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CASE REPORT

An unusual presentation of rhinofacial zygomycosis due to *Cunninghamella* sp. in an immunocompetent patient: a case report and literature review

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Zygomycosis is a rare fungal infection usually found in immunocompromised patients. It is a rapidly progressing infection with a high mortality rate. Our report describes an unusual case of rhinofacial zygomycosis due to *Cunninghamella* sp. in an immunocompetent patient, who presented with a slowly progressive swelling of the left cheek. An interrupted course of amphotericin B treatment caused regression of the lesion. Drug therapy was abandoned due to impairment of renal function. The patient was clinically and radiologically disease free for 2 years following cessation of therapy.
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Introduction

Zygomycosis is a rare fungal infection caused by saprophytic fungi of the class zygomycetes. These are often found in laboratory specimens as environmental or clinical contaminants and rarely as true pathogens (Ribes *et al*, 2000). They are opportunistic pathogens causing disease predominantly in immunocompromised. The disease presents in many forms, as rhinocerebral, pulmonary, gastrointestinal, cutaneous and disseminated. Nearly one half of reported cases of zygomycosis are of rhinocerebral form. It is usually rapidly progressive and fatal in outcome. The present report describes an atypical presentation of rhinofacial zygomycosis caused by the *Cunninghamella* sp. in an immunocompetent host.

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Case report

A 42-year-old male farmer from a remote area in Sri Lanka presented to the Dental Hospital, Faculty of Dental Sciences, University of Peradeniya, with a swelling of three months duration in the infraorbital region of left side of the face. Mild left hyperglobus, epiphora and periorbital oedema were evident. (Figure 1) The first left upper molar had been extracted 6 months before the illness. Past medical history revealed seven attacks of malaria within the last 10 years but no history of diabetes, immunosuppressive drug therapy or any other immunocompromised state.

Full blood counts and blood picture revealed microcytic hypochromic anaemia with anisopoikilocytosis and increased rouleux formation. White blood cell and differential count was normal. Fasting blood sugar was 4.8 mmol l^{-1}. HIV antibody test was negative and CD4 and CD8 counts were within normal range. Radiographically, opacity of left maxillary sinus was noted. Sinusitis, maxillary sinus malignancy and fibrous dysplasia were included in the differential diagnosis and further investigations were considered.

Haematoxylin and Eosin (H & E) sections of an incisional biopsy revealed focal areas of acute infection with central tissue necrosis within a chronic granulomatous inflammation containing numerous multinucleate giant cells. Peripheral nerves and blood vessels were involved in the disease process. Although not extensive, angioinvasion with accompanied haemorrhage into the tissue was evident. Periodic acid-Schiff and Grocott Methenamine Silver stained sections showed occasional large, non-septate fungal hyphae with wide angle branching within the granulomas and the infected foci (Figure 2). Some fungal hyphae were seen inside multinucleate giant cells.

The organism was identified as *Cunninghamella* sp. by slide culture. A rapidly growing white to grey colony was seen when cultured in Sabouraud's glucose agar with a broad-spectrum antibiotic at 26 and 37° C. The fungal

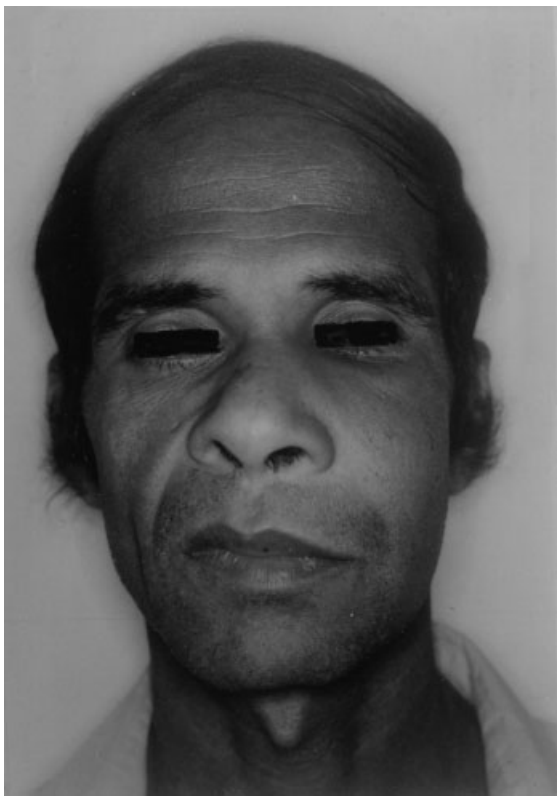

Figure 1 Anterior view of the patients face showing the swelling over the left infraorbital region

