

## Case Report

### **Rhino-Facial Conidiobolomycosis (RFC) (Rhino-entomophthoromycosis): presenting as a progressive nasal mass, A diagnostic dilemma**

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#### **Abstract**

A 42-year-old male patient presented with a mass lesion over the dorsum of nose and central face. Initially, all investigations including inflammatory markers, multiple biopsies and fungal stains failed in diagnosing the disease. Eventually, it was diagnosed as **rhino-facial conidiobolomycosis** by fungal culture and successfully managed with combination antifungal therapy.

**Key words:** Rhino-Facial Conidiobolomycosis (RFC), Combination antifungal therapy, Fungal culture.

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## Introduction

Granulomatous nasal conditions have wide variety of aetiologies and those can be classified as infective, inflammatory, neoplastic and vasculitis associated diseases. Disease may be localized and confined to the nose or may be a part of a systemic condition.

Infective aetiologies of fungal origin are such as aspergillosis, zygomycosis including conidiobolomycosis, dermatocytic infection, blastomycosis and histoplasmosis. Diagnosis of exact aetiology as in deep fungal infections are difficult and high degree of clinical suspicion is necessary due to the rarity of disease. There is a significant delay in diagnosing especially, when all the preliminary investigations and biopsies are inconclusive.

We faced such a challenging situation with a slowly progressive mass lesion over the nose and central face diagnosed as **Rhino Facial Conidiobolomycosis**. We present our experience to improve awareness among clinicians on this rare fungal infection because, it causes significant morbidity.

## Case History:

A 42-year -old male manual labourer (coconut plucker) presented with slowly progressive painless swelling over alar of nose for 08 months. Initially, it has started over left nasal alar and later spread to involve the whole external nose and bilateral cheeks. There was left sided nasal block but no nasal discharge, epistaxis, hyposmia , headache or complains related to vision. However, with progression of the lesion, he had intractable pain in and around the lesion. There were no other co-morbid illnesses such as, diabetes mellitus or other immunocompromised conditions. He had undergone left side lateral rhinotomy and medial maxillectomy six years back (2012) for a transitional cell papilloma of left nasal cavity and remained asymptomatic up to current complaint.

Lesion was distributed over the nasal dorsum and both cheeks. There was well demarcated hyperaemia over the involved skin with blanching on palpation (**Figure 1a**). Later, there was erythema over hard palate suggestive of early palatal involvement. Nasal endoscopy showed mucosal oedema of lateral nasal wall and anterior septum but no discrete mass lesions, crusting or muco-purulent discharge.

There was mild elevation of white cell count ( $11.16 \times 10^9/\text{mm}^3$ ) and C-reactive protein(CRP17.9g/dl) However, ESR, blood sugar, urine analysis, antinuclear cytoplasmic antibody (cANCA) and serum immunoglobulins/ IgG and chest xray were normal. Contrast enhanced computed tomography(CECT) scan of nose and paranasal sinuses revealed contrast enhancing diffuse lesion involving skin and subcutaneous tissue of external nose and cheeks without sinus involvement or bony erosions (Figure1c). There was evidence of previous medial maxillectomy in which he had undergone 06years back in 2012.

Several intranasal biopsies had been done by the time the patient referred to our care and all were inconclusive but we did repeat deep biopsies of lateral nasal wall, septum and deep incisional biopsy over skin lesion and the samples were sent to the local laboratory and also to the Department of Mycology, Medical Research Institute (MRI) Colombo. Histology revealed only diffuse granulomatous inflammation with inflammatory cellular infiltrates of lymphocytes, plasma cells and eosinophils and granulomata composed of epithelioid histiocytes, multinucleated giant cells but **fungal stain (Periodic acid-schiff/PAS stain) was negative**. There was no “Splendore- Hoepplie Phenomenon” (histological appearance of eosinophilic granuloma with broad aseptate fungal filaments surrounded by a halo of eosinophils is called as “ **Splendore – Hoeppli Phenomenon**”).

