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CASE REPORT

Against all odds: surviving rhino–orbital–cerebral mucormycosis: a case report

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Introduction

Mucormycosis, also known as zygomycosis, is a life-threatening infection typically occurring in the setting of diabetic ketoacidosis, immunosuppression, or trauma. Mucormycosis is subdivided into rhino–orbital–cerebral (ROCM), pulmonary, disseminated, gastrointestinal, or cutaneous forms. Zygomycetes are ubiquitous in nature, and can be found on decaying vegetation and in soil. All humans have ample exposure to these fungi during day-to-day activities. That mucormycosis occurs rarely is a testament of the effectiveness of the intact human immune system in controlling this infection. ROCM is the most common form in which the airborne spores invade the nasopharynx or paranasal sinuses and spread to the retro-orbital region and may extend to the brain. Unfortunately, despite disfiguring surgical debridement and early institution of appropriate antifungal treatment, the overall mortality of (ROCM) remains >50%, particularly in the presence of CNS extension (Reed et al. 2008). The following case report describes a patient who developed ROCM and survived with antifungal treatment despite extensive involvement, late diagnosis, and minimal debridement surgery.

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Case report

A 50-year-old man with type II diabetes mellitus and hypertension presented to the emergency department complaining of severe headache of 10 days duration, fever, double vision, and weakness in muscle of mastication with an inability to close his jaw.

On physical examination, the patient was conscious, alert, and oriented. Apart from an oral temperature of 38.5°C, vital signs were otherwise normal. He demonstrated bilateral olfactory nerve deficit, right-sided ophthalmoplegia with a fixed dilated pupil and proptosis. There was left-sided abducens palsy. The left pupil was reactive. He also exhibited bilateral lower motor neuron facial nerve palsy, bilateral motor trigeminal impairment with left-sided V1 sensory deficit, deviation of the tongue to the right on protrusion with weakness, deviation of the uvula to the right, and an impaired gag reflex bilaterally. He also had mild subjective decreased hearing. His eyes and mucosal membranes were dry, and there was swelling of the right temperomandibular junction. The examination was otherwise unremarkable. Over the next day, the facial swelling increased and ultimately involved all salivary glands bilaterally. With the exception of cranial nerves VIII and XI, all cranial nerves were eventually affected.

Laboratory evaluation showed a leukocytosis of 20.6×10^6/l with a neutrophil predominance, an erythrocyte sedimentation rate of >100 mm/h, C-reactive protein of 192, serum glucose level of 17.6 mmol/l, and a glycosylated hemoglobin level of 11.4%. Arterial blood gasses were

within normal limits, urine ketones were negative, and there was no evidence of ketoacidosis.

Magnetic resonance imaging (MRI) of the brain with gadolinium enhancement was done and showed no intracranial pathology but revealed bilateral mucosal thickening in the ethmoidal and maxillary air cells and an ill-defined heterogeneous enhancing soft tissue fullness infiltrating the subcutaneous tissue of the right temporal region which appeared inseparable from the parotid gland. It extended into the right retro-orbital space and displaced the globe anteriorly. A lumber puncture was done, and the only abnormality was a mild elevation in the protein. The next day, a trucut biopsy of the parotid swelling was done and showed non-specific sialadenitis with no granulomas. All cultures came back negative.

At this time, the patient was given the diagnosis of acute sarcoidosis and was started on steroids. By the second week, the patient had worsening of his visual symptoms and became completely blind with bilateral fixed dilated pupils and bilateral complete ophthalmoplegia. He also developed impaired ciliary body function on the right with progressively decreasing intraocular pressure which reached zero and resulted in a collapsed globe. The patient was scheduled for debridement surgery and intraocular injection of gas and steroids under local anesthesia to preserve the shape of the globe. A preoperative MRI was ordered and showed a right temporal lobe enhancing lesion that was hypointense on T1-weighed imaging and hyperintense on T2 and FLAIR sequences with a central hypointense area and no mass effect (Fig. 1). The patient and his family only consented to minimal debridement and refused drainage of the intracranial abscess at that time. A percutaneous gastrostomy tube was inserted for feeding to decrease the risk of aspiration pneumonia.

