Case Report

Rhino-Orbital Mucormycosis and Aspergillosis in A Child With Thalassemia Major on Deferoxamine Therapy

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Abstract

Rhino-orbital mucormycosis and aspergillosis is a rare potentially fatal opportunistic infection caused by saprophytic fungi. Mucormycosis is described almost exclusively in patients with compromised immune systems or metabolic abnormalities like poorly controlled diabetes. Iron overload states predispose to invasive mucormycosis. Coexistance of mucor and aspergillus is rarely observed and no case has been reported in a child with thalassemia major on deferoxamine therapy. Our patient developed unilateral blindness secondary to invasive fungal infection causing orbital cellulitis. Her journey over seven years of treatment and rehabilitation is described.

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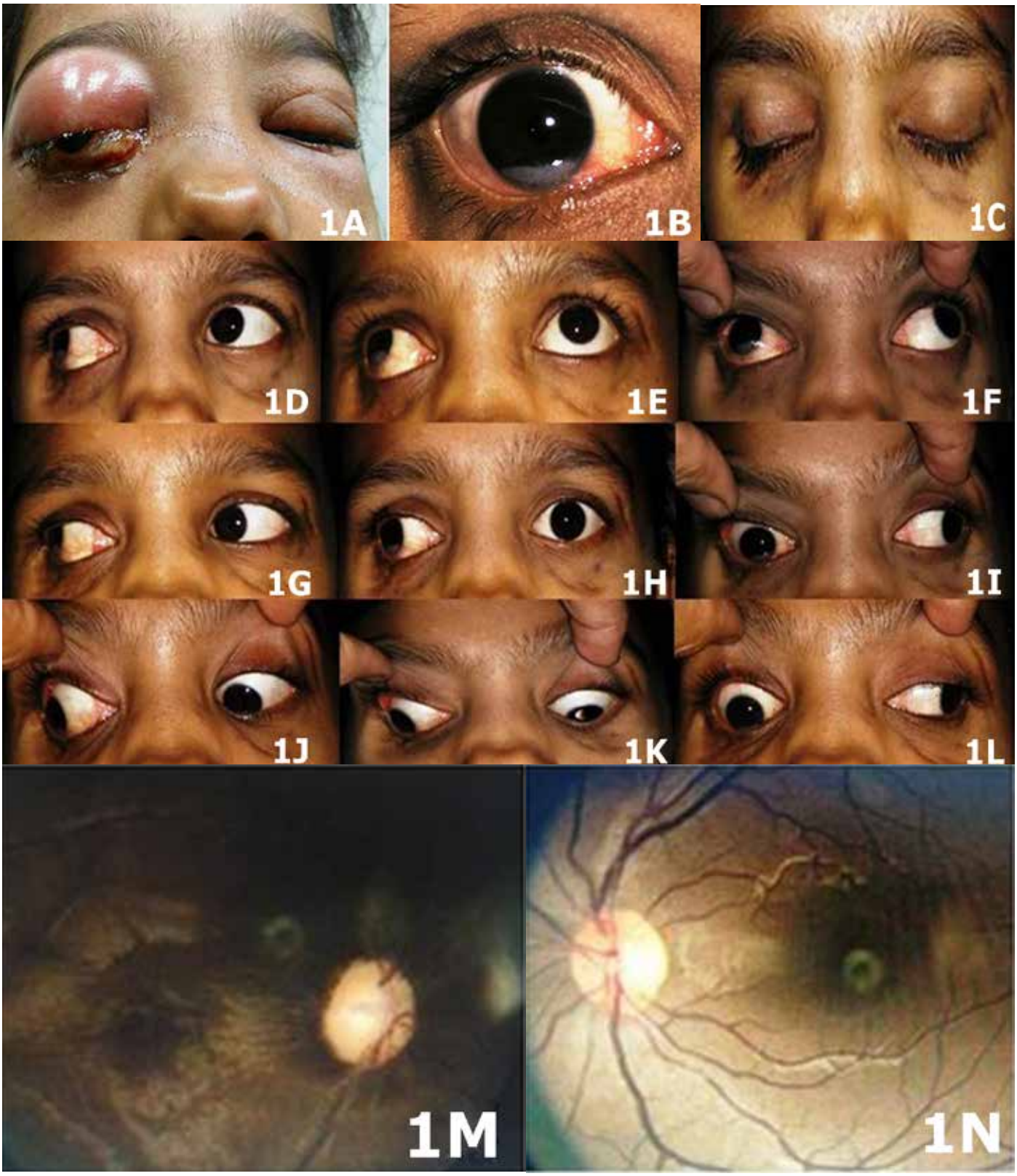
Introduction