Clinical findings and investigations were highly suggestive of invasive fungal infection and lesion was progressive and has started to spread to hard palate and towards the lower eye lids. As the disease extending towards orbit, multidisciplinary decision (Otorhinolaryngology, Mycology, Microbiology,

Dermatology and Immunology) was taken to start systemic antifungal therapy even though initial fungal staining was negative, while awaiting culture result.

Intravenous Liposomal Amphotericin (0.3mg/kg daily) was started and there was a significant response after first 24 hours of therapy. Fungal culture report was available after 72 hours of incubation and revealed growth of fungal species of *Conidiobolus*. IV Liposomal Amphotericin (0.3mg/kg daily) continued for two weeks and showed remarkable improvement and regression of the lesion. Then, it was converted to tripple therapy of oral Itraconazole (200mg two times daily), oral Terbinafine (250mg two times daily) and oral drops of saturated solution of Pottasium Iodide (KI) but patient could not have tolerated pottasium iodide and had to withhold. Treatment plan was to continue combination therapy of Itraconazole (200mg twice daily) and oral Terbinafine (250mg twice daily) for six months. There was significant improvement after five months of therapy (Figure 1b).



1a: A photograph of patient prior to antifungal therapy



1b: A photograph of patient after 5 months of antifungal therapy.



**1c:** CECT scan (axial view) shows contrast enhanced subcutaneous lesion without bony erosions or sinus involvement. (There is evidence of past left medial maxillectomy).

## Discussion

Rhino- facial conidiobolomycosis is an infection of skin and subcutaneous tissue of nose and the central face caused by a saprophytic fungus called *Conidiobolous coronatus* which belongs to order Entomophthorales<sup>2, 3, 4</sup>. This organism lives in soil, decaying vegetations, droppings of insects, amphibians and lizards. It infects both insects and mammalians<sup>2</sup>. Human infections are frequently seen in tropical and subtropical counties with high humidity (98%-100%) and high temperature (16°C -30°C) like in African, Asian and some of American countries. Infections are sporadic and more common in males (male: female = 8:1)<sup>2</sup> who are engaged in outdoor occupations.

Rhino -facial conidiobolomycosis is an infection of immunocompetent adults. It is thought that it transmits via inhalation of fungal spores or direct inoculation with sticky conidia over damaged mucosa or skin. Recent literature is suggesting that it needs injured skin or mucosa in which the sticky conidia can get attached and invade into subcutaneous tissues to develop the disease<sup>2</sup>. There is a history past nasal surgery (lateral rhinotomy and medial maxillectomy) in this patient. He has been regularly engaging in outdoor activities in a area of high temperature and humidity of Sri Lanka (Wariyapola, North Western province of Sri Lanka) even after the procedure. Therefore, most probably he has acquired the infection via direct inoculation of the conidia over surgical site.

*Conidiobolous coronatus* favours facial region and typically infects subcutaneous tissue<sup>2</sup>. Host immune response to invading fungal elements causes vasculitis rather than angio-invasion which is seen in acute fungal sinusitis by *Mucorales* species in the immunocompromised host. Choon et al, suggests this pathological process as **chronic localized fibrosing leukocytoclastic vasculitis (CLFLCV)**<sup>5</sup>. Persisting fungal antigens lead to persisting immune response and immune complex deposition which eventually resulting layered deposition of fibrotic tissue resulting pseudo tumour formation. Later, fibrosis impairs lymphatic drainage resulting lymphostasis and lymph oedema of affected rhino facial region. This may lead to facial elephantiasis and permanent disfigurement if not treated early. Typical infection with *Conidiobolous coronatus* fungus is not angio-invasive so the dissemination is unlikely. Clinical features are slowly progressive painless nasal swelling with nodular formation, nasal obstruction, nasal discharge, epistaxis and patient may experience sinusitis due to obstruction of sinus drainage. There is a recently published proposal of pathological classification of Rhinofacial Conidiobolomycosis as **Atypical ( i ) , Early ( ii ) , Intermediate ( iii ) and Late ( iv)**<sup>6</sup>. Atypical disease is the infection with ulceration of skin and / or invasion of orbit, central nervous system or other viscera. Early disease is the infection of weeks and less than one month with mild swelling and rhinitis without nodular formation. The intermediate disease is the infection of months and less than a year with nasal

