycosis, usually in immunocompromised patients with high morbidity and a mortality rate of over 60%, depending on the type of the infection and the patients' comorbidities.[1]

Mucorales are ubiquitous saprophytic fungi usually found in the soil and decomposing organic matter.[2] This order includes several genres, the most common being the *Rhizopus*, followed by *Mucor*, as well as *Rhizomucor*, *Absidia*, *Apophysomyces*, *Cunninghamella* and *Saksenaea*.[3] Although exposure to these organisms occurs every day, their low virulence causes them to seldom originate disease. The true disease incidence is unknown, but it is believed that there are approximately 500 cases/year in the EUA.[4]

These fungi are classically characterised by non-septated, wide-shaped ribbon hyphae (10–15 (m microM), branching at right angles ranging from 45 to 90°.[5] Histopathologically, they originate tissue infarction and angioinvasion with thrombosis and tissue necrosis, a defining characteristic of the pathophysiology of this infection.[6]

Mucormycosis is a rare (10 to –50 times less frequent than invasive aspergillosis or candidiasis) but potentially fatal infection, and it is the third most common invasive fungal infection,[3] being described worldwide with a possible seasonal variation (some articles suggest a higher incidence from August to November).[7]

Fungi normally enter the host by inhalation, but it can also infect by ingestion or percutaneous inoculation. This infection usually presents with rhino-orbito-brain involvement (40–49%), but other forms of infection are possible, in particular pulmonary, disseminated, cutaneous or gastrointestinal, with the localisation normally depending on the patient's comorbidities and risk factors.[8]

Among the immunosuppression states, we highlight haematological malignancies (a major risk factor), transplantation (bone marrow or solid organ), neutropenia, diabetes mellitus, corticosteroid therapy and deferoxamine use. Mucormycosis is rare in solid organ tumours and in immunocompetent patients. When it occurs in such cases, it has been associated with a traumatic event. An infection with the HIV does not appear to increase the risk of mucormycosis, given the role of neutrophils (and not of lymphocytes) in the protection against this infection.

The authors decided to publish a case of rhino-orbito-cerebral mucormycosis in a woman with poorly controlled diabetes mellitus, because of its rarity and consequent diagnostic difficulties, associated with the lack of diagnostic methods, the need for a high index of suspicion and the limited treatment options. We also made a review of the literature, with a MEDLINE research for articles written in English since 1966 using the term mucormycosis, aiming to raise awareness towards a rare entity with high morbidity and an early diagnosis and treatment-dependent prognosis.

CASE PRESENTATION

We present the case of a 46-year-old woman with a poorly controlled type 2 diabetes mellitus (glycated haemoglobin of 8.3%), with 2 year of evolution, treated with oral antidiabetics and with microvascular lesions (retinopathy and nephropathy).

She went to the hospital with right side intranasal and periorbital pain of 1 month duration associated with II, III, IV, V, VI and VII cranial nerves deficits and sudden ipsilateral blindness plus palpebral ptosis. On physical examination, the patient had right-sided mydriasis, disc oedema, absence of the corneal and pupillary reflexes and facial paresis, without any other neurological signs.

INVESTIGATIONS

Analytically, the absence of leukocytosis, as well as an erythrocyte sedimentation rate of 90 s and hyperglycaemia (275 mg/dl), was noted.

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Brain CT scan was normal. Lumbar puncture was performed, with the finding of a lymphocytic cerebrospinal fluid without other changes. Ophthalmological observation found right central retinal artery occlusion (pale, milky, oedematous retina with attenuated arterioles and a cherry-red macula).

In this context, the patient was admitted for a diagnostic investigation.

Of the diagnostic complementary exams requested, we relevate: HIV, hepatitis C and hepatitis B viruses were negative, and the salivary glands ultrasonography and chest x-ray were normal. Cerebral MRI revealed signs of inflammation in some of the right anterior ethmoid cells and inflammation of the trigeminal nerve in its right cisternal route, extending above to the ipsilateral cavernous sinus and to the superior orbital fissure and right orbital apex. In view of these chances, the patient was observed by otorhinolaryngology, which described right middle turbine hypertrophy with pus that was harvested by a swab sample. Direct examination documented the presence of hyphae, with cultural identification of the fungus Rhizopus oryzae.

TREATMENT

After these findings, the therapeutic strategy was discussed with neurosurgery and otorhinolaryngology specialists. In an attempt to preserve as much of the affected tissues and structures as possible, we opted for medical treatment with liposomal amphotericin B at a dose of 5 mg/kg/day and right middle turbinectomy.

