Novel and successful antifungal combination therapy for disfiguring facial mycoses

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Abstract

Background: Disfiguring facial lesions are caused by many underlying diseases including deep fungal infections.

Objectives: To identify the exact causative fungal pathogen and best course of management.

Methods: Repeated biopsies and initiation of early empirical aggressive antifungal therapy.

Results: Significant improvement of such cases within a short period of time with triple antifungal therapy and surgical debulking.

Conclusion: Multidisciplinary team care with early empirical aggressive triple antifungal therapy, pending the results of fungal studies, can achieve remarkable improvement.

Introduction

Some fungal infections may lead to devastating destruction of face, sometimes followed by fatal consequences. *Conidiobolus coronatus* is a rare, but serious emerging fungal pathogen of humans, causing Conidiobolomycosis, commonly infecting nasal mucosa and with potential to extend to involve vital structures such as brain and eyes[1]. Mucormycosis, another fungal infection commonly caused by Mucor, is usually acquired when spores, are inhaled, commonly from the environment, leading to destruction of nose, sinuses and brain. Treatment of these infections is extremely difficult and can cause significant disfiguring sequale, unless aggressively treated. We illustrate three interesting cases, encountered within a short space of time affected by such infections and emphasize the need for thorough evaluation, investigation and aggressive initial treatment to achieve a good clinical response.

Case 1

A 55 year old lady, who works in a tea estate, presented with an asymptomatic progressive enlargement of nose of 4 months duration. The lesion extended to adjacent bilateral cheeks and forehead over a 2 month period. She had low grade fever and loss of appetite for 2 weeks. Patient did not give a history of epistaxis. There was a contact history of pulmonary tuberculosis 10 years back but no contact history of leprosy. There was no history of trauma to the nose. She did not have any cormorbidites. Examination revealed a non-tender erythematous indurated plaque over the nose extending over bilateral cheeks and mid-forehead. Nasal septum was destroyed, but hard palate was normal. ESR-120mm-1^{s}t Hr, Mantoux test 15mm, Chest X-ray – normal, Sputum for Acid fast bacilli – negative, and first skin biopsy showed vague granulomata with a suspicion for underlying Wegener's Granulomatosis. Slit-skin smears for lepra bacillus – negative.

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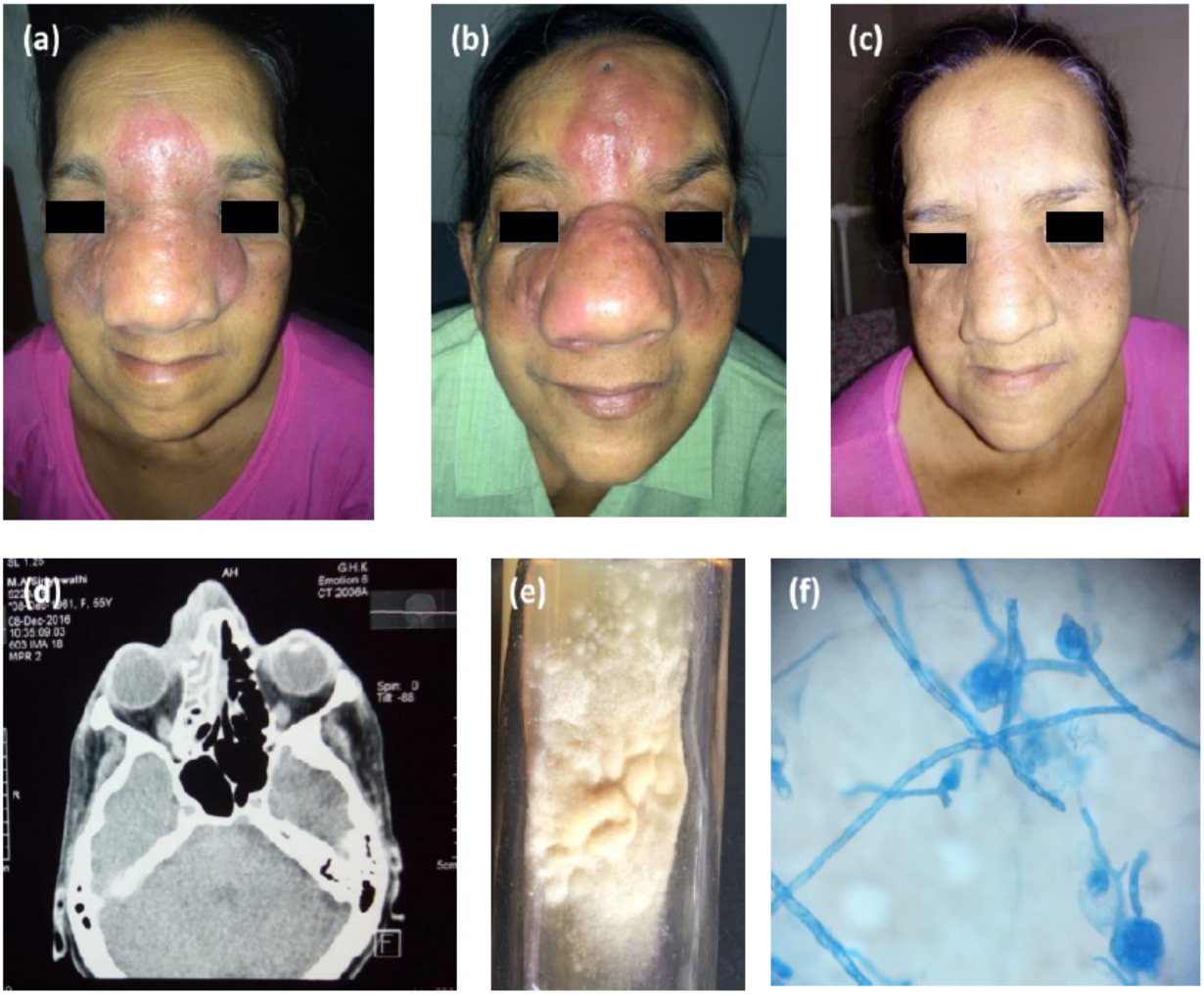

