CASE REPORT

Fatal rhino-orbito-cerebral mucormycosis in a healthy individual

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ABSTRACT

Rhino-orbital-cerebral zygomycosis is a potentially lethal, opportunistic, fungal infection with protean manifestations, rapid progression, unpredictable course and high mortality. It is associated with angioinvasion and infarction, usually observed in diabetic ketoacidosis, immuno-compromised states and rarely reported in an apparently normal host. We present a case of an18-year-old patient with a chronic, painful, non healing ulcer with necrotic margins over the right side of the face which extended to both orbits involving eyes within a period of 1.5 month. Later he developed severe headache, decreased vision, inability to speak, seizures and status epilepticus with fatal outcome. Awareness of its occurrence in normal patients with prompt diagnosis and appropriate management may improve the outcome and decrease mortality.

Key words: Angiotrophic fungus, chronic sinusitis, rhino-orbito-cerebral zygomycosis

INTRODUCTION

Mucormycosis or zygomycosis is a rare opportunistic, potentially lethal infection characterized by rapid progression and high mortality, which represents the third most common fungal infection after candidiasis and aspergillosis. These opportunistic pathogens are ubiquitous organisms, existing in the environment, soil, air, food, composite piles, animal excreta and play a pivotal role in the cycle of decomposition in the natural world. The usual human pathogens belong to genera Absidia, Mucor, Rhizomucor, Rhizopus and currently Apophysomyces.[1]

Unlike other fungal pathogens that target mainly immunocompromised hosts, these organisms infect a broader and more heterogeneous population.[2] It is rarely reported in an apparently normal immunocompetent host which comprise only 4% of total affected individuals, but most frequently occurs in patients with an underlying illness such as diabetic mellitus, leukemia, lymphoma and in transplant patients undergoing immunosuppressive therapy.[3]

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Clinically, the most common clinical form of mucormycosis is rhino cerebral (44–49%), followed by cutaneous (10–16%), pulmonary (10–11%), disseminated (6–11.6%) and gastrointestinal (2–11%) presentations.[4] Mucormycosis of the head and neck is divided into isolated nasal, rhino-orbital, rhino-orbito-cerebral mucormycosis (ROCM) according to the involved sites, indicating the course of the disease.[5] Here we describe a case of invasive ROCM to raise clinical awareness of this infection in an apparently normal individual and to emphasize the importance of early detection with clinical, neuroimaging, histopathological and culture findings.

Case presentation

An 18-year-old male farmer was admitted in the Government Ear Nose and Throat (ENT) Hospital with a history of non healing ulcer on right side of the cheek involving right and left eye with signs of orbital invasion (extensive proptosis, severe periorbital cellulitis and ulcer) from 1.5 month. The patient was suffering from high fever, complete blindness, severe headache and seizures; and he was non coherent and uncooperative. The lesion started as nonspecific sinusitis of 3 week's duration and was treated for symptomatic relief in a local hospital. The pain and discomfort continued to get worse and he developed a unilateral swelling on the right side of the cheek which was edematous, erythematous followed by formation of a small nodule which ruptured and formed an ulcer within 3 days. The patient approached a local physician where he was put on antibiotics, anti-inflammatory drugs and was also referred to a dentist to rule out dental infections. The dental infection was

ruled and he was asked to continue the prescribed medications, but there was no relief and the condition deteriorated with increased ocular discomfort, severe headaches, sloughing of the ulcer which extended rapidly and involving nose, both the orbits with gradual loss of vision in next 2 weeks. The patient was admitted to the hospital due to repeated seizures, altered sensorium, non-coherence and was uncooperative. Clinical examination showed large irregular ulcer approximately 12 × 10 cm in size on the right side of the cheek, which extended from the right lower margin of the mandible to the medial and lateral canthus of the eye, involving half of the right side of the lips, exposing alveolar gingiva and teeth [Figure 1]. The skin around the ulcer was necrosed, indurated and edematous. The submandibular and submental lymph nodes were palpable, enlarged, tender and firm. However, the primary cause was undetermined and broad spectrum antibiotic therapy was initiated that included intravenous cloxacillin 500 mg every 6h, cefuroxime 750 mg every 8h and metronidazole 500 mg every 8h along with anticonvulsant treatment for 1 week along with surgical debridement of the ulcer. The severity of the lesion prompted us to do a thorough clinical and radiological evaluation to rule out gangrenous stomatitis, chronic granulomatous disease and any malignancies.