obstruction, nodular formation, noticeable reddishness and involving nose and nearby tissues. This patient's disease classification is most probably the **intermediate (iii) disease**. The late disease is the chronic non treated disease of months and years with extreme deformity and facial elephantiasis.

## Diagnosis

Fungal culture of the infected tissue is the reliable diagnostic modality at present and the biopsy sample must be transported to the laboratory at room temperature in close containers. Incubation at 37°C in suitable culture media for 3 to 5 days will show the growth of colonies of *Conidiobolus* species<sup>2,3</sup>.

Fungal hyphae may be detected on a wet mount with fungal staining but those can be easily damaged during tissue processing. Sensitivity of detection of fungal hyphae on a wet mount can be improved by examining under fluorescent microscopy. Typical histological appearance is the eosinophilic granuloma with broad aseptate fungal filaments surrounded by a halo of eosinophils and the appearance is called as “**Splendore – Hoespli Phenomenon**”<sup>2,3,5</sup>.

This is not specific to conidiobolomycosis and also can be seen with some other fungal and parasitic infections in immunocompetent hosts but it is supportive in the diagnosis of rhino-facial conidiobolomycosis. But our patients' biopsy sample failed to demonstrate that phenomenon and the fungal stain also was negative. However fungal culture was positive and demonstrated growth of *Conidiobolus* species.

Therefore, it is essential to obtain fungal cultures in all the undiagnosed granulomatous nasal conditions to prevent delay in the diagnosis and the associated morbidity. Imaging with contrast enhanced computer tomography (CECT) scan supports the diagnosis and as this patient it provides the nature and the extension of the lesion (**Figure 1c**) and helps to exclude other aetiologies as well. Inflammatory markers are always essential to exclude other possible differential diagnosis early prior to the tissue sampling.

## Management

Optimal management of rhino-facial conidiobolomycosis is debatable at present, and literature provides several therapeutic strategies such as monotherapy with systemic antifungals, combination therapy with multiple antifungals (Amphotericin, Azoles and KI) with or without surgical debridement and hyperbaric oxygen therapy<sup>2,3,5</sup>. According to Shaikh et al, combination therapy is the best at present as multiple antifungals have synergistic effect over fungi. Early antifungal therapy is crucial to prevent permanent facial disfigurement and morbidity. Severe initial disease, as in our patient may need combination therapy with IV Amphotericin followed by long term oral combination antifungal therapy. Monitoring of renal and liver functions are essential to detect side effects of the antifungals.

Prognosis depends on several factors and according to Choon et al, meta-analysis on outcome of this disease, 83% of 199 cases have shown improvement or cure with antifungals and/or surgical excisions<sup>5</sup>. Following are associated with poor prognosis<sup>5</sup>, Late disease with delay in antifungal therapy, involvement of orbit or the brain, Immunocompromised patients, absence of Splendore-Hoespli Phenomenon, infection with atypical species other than *Conidiobolus coronatus* and female genders<sup>5</sup>.

## Conclusion.

Rhin-ofacial conidiobolomycosis should be included in differential diagnosis of centro-facial mass lesions of immunocompetent patients, who are engaged in outdoor activities in tropical and subtropical regions. Diagnosis is confirmed only by the fungal culture of infected tissue. Multidisciplinary approach helped us to diagnose and manage the patient without significant morbidity. Combination antifungal therapy have shown remarkable improvement in our patient at present and need to continue the therapy and follow the patient.

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