Figure 1. *Clinical improvement of conidiobolomycosis with antifungal therapy, imaging and fungal studies (a) Before antifungal therapy; (b) While on oral itraconazole; (c) After initiation of the triple therapy of antifungals with liposomal amphotericine B; (d) Bony destruction of the right side of nose; (e) Fungal culture of and (f) Direct microscopy of the Conidiobolus coronatus.*

Pending tuberculosis and fungal cultures, she was empirically treated with itraconazole 200mg b.d. and anti-tuberculosis therapy. pANCA, cANCA and ANA were negative. Meanwhile, repeated skin biopsies were done, which too failed to confirm either cutaneous tuberculosis or fungal infections. She continued to develop non-tender nodules in the nose and forehead despite therapy. In view of poor response, oral terbinafine 250mg b.d. and potassium iodide therapy were added. CECT [Contrast enhanced computed tomography] showed destruction of the right nasal Concha. Direct microscopy of the third biopsy from a different location of the lesion of the nose revealed fungal filaments, followed by positive fungal culture for *Conidiobolus coronatus*. Anti tuberculosis therapy was then withdrawn. Intravenous liposomal amphotericine B [4mg per Kg of body weight] was also added in addition to the triple antifungal therapy. She improved remarkably within three weeks of therapy.

Case 2

A 63 year old farmer presented with rapidly progressive destructive lesion of the nose and palate for 03 months duration. Initially, it has started as a crusted plaque in the nose and rapidly progressed to involve the hard palate, leading to nasal regurgitation of food. There was no contact or past history of leprosy or tuberculosis. There was no history of trauma to the nose. On examination, there was a collapse of nasal septum with crusted plaques with purulent discharge at alae nasi of the nose with palatal perforation.