The complete blood picture and biochemical investigations showed a neutrophilic leukocytosis 12,000 cell/mm^3 with left shift, differential leukocyte count of 76% neutrophils, 20% lymphocytes, 3–4% eosinophils, hemoglobin of 11 gm/dl, raised erythrocyte sedimentation rate (ESR; 40 mm at the end of 1h), random blood sugar of 140 mg%, and fasting blood sugar of 80 mg%. The patient was human immunodeficiency virus (HIV) and hepatitis B surface antigen seronegative; and the liver function and the renal function tests were within normal limits. The chest X-ray was clear and normal.Computed tomography (CT) scan of paranasal sinuses and the brain showed right maxillary and ethmoidal sinusitis with deviation of the bony nasal septum to the left, mild erosion of bony nasal septum and bone destruction. Widening of the optic nerve canal and the superior orbital fissure, probability of fungal etiology was also detected [Figure 2a and b]. Exploration of the ulcer and debridement of necrotic tissue were done under local anesthesia and sent for histopathology, culture analysis. Histopathological examination of the debrided tissue showed elongated, broad, nonseptate hyphae, marked areas of necrosis with giant cells, thrombosis of vessels, diffused infiltration of lymphocytes, eosinophils and few plasma cells [Figure 2c-e]. The Grocott–Gomori's methanamine silver staining showed nonseptate, twisted, ribbon-like hyphae of zygomycetes [Figure 2f]. Rhino-orbito-cerebral zygomycosis was suspected and partial surgical debridement of ulcer and surrounding necrotic area was done. Patient was put on intravenous liposomal amphotericin B 250 mg daily and itraconazole 200 mg twice daily for 10 days. The culture analysis on the Sabouraud–chloramphenicol–gentamicin agar after 2 days at 30 and 37°C grew a white cottony growth which covered the entire surface of the agar. The patient developed severe seizures, status epilepticus diminished reflexes and succumbed to death after 1 week of therapy.

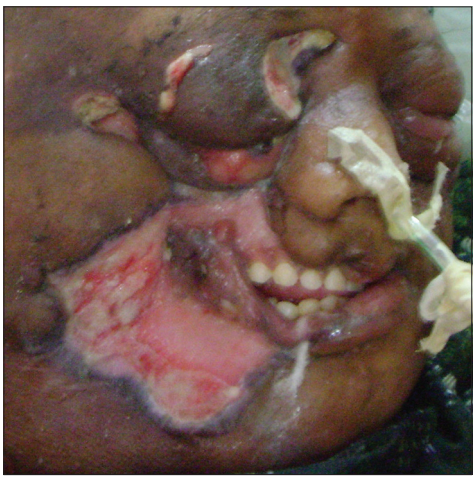

Figure 1: Nonhealing ulcer over right side of the cheek involving right and left eye with signs of orbital invasion (extensive proptosis, severe periorbital cellulitis and ulcer)

DISCUSSION

ROCM refers to the entire spectrum of the disease, which usually starts in the sinonasal tissue (limited sinonasal disease), progresses to the orbits (limited rhino-orbital disease) and finally affects central nervous system (rhino cerebral disease). Our patient had all the three classical stages of ROCM which had developed gradually over a period of 1.5 month with nasal stuffiness, local pain and headaches. Progression of the disease into orbital contents may be direct or due to vascular occlusion leading to preseptal and orbital cellulitis, chemosis, eyelid edema, severe proptosis, worsening opthalmoplegia, eventually blindness and ulcerations involving face indicating aggressive angioinvasion. Necrotic eschars in nasal cavity, black turbinate and palatal ulcers were not appreciated. Intracranial involvement might be from invasion by way of the superior orbital fissure, ophthalmic vessels, cribriform plate or is possible via a perineural route. More than one route might have been involved as the spread was extensive and of short duration, leading to seizures, status epilepticus, stroke with ultimate death in our case.[5,6]