OUTCOME AND FOLLOW-UP

After 1 month of treatment, a right neck swelling was noted. Owing to the suspicion that this neck swelling could be a pathogen reservoir, the patient underwent modified radical neck dissection with right occipital lymph node biopsy. The same agent was again identified. After this surgery, there was partial recovery of the neurological deficits, except for the right amaurosis and paresis of the VI and VII cranial nerves. Cerebral MRI control demonstrated rhinocerebral stabilisation of the disease. After 5 months of therapy, treatment with amphotericin B was suspended due to a total cumulative dose of 35 g. At the time of discharge from the hospital, the patient was clinically stable, keeping the neurological deficits described above. Since then, the patient was followed as an outpatient in Internal Medicine, Nephrology and Endocrinology consultations. Metabolic control in an ambulatory was very difficult, requiring the initiation of insulin therapy. In 2005, owing to the sequelae of mucormycosis, the patient was subjected to eventration of the right eyeball, with subsequent prosthetic replacement. There was no evidence of reactivation of infection at this time. Currently, 9 years after conservative surgery and medical treatment, the patient remains asymptomatic and without evidence of disease recurrence.

DISCUSSION

Mucormycosis usually begins on the palate or in the sinuses and progresses to the orbit and the brain, invading the retro-orbital, ethmoid and sphenoid sinus regions. It can affect one or more cranial nerves, particularly the III, IV and VI. Clinical manifestations may include black nasal secretions, fever, lethargy, headache, orbital pain, sudden loss of vision, ophthalmoplegia, proptosis, ptosis, mydriasis, corneal anaesthesia, chemosis, periorbital cellulitis, sinusitis, epistaxis, facial paralysis, loss of sensation in the trigeminal nerve territory and seizures.

Some patients develop a slower and insidious form that develops itself during more than 4 weeks (as it seems to be the case we described before), with an average time of symptom duration of 7 months.[8] Diabetes was involved in more than 67% of these cases and in several of them, surgical treatment was not required. In our patient's case, the involved risk factor for the infection was her poorly controlled diabetes. The typical manifestations of this entity did not raise the suspicion of mucormycosis in the emergency department, and it was only after the cerebral MRI changes that the diagnosis was considered and the observation by otorhinolaryngology doctors was requested. For all that has been exposed and given the rarity of the entity and the diversity of the manifestations, diagnosis in time is dependent on a high degree of suspicion; hence, the authors deem it appropriate to publish the case. Histological examination of the biopsy tissue with culture is the gold standard.[8] Other diagnostic methods include CT or MRI of the brain/face to document sinus or adjacent structures involvement, as was present in this case.

Therapeutic efficiency encompasses early diagnosis, correction of reversible causes, directed antifungal therapy with amphotericin B (liposomal formulation in the dose of 5–10 mg/kg/day) administered for months and surgery (early and aggressive debridement, often disfiguring, with removal of the palate, nasal cartilages and orbit). In this case, the best surgical option was discussed with several specialists, with the final decision being conservative intervention with turbinectomy and drainage of the sinuses. The initial course was unfavourable, with progression of the infection to the cervical region, requiring surgical intervention. There are a few poor prognostic factors described in the literature, including the delay in starting treatment in the six days after diagnosis, hemiparesis or hemiplegia and bilateral involvement of the sinuses, orbit and palate.[8] Many of these factors were present in the case described. Some studies have linked diabetes to a more favourable prognosis.[9] In the case described, the fact that the option was taken for more limited and less aggressive surgery did not interfere with the patient's favourable result and contributed to a lower morbidity. So, as some studies show, this can be an option. Given the rarity and severity of mucormycosis, the authors publish this case as a reminder of this clinical entity, aiming to warn about the new therapeutic challenges, particularly with less radical surgery.

Learning points

- Mucormycosis is a rare fungal infection, potentially fatal, that usually affects immunocompromised patients, and the rhino-orbito-cerebral presentation is the most common clinical form of the disease, often associated with diabetes mellitus.
- Clinical manifestations may include black nasal secretions, fever, lethargy, headache, orbital pain, sudden loss of vision, ophthalmoplegia, proptosis, ptosis, mydriasis, corneal anaesthesia, chemosis, periorbital cellulitis, sinusitis, epistaxis, facial paralysis, loss of sensation in the trigeminal nerve territory and seizures, and the most typical sign of infection is the presence of a necrotic ulcer in the palatal or nasal mucosa.
- Diagnosis in time is dependent on a high degree of suspicion.
- Symptoms of sinusitis associated with the sudden onset of blurred vision or diplopia in a diabetic or otherwise immunocompromised patient should raise the possibility of mucormycosis, with immediate diagnostic and therapeutic intervention.
- The treatment is complex, prolonged and involves the correction of reversible causes, administration of amphotericin B and surgery (including simple sinus drainage or even the radical debridement and excision of the orbit), but recent studies show increasing success without surgery or with minimal surgeries.

Competing interests None.

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