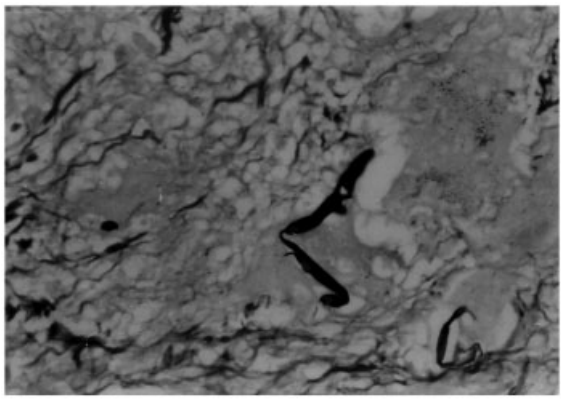

Figure 2 Large, non-septate, ribbon-like fungal hyphae with wide angle branching seen within a granuloma. Grocott Methenamine Silver stain (400 times magnification)

hyphae were ribbon like, broad and aseptate and showed wide angle branching (45–90°). The sporangiophores branched and terminated in vesicles and the sporangioles were seen on denticles on the vesicle surface.

A Computed Tomography (CT) Scan of the sinuses obtained prior to commencing treatment revealed mucosal hypertrophy of left maxillary sinus and a polyp in the right maxillary antral floor with possible extension of the lesion to left frontal and ethmoidal sinuses. There was no extension into the cerebrum, orbit, nose or mouth.

A daily intravenous infusion of 50 mg (1 mg kg^{-1} body weight) of conventional amphotericin B was commenced. Following 17 doses the patient developed polyuria and abnormal renal functions. Drug treatment was discontinued due to progressively deteriorating renal function.

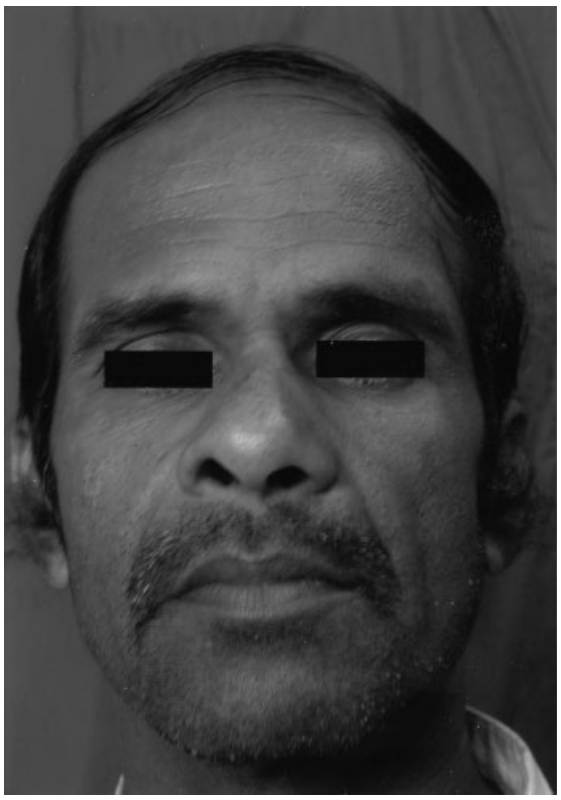

Figure 3 Anterior view of the patients face after cessation of treatment. The swelling has resolved completely and patient looks healthy

A reduced dose of intravenous conventional amphotericin B 25 mg (0.5 mg kg^{-1} body weight) daily was administered once again succeeding stabilisation of renal function in a few weeks. Patient's renal function deteriorated once more after 16 such doses and drug treatment was immediately stopped. Interestingly, the swelling progressively reduced during this time (Figure 3). The patient was followed up monthly as an outpatient. After 2 years he was clinically disease free and the latest sinus radiograph, showed no abnormality.