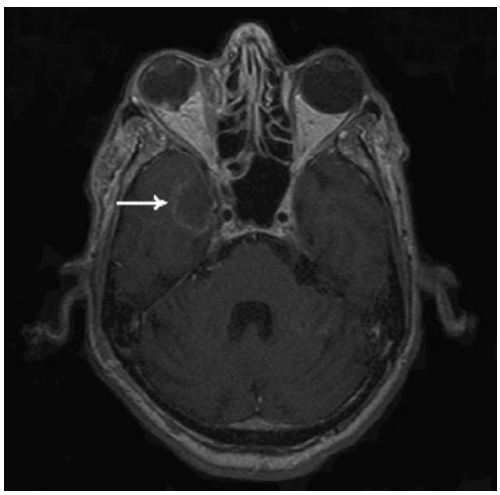

Fig. 1 Axial post-contrast T1 (TR=517, TE=15) image of the brain showing a ring-enhancing mass in the right temporal lobe (*arrow*)

About 1 month after admission, the patient developed profuse sinusitis with pus discharge from his nose and the palate with crusting and ulceration; physical examination showed eschars on the soft and hard palates. The area was cleaned, and samples were sent for histopathology staining and cultures. At this point, the patient was given the clinical diagnoses of ROCM despite negative cultures and histopathological staining and was started empirically on amphotericin B. Samples were sent repeatedly for histopathological staining, and 5 weeks after admission, histopathology showed both spores and broad non-septated hyphae (Figs. 2 and 3), consistent with the working diagnosis, and accordingly, the patient was switched to amphotericin B lipid complex 300 mg/day (5 mg/kg/day) in combination with echinocardin with a loading dose of 75 mg, followed by 50 mg daily. During this time, the patient was well hydrated and renal function was monitored daily. He developed one attack of acute hemolysis which was considered an acute reaction to amphotericin, and the drug was reinstituted at a slower rate.

Four months after admission, the family consented to craniotomy and drainage of the temporal abscess. Intraoperatively, the abscess was found to have a well-formed wall and the sac was drained and then removed (Fig. 4). The patient did not suffer any perioperative complications or any additional neurodeficits postoperatively. The pathological examination of the brain cyst showed a chronic abscess with an extensive granulomatous reaction in the wall. Histochemical stains were done on the specimen, and it stained non-septated broad-based fungal hyphae along with numerous fungal spores in a background of necrotic material. Pus cultures were negative.

The patient received amphotericin B lipid complex in combination with echinocardin for a total of 4 months after which he was discharged home on maintenance therapy with itraconazole 100 mg twice daily for an additional year. At a 2-year follow-up, he remained healthy though with permanent cranial nerve deficits despite complete resolution of the disease on cranial MRI.

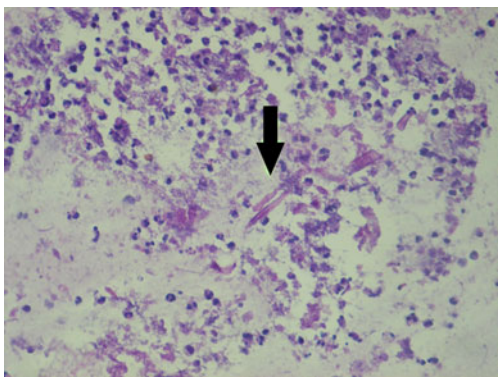

Fig. 2 Biopsy from the palatine ulcer showing broad, non-septated fungal hyphae (*arrow*) (Periodic acid-Schiff stain, ×400)

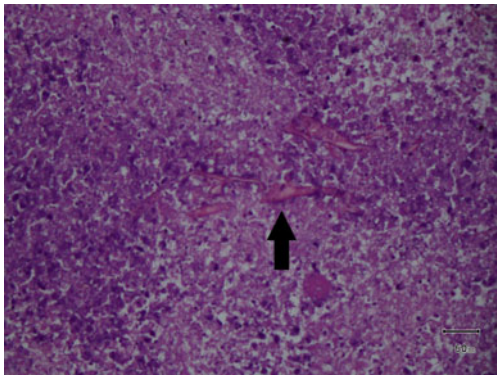

Fig. 3 Biopsy from the palatine ulcer showing broad, non-septated fungal hyphae (*arrow*) (hematoxylin and eosin stain, ×400)

Discussion

Rhino–orbital–cerebral zygomycosis is an uncommon, rapidly progressive, fatal fungal infection occurring almost exclusively in individuals with an underlying immunosuppression. Zygomycetes are a family of aerobic fungi ubiquitous in nature. These fungi grow rapidly and release large numbers of potentially airborne spores. The hyphae of the zygomycetes are distinct and allow for a presumptive identification from clinical specimens. The hyphae are broad (5 to 15 mm diameter), irregularly branched, and have rare septations (Cox et al. 2011). The lack of regular septations may contribute to the fragile nature of the hyphae and the difficulty of growing zygomycetes from clinical specimens. When they do grow, however, the growth is rapid and profuse on most media at room temperature. The genera most commonly found in human infections are *Rhizopus*, *Mucor*, and *Cunninghamella* (Roden et al. 2005). *Rhizopus* organisms have an enzyme, ketone reductase that allows them to thrive in high glucose, acidic conditions. Serum from healthy individuals inhibits growth of *Rhizopus*, whereas serum from individuals in diabetic ketoacidosis stimulates growth (Gale and Welch 1961).