The fungus shows little regard for tissue barriers and crosses the fascial planes.[3] It exhibits remarkable affinity for arteries and grows along the internal elastic lamina, causing thrombosis and infarction.[5] ROCM is suspected in patients with immunocompromised states but invasive fungal infections in immunocompetent/otherwise healthy patients are relatively rare.[7] In immunocompetent patients, the nose and/or maxillary sinuses appear to be the predominant source of infection. There is substantial increase in cases of mucormycosis with no known risk factors. In the present case, the patient was a farmer, who might have been possibly exposed to soil particles with infectious agent. He had a history

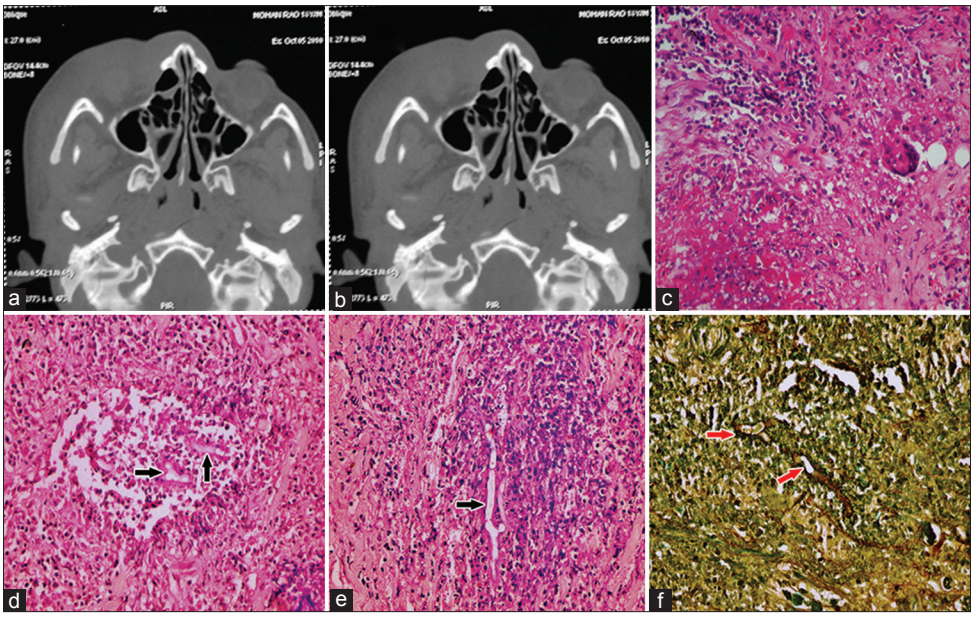

Figure 2: (a and b) Computed tomography (CT) scan of paranasal sinuses and the brain showed right maxillary and ethmoidal sinusitis, deviation of bony nasal septum to left side with mild erosion of bony nasal septum,bony destruction; and widening of the optic nerve canal and the superior orbital fissure. (c-e) Histopathological examination of the debrided tissue showed elongated, broad, nonseptatehyphae, marked areas of necrosis with giant cells, thrombosis of vessels, diffused infiltration of lymphocytes, eosinophils and few plasma cells (H&E stain, x100). (f) The Grocott–Gomori's methanamine silver staining showed nonseptate, twisted, ribbon-like hyphae typical of zygomycetes (Grocott-Gomori stain, x100)

of chronic sinusitis probably allergic rhinitis, bacterial- or viral-induced sinusitis which was a nonspecific symptom to suspect any serious pathology. In recent studies, it is speculated that chronic sinusitis may be a predisposing factor which causes alteration of first-line barrier of upper airway sinonasal mucosa due to impairment of mucociliary clearance, loss of defense and reduction in molecules of epidermal differentiation complex necessary for maintenance of barrier function. This renders sinonasal mucosa vulnerable to fungal colonization of previously damaged epithelium. It is likely that Mucor sporangiospores are also capable of secreting several toxins or proteases, which may directly destroy endothelial cells in mucosal membranes with a widespread disease, thus invading the mucosal sinuses spreading along the vascular and neuronal structures or eroding through the walls of the sinus. It has been suggested, if sporangio spores are larger than 10 micron, they remain localized to upper airways and colonize.[1]

