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RHINOCEREBRAL MUCORMYCOSIS: CASE REPORT

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SUMMARY

Rhinocerebral mucormycosis is a rare, fulminating opportunistic fungal infection caused by a fungus of the order mucorales. These fungi are ubiquitous, subsisting on decaying vegetation and diverse organic material. Although the fungi and spores of mucorales show minimal intrinsic pathogenicity towards normal persons, they can initiate aggressive and fulminating infection in the immune compromised host. Because rhinocerebral mucormycosis occurs infrequently it may pose a diagnostic and therapeutic dilemma for those who are not familiar with its clinical presentation. We present a patient with classical presentation of rhinocerebral mucormycosis involving the paranasal sinuses, the orbit and cranial base who, was treated by a combination of aggressive surgical and medical therapy and subsequently had surgical repair of the oral defect. The purpose of this presentation is to draw attention to the clinical presentation and pathogenesis of rhinocerebral mucormycosis and to emphasise the need for high index of suspicion in its diagnosis and management.

INTRODUCTION

Mucormycosis is a rare fulminating opportunistic fungal infection, which frequently ends in death. The infection is caused by fungi belonging to four families of the order mucorales, which is a member of the class zygomycetes(1). These fungi are ubiquitous, subsisting on decaying vegetation and diverse organic material. Although the fungi and spores of mucorales show minimal intrinsic pathogenicity toward normal persons, they can initiate aggressive and fulminating infection in an immunocompromised host.

The prognosis of rhinocerebral mucormycosis is very poor. Even with early diagnosis and aggressive surgical and medical therapy the mortality rate is high.

We present a patient with classical presentation of rhinocerebral mucormycosis involving the paranasal sinuses, the orbit and cranial base who was treated by a combination of aggressive surgical and medical therapy and subsequently had surgical repair of the oral defect.

This case is presented to emphasize the need for high index of suspicion in the diagnosis and management of rhinocerebral mucormycosis.

CASE REPORT

A 56 year old male patient with a 5-year history of non-insulin dependant diabetes mellitus was referred to Kenyatta National Hospital on 15th March 2000 from a peripheral medical facility with complaint of abdominal pain, vomiting, dyspnoea, left facial palsy and left orbital cellulitis and endophthalmitis.

He had been well until 1st March 2000 when he developed severe backache, abdominal pain and general body

weakness for which he was admitted at the peripheral health facility. At that first admission he was found to be febrile, severely dehydrated, and with bilateral pitting oedema. He was however, alert and well oriented to person, time and space. His blood pressure was 168/100 and his random blood sugar was 17mmol/L. He was started on soluble insulin, fluid therapy and broad-spectrum antibiotics. The patient showed some improvement after three days and the insulin dose was scaled down to 10 units 8 hourly.

On 12th March 2000 the patient developed severe abdominal pain, vomiting and dyspnoea. Investigations showed random blood sugar of 15 mmol/L, urea, 6 mmol/L, Na⁺, 155 mmol/L and K⁺ 3.8mmol/L. Treatment with IV fluids, soluble insulin and antibiotics was continued with addition of sodium bicarbonate.

On 14th March 2000 the patient developed left facial palsy, swelling of the left eye and left orbital cellulitis. A decision was then made to transfer the patient to Kenyatta National Hospital. The patient was received at Kenyatta National Hospital on 15th March 2000. At admission he was conscious and well oriented to person, space, and time. He complained of severe headache, nose bleeding, swelling of the left eye, difficulty in passing stool and swelling of both legs. On examination he was sick looking, had bilateral pitting oedema, proptosis of the left eye and total ophthalmoplegia of the left eye. Crusting of the nasal mucosa was also noted. Investigations at admission showed the following, Na⁺ 142 mmol/l, K⁺ 4.4 mmol/l, Random blood sugar 14 mmol/l, white blood cell count, 26 x 10⁹/l, with 91% neutrophilia. Hb 13g/dl, platelets 521 x 10⁹/l, haematocrit 65, BUN, 5.5 mmol/l, creatinine 117 umol/l, total serum protein 64g/l. Albumin 29g/l, Alanine transaminase (ALT) 7 u/l, Aspartate transaminase (AST), 8 u/l, Alkaline phosphatase (ALP) 199 u/l, Bilirubin; total 4.7 mmol/l, direct 4. mmol/l, uric acid 320 mmoUl., urinalysis, normal microscopy, no growth on culture. Chest X-ray was normal.

The differential diagnosis of orbital cellulitis, cavernous sinus thrombosis, mucormycosis and Wegner's granulomatosis were made. Treatment with soluble insulin, broad spectrum antibiotics and IV fluid was continued, but after three days of no response IV amphotericin B was commenced; starting at 0.25 mg/kg/day gradually increasing to 1 mg/kg/day.