Increased levels of serum iron and long term intake of deferoxamine have been recently observed to be associated with increased predisposition to mucor infection.[1] Rhizopus species can utilize deferoxamine as a xenosiderophore to supplement the previously inaccessible iron and accumulate it 8 to 40-fold greater amounts.[2]

Case report

An 11 year old female suffering from beta thalassemia major was receiving repeated blood transfusions along-with deferoxamine since the age of five years. She presented to us in April 2012 with fever for two weeks followed by mouth ulcers and a black eschar on the palate for which she was prescribed chloroxylenol (Dettol) mouth gargles by a village practitioner. After five days she developed a painless swelling over both the eyes, protrusion of the right eyeball (Figure 1A) and blood stained nasal discharge. On presentation, unaided visual acuity was 6/60 in the right eye (OD) with inaccurate projection of rays, progressively increasing abaxial proptosis, inferior corneal exposure keratopathy (Figure 1B) and complete limitation of all ocular movements. The presence of a relative afferent pupillary defect along-with a hyperemic swollen optic disc with a macular star was suggestive of papillitis and neuroretinitis in this child with orbital cellulitis. Left eye was normal in terms of visual acuity, ocular motility and fundus (Figure 1N). A blackish discolored area was noted in the right nasal cavity with nasal septal perforation. A working diagnosis of invasive mucormycosis causing orbital cellulitis was established. Intravenous (I.V) liposomal Amphotericin B (7.5 mg/kg/day) and I.V antibiotic (Ceftrixone + metronidazole) therapy was initiated on the day of presentation along-with oral methylprednisolone in a dose of 1 mg/kg body weight/day. A polypoidal growth from the nasal cavity was sent for microbiological analysis which revealed aseptate hyphae on KOH mount and mucor species was isolated on culture. Another specimen in the form of nasal scrapings demonstrated hyaline, septate branching hyphae on KOH mount and multiple colonies of aspergillus were isolated from culture. Meanwhile, a consultation with otorhinolaryngologist was sought for a localized area of necrosis of hard palate with areas of mucosal loss without bony erosion and a contrast enhanced computed tomography (CT) scan was performed which revealed bilateral chronic maxillary sinusitis with erosion and rarefaction of bone structures adjacent to orbit with extension into right orbit suggesting orbital cellulitis. MRI brain and orbit demonstrated non-involvement of intracranial structures with an ill-defined heterogenous area in soft tissue of right retro-orbital primarily inferolateral region with encasement of the optic nerve, lateral and inferior rectus muscle along-with proptosis. Orbital decompression was performed through the medial orbital wall. Proptosis and eyelid swelling decreased over a span of five to six days however despite all treatment the child developed central retinal artery occlusion and lost vision OD. I.V liposomal amphotericin B was substituted with I.V voriconazole after three weeks that was continued for two months subsequently. She was discharged after two months of hospital stay on oral linezolid (600 mg twice daily), tablet voriconazole (200 mg BD for two months), oral multivitamin B complex and vitamin C along-with tablet deferasirox 500 mg once a day. Corneal exposure keratopathy healed with scarring and the patient had incomplete eyelid closure (Figure 1C), exotropia (Figure 1H), optic atrophy (Figure 1M) and limitation of ocular motility in levoelevation, levoversion and levodepression OD (Figure 1D-L). One year later she developed recurrent proptosis OD and mild swelling in the left eyelid. CT scan at this stage did not show any new event. Oral voriconazole was administered for one month. Purulent discharge drained spontaneously at about one and half month from the right infraorbital region leaving a scar behind (Figure 1C) and proptosis settled down. On her presentation seven years later in 2019, she still had an exotropia of 70 prism diopters OD. A painless hard palate fistula (Figure 2A) was observed causing difficulty in deglutition. A repeat CT scan demonstrated hyper-densities within the right maxillary sinus (Figure 2B) along-with a defect in the hard palate communicating with the nasal and