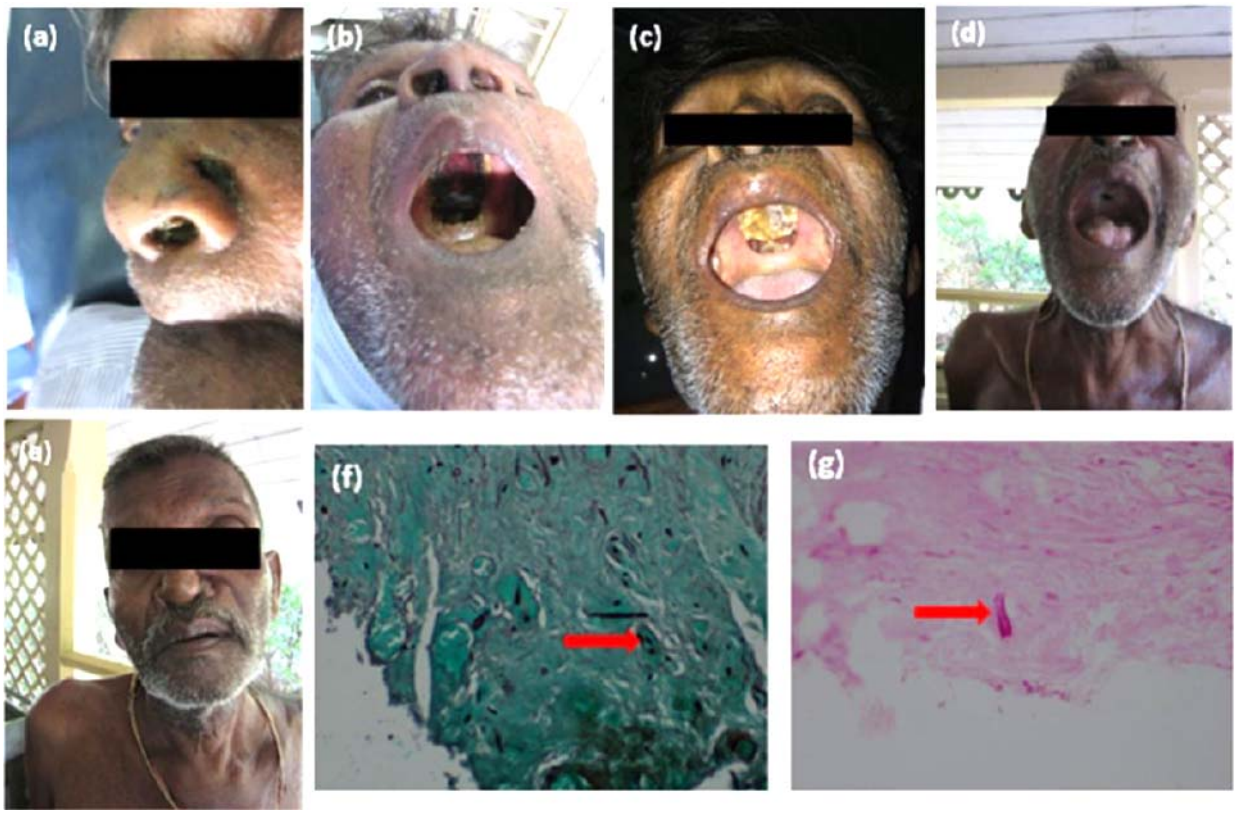

Figure 2. *Clinical improvement of mucormycosis with antifungal therapy (a,b,c) before therapy; (d,e) 06 months after therapy; (f) PAS staining; and (g) Grocott's staining.*

Palatal biopsy revealed fungal hyphae, which were thin walled non-septate, branched haphazardly, often at right angles to the parent hyphae, highly suggestive of mucormycosis. Fungal culture was negative. Skin biopsy was non-specific. A diagnosis of deep fungal infection due to mucormycosis was established in a non diabetic/non immunocompromised patient. Patient was treated with triple therapy including oral itraconazole 200mg two times a day + potassium iodide 600mg daily and oral terbinafine 250mg two times a day. All lesions healed within 06 months of the therapy with residual palatal perforation. Triple therapy was further continued for 04 months until repeated nasal scrapings proved negative and the reconstructive surgery of the palatal perforation was performed.

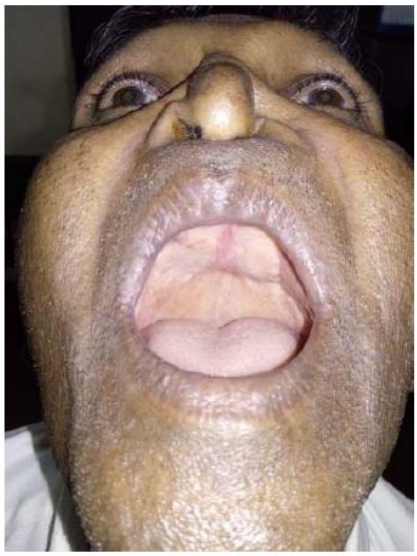

Figure 3. *After the palatal reconstructive surgery.*

Case 3

A 40 year old patient with Poly Cystic Kidney Disease [PCKD], not on any renal supportive or other therapy, had developed progressively worsening headache with intermittent epistaxis for 02 months duration. There was no history of nausea, vomiting, behavioural changes, visual impairment or seizures. Later, he developed left sided nasal blockage with frequent episodes of mild epistaxis for 02 weeks. On Ear, Nose and Throat [ENT] examination, a polyp was detected in the left side of the nose, which was biopsied and found to be supportive of fungal infection although no fungal hyphae were identified and he was commenced on oral itraconazole 200mg b.d. in the ENT unit. Contrast Enhanced Computed Tomography [CECT] of brain revealed left sided fronto-ethmoidal "neoplasm". 02 months later, he complained of severe painful progressive loss of vision of the left eye for 01 week. Examination found marked left eye proptosis and tender erythematous plaque in the left side of the face.

