

Conidiobolomycosis: An Unusual Fungal Disease—Our Experience

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Received: 20 September 2016/Accepted: 12 August 2017/Published online: 20 August 2017
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Abstract Conidiobolomycosis is a rare mycotic disease caused by *Conidiobolus coronatus*. Very few cases have been reported in English literature. Often it is clinically misdiagnosed as soft tissue tumour. A prospective case study was done from 2006 to 2015 in a tertiary care hospital of West Bengal, India. The objectives of our study were to describe the epidemiological and clinical features and treatment of Conidiobolomycosis to prevent disfigurement. Patients clinically suspected to be suffering from Conidiobolomycosis were subjected to biopsy followed by histopathological and mycological examinations. Then they were treated with oral saturated solution of potassium iodide along with other drugs. Total six cases were histopathologically proved to be suffering from Conidiobolomycosis. Fungus was isolated and identified in one case. Complete resolution was seen in five patients. Conidiobolomycosis should be brought into mind as differential diagnosis of subcutaneous swelling in the rhinofacial region.

Keywords Conidiobolus · Biopsy · Microscopy · Potassium iodide · Azoles

Introduction

Conidiobolomycosis is a rare, chronic, localized, subcutaneous zygomycosis of rhinofacial region [1, 2]. It is caused by *Conidiobolus coronatus* [3]. It is characterized by painless, woody swelling of rhinofacial region [1, 2], often clinically misdiagnosed as soft tissue tumour [4]. The disease occurs mainly in South East Asia, Africa, South and Central America. Very few cases have been reported from India [5]. Due to the small number of cases reported in the literature, treatment protocol is not yet standardized [6]. Here we describe six cases, diagnosed on the basis of clinical knowledge and histopathological features.

Materials and Methods

We conducted our study over 10 years (from January 2006 to December 2015) in a tertiary care hospital of West Bengal, India. We treated patients referred to our hospital from all over West Bengal. The objectives of our study were to describe the epidemiological features, and diagnostic and treatment protocols of patients of Conidiobolomycosis.

Patients clinically suspected to be suffering from Conidiobolomycosis were subjected to biopsy followed by histopathological and mycological examinations. Informed consent was obtained for participation in this study and publication also. This study was approved by the institutional ethical committee. Total six cases were histologically and/or mycologically proved and included in our study (Figs. 1, 2, 3, 4, 5, 6). A detailed history was taken and local examination was done (Tables 1, 2). General and systemic examinations were also done. All patients underwent routine blood tests and CT scan of nose and paranasal sinuses (Fig. 7). Biopsy was taken from the

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Fig. 1 Clinical photograph of patient no. 1



Fig. 3 Clinical photograph of patient no. 3



Fig. 2 Clinical photograph of patient no. 2



Fig. 4 Clinical photograph of patient no. 4

swelling in anterior end of inferior turbinate or ala of nose and tissue was sent for histopathological examination and mycological culture. Patients were treated with oral saturated solution of potassium iodide (SSKI) along with other drugs (Table 3). Patients were advised to take SSKI with fresh fruit juice. Initially it was given 5 drops/dose thrice daily and gradually increased up to 15 drops/dose thrice daily. Before and during treatment, patient's thyroid function test, liver function test and serum potassium were monitored. We advised local hot compression over nose and face, and mouthwash with luke warm water in cases having involvement of oral cavity. We also prescribed natamycin topical 5% suspension intra-nasally. Regular follow up was done and treatment was continued for another 3 months after complete resolution.

Results

In our series total number of patients was six. All were from rural area. Five of them were male, one was female. All patients were involved in agricultural activity either directly or indirectly. Nasal obstruction was the most common and earliest symptom. None of them had history of fever or trauma to nose. All of them had swelling either in the ala or inferior turbinate of nose along with swelling of dorsum of nose, cheek, upper lip or glabella. The margin of the swelling was ill-defined, surface was smooth and shiny. Slight coppery discoloration was obvious on the skin over the swelling in some cases but there was no ulceration. On palpation there was no tenderness, no hypoesthesia or hyperaesthesia



Fig. 5 Clinical photograph of patient no. 5



Fig. 6 Clinical photograph of patient no. 6

over the swelling, the consistency was firm and the overlying skin was thickened and fixed. Local temperature was not raised and the swelling was not pulsatile. There was no significantly palpable lymph node in neck. Systemic examinations were within normal limits. Histopathological examination of biopsied specimen showed sparse hyphal elements ensheathed by amorphous eosinophilic Splendore-Hoepli material (Fig. 8). Culture was positive in only one patient that was too on second attempt, which showed white waxy to powdery colonies (Fig. 9). On microscopy, broad septate hyphae with unbranched short, erect conidiophores were seen (Fig. 10). Complete resolution was seen in five patients. There were multiple recurrences in one patient. In one patient it recurred due to discontinuation of treatment in the midway.