Figures 1: *The child at 11 years of age developed orbital cellulitis in the right eye characterized by painless swelling over both the eyes, protrusion of the right eyeball (Fig.1A) and conjunctival chemosis with limitation in ocular motility. After treatment corneal exposure keratopathy healed with scarring (Fig. 1B) but the patient had incomplete eyelid closure (Fig. 1C), limitation of ocular motility in levoelevation, levoversion and levodepression in the right eye (Fig. 1D-L), exotropia (Fig. 1H) along-with optic atrophy (Fig. 1M). Left eye fundus was normal (Fig. 1N).*

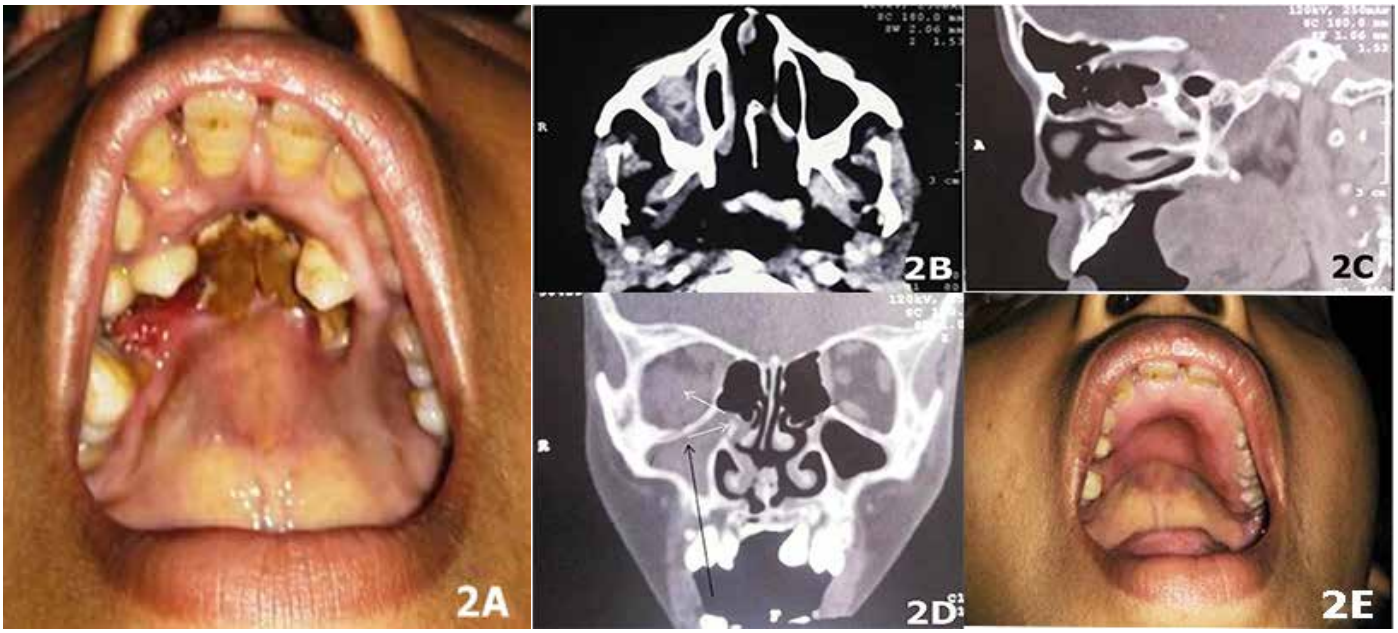


Figure 2: *A painless hard palate fistula (Fig.2A) was observed in this patient at 17 years of age. A computed tomography scan demonstrated a soft tissue with hyper-densities within it, in the right maxillary sinus (Fig.2B) along-with a defect in the hard palate communicating with the nasal and oral cavities (Fig.2C). The infection possibly traversed from the oral cavity through the palatal fistula to the nasal cavity and eventually into the orbit (Fig.2D). She underwent palatal reconstruction (Fig. 2E) for the fistula.*

oral cavities (Figure 2C and 2D). She underwent palatal reconstruction (Figure 2E) with a tongue flap repair under general anesthesia and is doing well.

Discussion

Normally iron is sequestered in serum by specialized iron-binding proteins, phagocytes and endothelial cells which prevent proliferation of mucor.[3] Predisposed individuals typically have either decrease in the number of phagocytes or their activity because of an impaired glutathione pathway which accounts for fungal growth.[4] Deferasirox, a new iron chelating agent has direct fungicidal effects against mucorales in vitro and in animal models as it deprives the fungus of iron.[5] The diagnosis of invasive fungal infections is challenging in more than 50 % of the cases because the fungus can rarely be isolated from blood or tissue cultures.[6] Chloroxylenol gargles administered to this child possibly had a corrosive action on the mucosa of the floor of the maxillary sinus hence the infection traversed through maxillary sinus to the nasal cavity resulting in orbital cellulitis.