Rhino–orbital–cerebral and pulmonary zygomycosis is acquired by the inhalation of spores. In healthy individuals, cilia transport these spores to the pharynx, and they are cleared through the gastrointestinal tract. In susceptible individuals, infection usually begins in the nasal turbinates or alveoli (Ferguson 2000). The zygomycetes are angioinvasive; thus, infarction of infected tissues is a hallmark of invasive disease (Greenberg et al. 2004). Perineural involvement in zygomycosis has been described in literature. One series describes 20 patients with zygomycosis with three disease presentations: rhinocerebral, pulmonary, and fungus ball. In this series, all patients had pathological evidence of zygomycosis in biopsy or autopsy specimens but only ten had culture-confirmed disease. Nerve biopsies were present for examination in ten specimens in which perineural invasion was noted in the vast majority of patients; 90% (Frater et al. 2001).

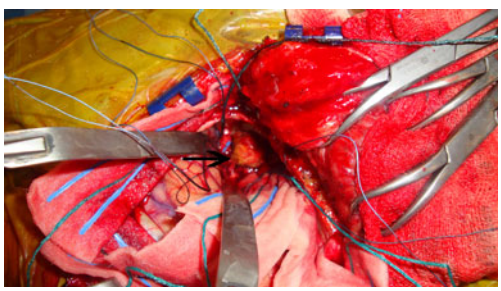

Fig. 4 Intraoperative photograph of the intracranial abscess (*arrow*). Note the well-formed wall of the abscess and absence of extension into surrounding tissue

Zygomycosis is difficult to diagnose, and a high index of suspicion is required for a timely diagnosis. Diagnosis relies on both the identification of the organism by histopathological staining and confirmation by microbiologic cultures (Cox et al. 2011). The fungus is difficult to grow from infected tissue and, in some cases, cultures yield no growth; therefore, more invasive measures are needed for timely diagnosis. Mucormycosis is a challenging infection to treat. Treatment consists of antifungal therapy and the correction of predisposing conditions, and extensive surgical debridement has been a fundamental component of treatment. Unfortunately, despite disfiguring surgical debridement and polyene antifungal therapy, the overall mortality of ROCM remains >50%, particularly in the presence of CNS extension (Reed et al. 2008).

Amphotericin B is the cornerstone of treatment in mucormycosis. Most physicians prefer the use of liposomal amphotericin B or amphotericin B lipid complex because of lower nephrotoxicity and better penetration into the cerebrospinal fluid. The prognosis is markedly improved with earlier initiation of therapy as illustrated in a retrospective study of 70 patients with hematologic malignancies who acquired the infection. The study showed a twofold increase in mortality with delayed initiation of therapy (starting by >6 days after diagnosis) (Chamilos et al. 2008). The usual starting dose of amphotericin B is 5 mg/kg/day and may be increased up to 10 mg/kg/day. Total dose and duration of therapy have not yet been studied, but most clinicians would continue therapy until the patient shows a favorable response.

Although in vitro studies have not demonstrated any activity for echinocardins against mucormycosis, one study reports that patients with ROCM who were treated with combination polyene–caspofungin had a more significant improvement 30 days after hospital discharge in addition to improved long-term survival compared to patients treated with polyene monotherapy. In this study, all four patients with rhino–orbital–cerebral zygomycosis who received

combination therapy survived compared to the survival of 4 out of the 16 patients who received amphotericin B monotherapy (Reed et al. 2008).

Posaconazole (PCZ) is an extended-spectrum triazole antifungal agent with activity against the *Mucorales*. It is administered orally either as a combination salvage therapy with amphotericin in patient with refractory mucormycosis or as an oral step-down therapy in patients who have responded to treatment with amphotericin B. No other antifungal agents have been studied for this purpose, and there is no strong literature supporting PCZ as a single agent for the treatment of mucormycosis. Unfortunately, PCZ is not available in Jordan; therefore, itraconazole was used. Itraconazole has a broad spectrum of activity, but not as broad as PCZ and does not have any in vitro activity against *Mucor*. Also, itraconazole has virtually no penetration into the cerebrospinal fluid. Itraconazole was used in our patient since it is the only available option in Jordan. Also, craniotomy showed the brain abscess to have a well-formed wall and was completely resected intraoperatively. So, our goal of continued antifungal therapy was mainly to maintain the suppression of the extracranial infection, rendering CSF penetration less relevant. In a recent article describing two new *Mucor* organisms isolated from human clinical specimens in the USA, the in vitro antifungal susceptibility of the new species showed that amphotericin B was active against all isolates and posaconazole and itraconazole showed low activity (Alvarez et al. 2011). At 2-year follow-up, our patient has remained disease-free with no new deficits. Our patient is truly unique having exhibited a remarkable survival despite a delayed diagnosis and the absence of widespread debridement for his extensive disease. The addition of echinocardin to his amphotericin and the long-term therapy with itraconazole may have both contributed to his favorable course.

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