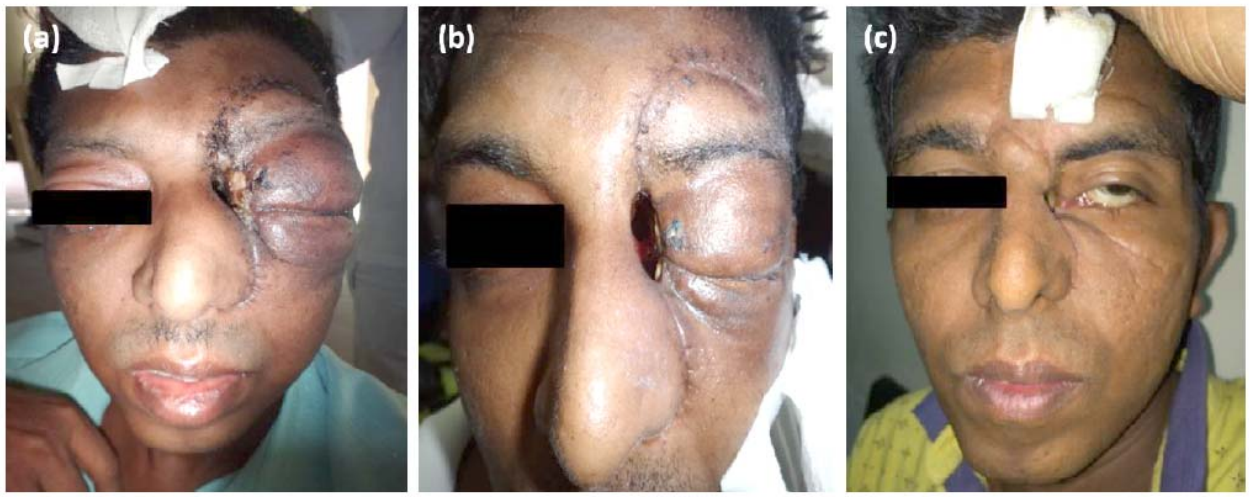

Figure 4. *Clinical sequels of conidiobolomycosis with antifungal therapy. (a) Initial presentation only with oral itraconazole therapy (b) at 02 months after triple antifungals and (c) 06 months after therapy.*

Meanwhile, he had undergone combined surgery (Extended lateral Rhinotomy + medical maxilectomy + frontal sinus exploration) and tissue excision revealed fungal elements in the microscopy, followed by positive culture of *Conidiobolus coronatus* in the fungal culture. As he had a poor response to oral itraconazole, he was referred to dermatology department and was commenced on triple antifungal therapy with oral itraconazole 200mg b.d., oral terbinafine 500mg b.d. and potassium iodide 1% 15 drops daily. As he was a patient with PCKD, intravenous amphotericine B was not added. Nasolabial flap was performed 03 months' of therapy. Repeat CECT of brain did not reveal any evidence of intraorbital masses. He had remarkable improvement with the triple antifungal therapy. Forehead rotational flap surgery was performed 02 months later. Interestingly, 06 months later, he presented with an exacerbation, at which time, nasal scraping revealed *Aspergillus* on fungal culture, which was considered to be a superinfection and it responded rapidly to intravenous voricanazole therapy.

Discussion

These pathogens are saprophytic and usually found in soil and decaying organic materials in the environment with a high prevalence in tropical and subtropical regions[1-3]. These infections are not only seen in immunocompromised patients but also commonly seen in immunocompetant individuals[2,4-6]. In rhinofacial infections, once the spores of the fungus are deposited in the nasal mucosa either by inhalation or by trauma, they progressively invade the subcutaneous tissues, causing gradual destruction of the nose and adjacent tissues followed by significant facial mutilation[7-10]. These infections mimic lupus vulgaris, leprosy, cutaneous leishmaniasis, all of which are commonly seen in the tropics. Other differential diagnoses to be considered are Wegener's granulomatosis and nasal lymphomas especially, NK cell type. Therefore, good histology, if necessary from multiple sites as well as deep surgical biopsies are required for initial evaluation. Once granulomatous

inflammation due to a possible infection is favored, proper investigations for evaluation of underlying pathology, such as, slit skin smears for leprosy and leishmaniasis, PCR and cultures for tuberculosis and leishmaniasis need to be carried out and identification of the fungus by fungal culture as well as direct microscopy is also of paramount importance. With regard to our above mentioned clinical cases, we wish to emphasize the fact that, early clinical suspicion of fungal aetiology in such presentations, identification of fungal elements by repeated biopsies and initial aggressive empirical combination of antifungal therapy, pending culture results as well as surgical support in the form of debulking and tissue reconstruction together with multidisciplinary team care extended by dermatologist, mycologist, ENT, plastic and reconstructive surgeons, will help patients to achieve unbelievable clinical response and to have normal or near normal lifestyles.

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