Amphotericin B is the primary antifungal used in patients with mucormycosis and aspergillosis. Its liposomal formulation although costly, averts the dose-limiting nephrotoxicity.[7] In patients with hematopoietic disorders, stem cell transplant recipients and on chemotherapy for malignancies, the most commonly used antifungals are fluconazole, mould-active azoles including voriconazole and lipid formulations of amphotericin B.[8] Oral steroids have demonstrated improvement in mucosal disease and symptoms in patients suffering from allergic fungal rhinosinusitis (AFRS) immediately following sinus surgery and results in improvement of the endoscopic grading of the mucosal disease.[9] They cause reduction in the level of inflammatory markers including interleukin-3 (IL-3), interleukin-5 (IL-5), eotaxin, and monocyte chemoattractant protein-4 (MCP-4).[10] The use of corticosteroids (oral and topical) is widely shown to be helpful in AFRS. Suppression of inflammatory response, eosinophilia and serum levels of IgE has been documented.[11] A definitive regimen for oral steroid therapy has not been reported in literature however short course of pulse therapy compared with a prolonged course with tapering doses have been described.[12] Oral steroid therapy should be initiated only under the antifungal cover to curtail the flaring up of the disease and provoke adverse side effects.[13]

To the best of our knowledge, only a few isolated case reports exist in literature pertaining to the occurance of invasive fungal infections in children suffering from beta thalassemia major. A case of primary cutaneous mucormycosis has been reported in a Beta-Thalassemia patient who was treated with surgical debridement and amphotericin B.[14] Another child who was 11 years old boy suffering from with beta-thalassemia who was on deferoxamine therapy was found to develop cutaneous mucormycosis after splenectomy and leg fracture and was cured after debridement, amphotericin B infusion and skin graft.[15] Successful treatment of invasive Rhizopus infection in a child with thalassemia has been documented to be successfully treated with a combination therapy including aggressive sinus debridement, high dose liposomal amphotericin B, granulocyte colony stimulating factor (G-CSF), hyperbaric oxygen, local amphotericin B infusion and long-term posaconazole therapy.[16]

Mucor is angioinvasive and can involve neuronal structures.[17] Recurrence may be noted after a significant interval and warrants a close observation for such events.[18]

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