Discussion

Zygomycetes fall into the phylum Zygomycota. It comprises of organisms, which form wide, ribbon like, non-septate, hyaline hyphae and sexually reproduce by forming zygospores. Human pathogens fall into two orders, Mucorales and Entomophthorales. Family Cunninghamellaceae and genus *Cunninghamella* come under Order Mucorales (Ribes *et al*, 2000).

In the family of Cunninghamellaceae, the commonest species reported to cause disease in humans is *C. bertholletiae*. *Cunninghamella elegans* and *C. echinulata* have also been reported as human pathogens.

Zygomycosis is usually seen in immunocompromised since normal healthy individuals are naturally immune to opportunistic pathogens. Majority of reported cases of *Cunninghamella* sp. infections was in the immunocompromised (Cohen-Abbo *et al*, 1993). Our patient gave a history of seven attacks of malaria in the past but its significance in rendering him susceptible to zygomycosis is not clearly understood. The patient appeared immunocompetent as revealed by examination and investigations.

Fungi causing zygomycosis are known to be aerogenous. Rhinocerebral and rhinofacial forms of the disease may occur by inspiration of fungal spores that provide them access to the paranasal sinuses. Initial symptoms of rhinocerebral/rhinofacial disease are similar to chronic sinusitis. Our patient was also suspected of having chronic sinusitis at the initial presentation. Although it is known to be rapidly progressive and extending into neighbouring tissues, the progression in this patient was atypical. That may be due to the fact that he is immunocompetent. Infection from the nose and paranasal sinuses may extend to the retro-orbital region and ultimately into the orbit. Infraorbital paraesthesia, epiphora, periorbital oedema and congestion of the conjunctiva of the left eye were present in our patient even though the CT scan showed no extension into the orbit. Dental extraction sites as the portal of entry for the fungi have been reported (Kim *et al*, 2001). There were no signs of oral spread of the disease or vice versa, as the maxillary dental extraction site had healed normally. Central nervous system was not involved and spread of disease in our patient is therefore, best reported as rhinofacial rather than rhinocerebral zygomycosis.

Typically, the microscopic features of rhinofacial zygomycosis include abscess formation, suppurative necrosis and vascular wall invasion by the organisms resulting in thrombosis and infarction. In the present case, the microscopic features were atypical and showed a granulomatous inflammation with multinucleate giant cells, which was suggestive of a patent immune reaction. Suppuration and angioinvasion was also not extensive and only foci of necrosis were seen. Correct identification of the species requires novel methods such as the Polymerase Chain Reaction (PCR) and sequencing of the Internal Transcribed Spacer (ITS) region (Lemmer *et al*, 2002).

The foundation for management of zygomycosis is early diagnosis. Correction or management of the underlying predisposing condition/s is of paramount importance. This is supported by an analysis by Blitzer *et al* on 179 patients with paranasal sinus mucormycosis. The study revealed that 75% of the patients without any immunocompromised status survived with surgical and medical therapy; only 60% of those with diabetes and 20% of patients with other systemic disease were cured of it (Blitzer *et al*, 1980).

Intravenous amphotericin B (conventional or liposomal) remains the gold standard for successful treatment of zygomycosis. However its usage is limited by potentially severe side effects. Impairment of renal functions often leads to cessation of therapy as seen in our patient. The liposomal preparation of amphotericin B may alleviate this problem to a considerable extent and allow for higher doses to be administered. Furthermore, it tends to be superior to conventional amphotericin B in efficacy, tolerability, curative effect, fungal clearance rate and adverse effects (Bodhe *et al*, 2002).

To conclude, this case illustrates an atypical presentation of a potentially fatal deep fungal infection in the absence of a predisposing cause. The patient was not completely cured at the time drug treatment was ceased for the second time. However, after 2 years of review the patient had improved without further treatment, which may be attributed to the favourable immune status. To the best of our knowledge, this is the first case of rhinofacial zygomycosis caused by *Cunninghamella* sp. in an immunocompetent patient who was managed with drug treatment alone and had a favourable outcome.

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