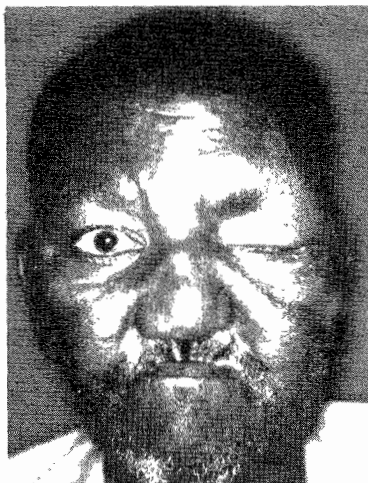
On 23rd March 2000 necrosis of the palate was noted. The following day the patient developed right hemiplegia without right facial palsy and lapsed into semi-consciousness and delirium. At this stage CT scan showed bilateral maxillary sinus opacity but without significant brain findings. Punch biopsy of the palatal ulcer was carried out but did not demonstrate fungal infection. The c-ANCA test for Wegner's granulomatosis was also negative. In spite of the negative finding for fungal infection IV amphotericin B was continued on the strength of the clinical presentation.

On 25th March 2000 the patient developed corneal perforation with uveal prolapse. The patient's general condition remained stormy with poor blood sugar control. On 18th March 2000 the patient was taken to theatre for aggressive surgical debridement. At operation extensive necrosis of the maxilla, zygomatic bone, orbital floor left eyeball and cranial base was noted. The patient had subtotal maxillectomy, left ocular evisceration and debridement of necrotic tissue on the mid-face. Histological examination of the excision specimen confirmed mucormycosis. Following the surgery the patient made a slow but steady progress. He eventually regained consciousness but his right hemiplegia persisted and his speech remained slurred.

He was taken back to theatre on 11th July 2000 and had reconstruction of the palatal defect with left temporalis muscle flap. The patient was eventually discharged on 21st July 2000 after about five months hospital stay. At the end of treatment the patient had had five weeks of amphotericin B at a maximum tolerated dose of 50 mg/day. His renal function was severely depressed during treatment, and therapy was stopped before the 12 weeks recommended. Renal function fully recovered after discontinuation of the amphotericin B. At a review, 13 months after discharge the patient continued to do well though he had substantial residual defects and was confined to a wheel chair (Figure 1).

Figure 1

Patients facial view 13 months postoperatively showing left facial paralysis, loss of left eye and maxillary defect



DISCUSSION

Mucormycosis is an opportunistic fungal infection caused by fungi belonging to four families of the order mucorales, which is a member of the class zygomycetes(1). Most infections are caused by the three generations of the family mucoraceae; rhizopus, mucor, and absidia(1). The organisms are ubiquitous in the environment and become pathogenic in the setting of an immune compromised host. The most common pre-disposing factor is poorly controlled diabetes with ketoacidosis. Other predisposing conditions include acidosis of any cause, high local iron concentration, acute leukaemia, aplastic anaemia, myelodysplastic syndrome, transplantation associated immune suppression, thermal injury and congenital heart disease(1-5). The disease has also been described in patients with no apparent predisposing factors(6,7,8).

Histologically, the fungi are characterised by broad, thick walled, non-septate hyphae that branch at right angles(1). The fungi have a predilection for invasion of blood vessels with subsequent development of thrombus and resultant ischaemia and infarction or dissecting aneurysm(6). The rhinocerebral form of the disease, affecting the paranasal sinuses, orbits, and brain accounts for 80 to 90% of cases(7). Less commonly, pulmonary, disseminated, cutaneous, and gastro-intestinal forms may be observed.

Rhinocerebral mucormycosis results from entry of the fungus into the nasal mucous membrane or palate with subsequent spread to the paranasal sinuses, the skin of the face, the orbit and the brain by direct extension or through vascular channels. The infection has been described to develop in three stages(9). The first stage occurs after inhaled spores infect the paranasal sinuses. Necrotic lesions of the nasal mucosa, turbinates and hard palate appear. These may be mistaken for dried blood in severely ill patients(11). Epistaxis may be a prominent sign of the infection at this stage. The second stage, orbitofacial infection, occurs by either direct extension through the nose and maxillary sinus or through the blood vessels. Characteristic signs and symptoms of this stage include facial pain, facial anaesthesia, proptosis, chemosis, orbital and facial cellulitis, facial gangrene, and ophthalmoplegia. Occlusion of the central retinal artery can cause visual loss. In the third stage, infection spreads intracranially via the cribriform plate or orbital apex. By the time orbital involvement becomes manifest, 80% of patients already have meningeal involvement(10). Intracranial extension can cause meningitis, cerebritis, infarction, abscess formation, cavernous sinus thrombosis and internal carotid thrombosis. Neurological manifestation of rhinocerebral mucormycosis are usually non-specific (e.g. headache, lethargy, fever, facial pain) but focal signs, seizure and signs of cavernous sinus and internal carotid artery thrombosis may be present.

