Case Report

Cranial nerve palsy: an unusual presentation of a fulminant fungal disease.
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Running title: Infectious cranial nerve palsy

SUMMARY
Mucormycosis is a rare and dramatic fungal disease with a high mortality rate. We report a case of rhino-orbital mucormycosis, which commenced as cranial nerve palsy, in a woman with ignored diabetes mellitus. Mucormycosis should therefore be taken into consideration during the differential diagnosis of cranial nerve palsy, especially in diabetic or immunocompromised patients.

Keywords: Mucormycosis; cranial nerve palsy; mycoses; rhino-orbital mucormycosis; diabetes mellitus

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INTRODUCTION

Mucormycosis (MM) is a severe infection, characterized by an extensive tissue invasion by hyphae of various fungal species of the order Mucorales. The most frequent agents are *Rhizopus*, *Mucor*, and *Lichteimia*, whereas *Cunninghamella*, *Saksenaea*, *Apophysomyces*, *Cokeromyces*, *Rhizomucor*, *Syncephalastrum*, and *Actinomucor* are responsible only for 1-5% of cases (Kwon-Chung 2012, Gomes et al 2011).

It is a rare fungal disease, but one which has been increasing in frequency in the last few years, due to the rise in immunosuppression in hospitalized patients, both as a result of various diseases and therapy (Petrikkos et al 2012). It is one of the most rapidly fatal fungal infections. Despite aggressive treatment, the overall mortality rate for mucormycosis remains high, with figures ranging from 20 to 50% (Lanternier et al., 2012, Zilberberg et al., 2014, Skiada et al., 2011).

Mucorales are widely distributed in the environment, especially in organic substrates: vegetable matters, decaying fruits, bread, soil, animal excreta, excavation and construction sites. They are easily aerosolized as sporangiospores and so inhaled (El-Herte et al 2012). The spread of infection is seasonal, with peak incidence in summer and early autumn (Shpitzer et al 2005).

CASE REPORT

We reported a patient who, for symptoms and for ignored diabetic conditions, made the diagnosis even more difficult. On admission to the Emergency Room, a 78-year-old woman mentioned a painless swelling in the left malar region, and ptosis. The patient was already being treated with steroids for about two weeks, due to a left peripheral and incomplete facial nerve palsy. Despite the treatment, symptoms had worsened. Furthermore, she had consulted a dentist, who had ruled out diseases of the teeth. On examination, the swelling was tense, painless, and was covered with warm erythematous skin. There was also left eyelid ptosis with proptosis, a slight deviation of the jaw to the left, and hypoesthesia in the skin area innervated by the mandibular ramus of the left trigeminal nerve. There was no fever or other symptoms. Blood pressure was 160/90 mmHg, and heart rate was 80 bpm. Laboratory tests showed a slight increase in white blood cells (15,400/mmc) and hyperglycemia (37.22 mmol/L). The patient reported no history of diabetes mellitus, but remembered an onset of polyuria during the previous week. The paranasal sinus view showed haziness of the left maxillary sinus (Figure 1). On admittance to hospital, she was subjected to rehydration, insulin, and antibiotic therapy. After approximately two days, in spite of treatment, there was no improvement.
A noncontrast CT scan revealed severe opacification of the left maxillary sinus, with erosion of the nasal wall and inferior turbinate (Figure 2), moderate opacification of ethmoid sinus with erosion of the left orbital plate (Figure 3).

Furthermore, left orbital cellulitis was visible. The biopsy confirmed the suspicion of mucormycosis, showing the presence of pathognomic picture of mucormycotic hyphae. Unfortunately, better etiological characterization was not possible in our laboratory. The patient was administered liposomal amphotericin-B 5 mg/kg/day intravenously. She refused surgical treatment and, after a few weeks, she died at home.

DISCUSSION

MM usually occurs in immunocompromised patients. The main predisposing conditions for MM are: hematological malignancies, stem cell transplantation, solid organ malignancies, solid organ transplantation, diabetes mellitus and ketoacidosis, corticosteroid use and rheumatic diseases, iron overload and chelation therapy with deferoxamine, prolonged use of voriconazole (Sun et al 2011).

Rarely the infection can affect individuals with no predisposing conditions (Mignogna et al 2011, Torres-Narbona et al 2007).

Mucormycosis is typical air-borne infection, even if there are other portals of entry such as the digestive tract, skin lesions, and venous catheters (Richardson 2009).

The pathophysiological risk factors involved in the onset and dissemination of infection are: immunosuppression, hyperglycemia, low pH, skin barrier lesions (Chinn et al 1982).

Furthermore, the Zygomyces require iron to grow and multiply. Therefore, iron overload and chelation therapy with deferoxamine (where the drug acts as a bacterial xenosiderophore), provide a predisposition for infection (Boelaert et al 1993).

Mucormycosis is characterized by fungal vascular invasion, with thrombus formation and consequent tissue necrosis. A further important histological feature is perineural invasion (Sravani et al 2014). The most common sites of infection are: rhino-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated.

Rhino-cerebral mucormycosis is the most common form of mucormycosis in diabetic patients. The sporangiospores penetrate into the paranasal sinuses by inhalation. If they find favorable conditions, they proliferate and invade surrounding tissue: the palate, the sphenoid and ethmoid sinuses, the orbit, the cavernous sinus, and the brain (Petrikos et al 2012). Clinical presentations are usually sinusitis, periorbital cellulitis, and facial pain. There may also be cranial nerve palsy. An alarming triad can be represented by diabetes, facial pain, and evidence
of infection (University of South Alabama Headache Center 2004). Other distinctive symptoms are necrotic eschar, fever, and leukocytosis, but these may be absent. In patients surviving the disease, the infection usually leads to an extensive destruction of facial tissue with serious functional and disfiguring consequences: a disease that will not be forgotten.

In the case reported above, the diagnosis was made more difficult by the onset of disease, with peripheral and incomplete paralysis of the facial nerve and mandibular ramus of the trigeminal nerve, by the extension of infection to the infratemporal fossa, and by unknown diabetes mellitus (Meas et al., 2007). Initial steroid therapy, undertaken by the patient for the treatment of facial paralysis, together with inadequate antimicrobial therapy definitely contributed to the worsening of conditions favoring this infection through hyperglycemia and immunosuppression (Ferguson 2007).

CONCLUSION

Mucormycosis is a medical emergency and should always be suspected in patients with sinusitis, especially if they are decompensated diabetics or immunocompromised patients. In fact, early diagnosis and therapy can reduce the already high mortality rate of infection (Chamilos et al., 2008). Guidelines to therapy have been published (Cornely et al., 2014). The treatment of this disease requires an immediate and extensive surgical resection for topical control of the disease, with liposomal amphotericin B as the first-line drug, with a minimum dose of 5 mg/kg/day. For salvage treatment, the guidelines strongly recommend posaconazole 400 mg four times daily. The reversal of predisposing conditions is also very important and strongly recommended: the use of granulocyte colony-stimulating factor in hematological patients with neutropenia, controlling ketoacidosis and hyperglycemia in diabetic patients, limiting glucocorticosteroids to the minimum dose required, and avoiding the use of deferasirox in hematological or diabetic patients. A new antifungal isavuconazole, with promising results, is currently being studied (Seyedmousavi et al., 2015).
REFERENCES


Figure 1: View of the paranasal sinus showing haziness of the left maxillary sinus
**Figure 2**: Noncontrast CT scan revealed severe opacification of the left maxillary sinus and erosion of the nasal wall and inferior turbinate.
Figure 3: CT scan revealed moderate opacification of ethmoid sinus with erosion of the left orbital plate