Normal diagnostic tests are inconclusive and Mucor cannot be readily cultured from nasal secretions, cerebrospinal fluid (CSF) and blood.[1] Diagnosis of ROCM is classically dependent on direct morphologic identification of mycotic elements and from culture, but clinical findings and imaging also plays an important role in defining the extent of involvement and presence of intracranial disease. The CT and MRI detect early vascular invasion and intracranial extent of the fungal infection. The CT features include opacification and bony destruction of the paranasal sinuses, orbital extension from the ethmoidal sinuses producing proptosis, chemosis and obliteration of the nasopharyngeal tissue planes. Intracranial extension produces low absorption abnormalities, particularly in the anterior cranial fossa in frontal lobes with mass effect and contrast enhancement.[5,6]

Even though culture remains a gold standard for diagnosis and species identification, recovery of fungi in culture was negative in many reports, especially due to aggressive processing of specimen, less fungal load and contamination of cultures. Diagnosis is mainly based on suggestive clinical manifestations and morphologic finding of Mucor hyphae in tissue specimen. The necrotic tissue must be well sampled to identify the fungal elements as density of fungal organisms is higher in such tissues. In the present case, the tissue was sampled from necrotic ulcerative margins from different locations. Histological examination of necrotic tissue revealed extensive areas of inflammation, necrosis, granulomas with multinucleated giant cells and presence of aseptate branching hyphae, which stained with periodic acid–Schiff and Gomori's–methanamine silver stains. The histopathological appearance showed predominantly granulomatous response than acute response. Here, in our case, the colony morphology on Sabouraud–Chloramphenicol–gentamicin agar was a cottony, creamy-white growth filling up the entire agar plate.[8,9]

Effective therapy requires prompt surgical intervention, systemic antifungal drug administration, and reversal of the underlying risk factors. A combination of radical surgical debridement and intravenous liposomal amphotericin B is the treatment of choice, but is limited by frequent side effects of the drug, most importantly the dose-limiting

nephrotoxicity. Fungi thrive in necrotic tissue, debridement is necessary and should be carried out well close to the bleeding periphery, as the drug may not be effectively distributed in thrombosed vessels. Surgical debridement usually proceeds quickly because of an almost bloodless field and serial debridements are usually required. Vacuum dressings are a good alternative to more labor-intensive and painful dressings.Negative pressure dressings have been shown to improve wound healing by increasing tissue oxygenation via reduction of interstitial fluid and bacterial count in the wound.[5,6,10]

Recent literature review has shown worldwide distribution of mucormycosis in immunocompetent patients, with India being the most affected country probably related to climate, socioeconomic state, scarce hygienic condition, and, last but not least, diagnostic delay.[1] Mortality rate is higher than 50% with incidence ranging from 62.5% in rhino cerebral form to 100% in disseminated form. Its high morbidity and mortality rates are related to its capacity for rapid vascular invasions, with subsequent tissue necrosis and infarction.[1] The survival rate depends on the multiple factors and early initiation of treatment and also depends on the fungal load, fungal hyphal diameter and granulomas with giant cell response. Even initiation of the treatment within 24 h has not prevented the mortality rate which is 82%.[5,9]

CONCLUSION

The poor prognosis in our case was related to the advanced stage, delay in diagnosis since he was an apparently healthy immunocompetent individual. Greater awareness, early understanding of clinical course and early suspicion when the disease is refractory with prompt management may improve the prognosis.

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