Typically, the cerebrospinal fluid findings in patient with rhinocerebral mucormycosis are non-specific. If a lumbar puncture is not contra-indicated, the CSF chemical analysis may be normal or may reveal a pleocytosis with increased protein. Glucose levels are typically in the normal range, whereas culture and microscopic examination tend not to demonstrate organism. Blood cultures are most often negative and haematological examination may not show a leucocytosis in a patient who is immune compromised.

Computed tomographic scans of the head may reveal nodular thickening of the sinus mucosa, sinus wall destruction and intra orbital involvement(9). The finding of air/fluid levels, as seen in purulent bacterial sinusitis, is not characteristic of infection by microraceae(9,10). MRI is helpful for more clearly defining the extent of intracranial extension. Regions of intracerebral inflammation are usually hyperintense on T2-weighted MRI scans(12,13) Cerebral angiography may reveal vascular occlusion, aneurysmal dilation, or filling defects(10).

The definitive laboratory diagnosis of rhinocerebral mucormycosis requires a tissue specimen containing organisms. Because fungi in the family mucoraceae can inhabit the nasal cavity in healthy individuals, swab cultures of the area in a patient suspected of having rhinocerebral mucormycosis may provide a false positive result(1,13). The classic histologic appearance shows large broad, non-septate hyphae with right angled branching and distinct vascular invasion(1). Examination of the crushed tissue specimen with direct light without staining can establish the diagnosis within minutes after the biopsy procedure.

Current treatment of rhinocerebral mucormycosis involves the use of intravenous amphotericin B, aggressive surgical debridement of the infected tissue, and containment of the pre-existing disease, if present. Because amphotericin B has fungistatic rather than fungicidal effect on mucormycosis, prolonged treatment with this medication is required. Other adjunctive measures include intra-lesional injection and local irrigation with amphotericin B(14,15) and hyperbaric oxygen therapy(16).

The prognosis of rhinocerebral mucormycosis, once considered a universally fatal disease, remain poor. Even with early diagnosis and aggressive surgical and medical management the mortality rate is approximately 20%. Among the survivors a large number has been characterised by devastating sequelae including orbital exenteration, enucleation, permanent ophthalmoplegia, monocular blindness, palatal defect, organic mental syndrome and facial defects requiring extensive reconstruction.

The two most important determinants of clinical outcome are; (i) the prognosis of the underlying disease and (ii) the extent of the infection. In a retrospective analysis of 179 patients treated for rhinocerebral mucormycosis, the underlying disease was the most

important determinant of survival. Survival rates in patient without underlying compromised state, patients with diabetes mellitus and patients with other systematic disorders were 75%, 60%, and 20% respectively(17). A more recent review of 11 patients with rhinocerebral mucormycosis revealed that all seven patients treated with intracranial extension died, whereas all four patients with disease localised at the orbits and sinuses survived(18).

The management of our case had a significant short fall both in the difficulty to control the blood sugar and failure to make early diagnosis with subsequent delay in commencement of antifungal therapy. Our patient's diabetes had been poorly managed from the onset. It took long for the blood sugar levels to be stabilised. It was suggested that glycated haemoglobin (HbA1c) assay would have been a better marker for long-term diabetic control but this was not available in our situation.

The clinical presentation was most perplexing with unexplained abdominal pain, vomiting, dyspnoea, oedema, high neutrophilia, negative c-ANCA test and a biopsy that did not show fungal infection. This made definitive diagnosis hard to arrive at.

The difficulty in showing fungal infection in the biopsy and resection tissue was most frustrating. Although the organisms are difficult to grow, histological demonstration in the tissue should be relatively easy.

A normal CT scan of the brain in spite of developing hemiplegia was most interesting. It demonstrates that while gross changes will show in the CT scan, subtle but significant ischaemic changes of the brain may not. A normal CT scan does not necessarily rule out areas of infarction. It is possible that MRI would have been a better diagnostic tool.

Our patient had five weeks of amphotericin B at a maximum tolerated dose of 50 mg/day. His renal function was so severely depressed during the treatment that treatment had to be stopped earlier than the recommended 12 weeks. This aggressive medical and surgical intervention had been deemed necessary to control the extensive infection and the inability to complete the therapy was a source of concern.

Under circumstances such as ours the prognosis of mucormycosis can be expected to be poor. It is significant that the patient survived, albeit with severe sequelae, in spite of these failures.

CONCLUSION

A high index of suspicion is critical for early diagnosis and treatment of mucormycosis. The new complaint of facial or orbital pain in a patient with underlying diabetes mellitus or immunosuppression should serve to raise the suspicion of complicating mucormycosis. Generalised headache, pain related to sinus involvement, facial anaesthesia and fever should

further heighten this suspicion. A black nasal discharge in a severely ill patient is often ignored and commonly mistaken for dried blood. Careful inspection of the pharynx and palate for necrotic ulceration is mandatory. Diagnosis is confirmed by histological examination. Where diagnosis of mucormycosis has been made, prompt and energetic treatment is mandatory.

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