Discussion

Conidiobolomycosis is a chronic, localized, subcutaneous zygomycosis [1, 2]. It is caused by *Conidiobolus coronatus*, a mould belonging to the order Entomophthorales of the class Zygomycetes [3]. Because of its initially central facial presentation affecting the nose first, the disease is known as rhinoentomophthoromycosis [6]. The name Entomophthorales has been derived from Greek word “Entomon”, which means insect [1]. These are saprophytic fungi present in soil, decaying fruit and vegetable matter as well as in the gut of amphibians and reptiles. Basically these fungi are pathogens infecting insects [5]. The human pathogens in this order include *Basidiobolus ranarum* and *Conidiobolus coronatus* [7]. Infection by *B. ranarum* manifests itself as a subcutaneous tumefaction located on the trunk, buttocks, or proximal portion of the limbs [6]. The infection is transmitted by inhalation of spores, insect

Table 3 Distribution of patients according to treatment and outcome

Serial no	Treatment	Outcome
1	Saturated solution of potassium iodide (SSKI) for 2 months + Clotrimazole for 5 months → Cured, recurred after 6 months → SSKI + Oral steroid → SSKI for 1 month + Ketoconazole for 5 months → Cured, recurred after 8 months → Itraconazole 100 mg twice daily for 6 months → Cured, recurred after 6 months → Fluconazole 150 mg twice daily for 6 months → cured, recurred after 5 months	Recurrence
2	SSKI for 2 months + Fluconazole 150 mg twice daily for 6 months	Complete resolution
3	SSKI for 2 months + Itraconazole 100 mg twice daily for 5 months	Complete resolution
4	SSKI for 2 months + Terbinafine 250 mg thrice daily for 5 months	Complete resolution
5	SSKI for 2 months + Fluconazole 150 mg twice daily for 2 months → Partial resolution → Discontinued, recurred → SSKI + Oral steroid → SSKI for 2 months + Terbinafine 250 mg thrice daily for 6 months → cured	Complete resolution
6	SSKI for 2 months + Itraconazole 100 mg twice daily for 5 months	Complete resolution

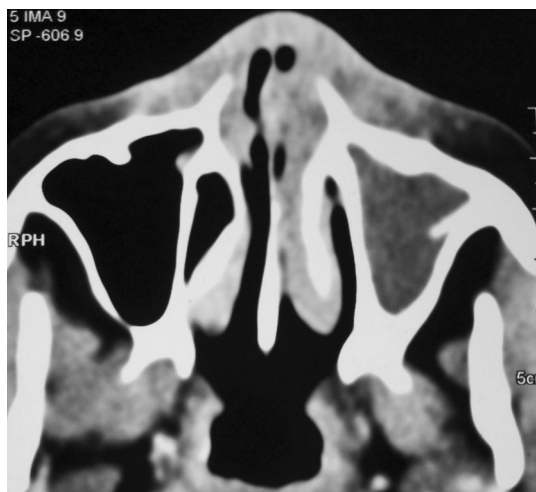


Fig. 7 CT scan of nose and paranasal sinuses of patient no. 5 of our series showing heterogeneous opacity involving left inferior turbinate, ala and cheek

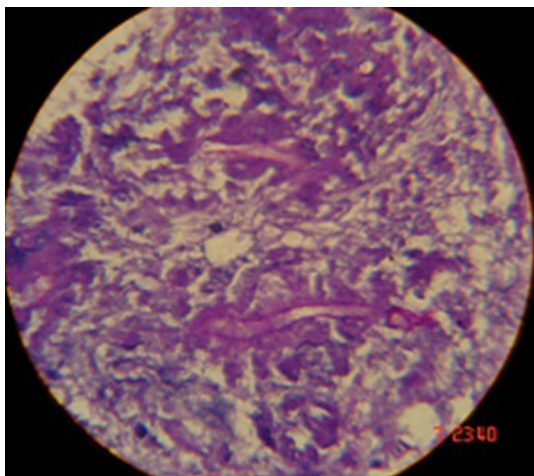


Fig. 8 High power magnification of H and E stained section of the nasal mucosa showing hyphal elements surrounded by Splendore-Hoeppli material and inflamed stroma

bites or their introduction into the nasal cavities by soiled hands [8]. *Conidiobolus coronatus* was first identified as an agent of nasal granulomatous disease in horse in Texas in 1961, while the first human infection was reported in Jamaica in 1965 by Bras et al. [1]. It occurs predominantly in males with agricultural or outdoor occupations, with a male to female ratio of 10:1 [9]. In our study the ratio was 5:1. All of them came from rural area and were involved in agricultural activity either directly or indirectly. The disease is usually seen in immunocompetent patients. However, there have been reports in HIV infected patients and renal transplant patients [10, 11]. The disease seems to start in inferior turbinate followed by submucosal spread to the subcutaneous tissues of dorsum of nose, cheeks, forehead, periorbital region and upper lip [12, 13]. Nasal obstruction

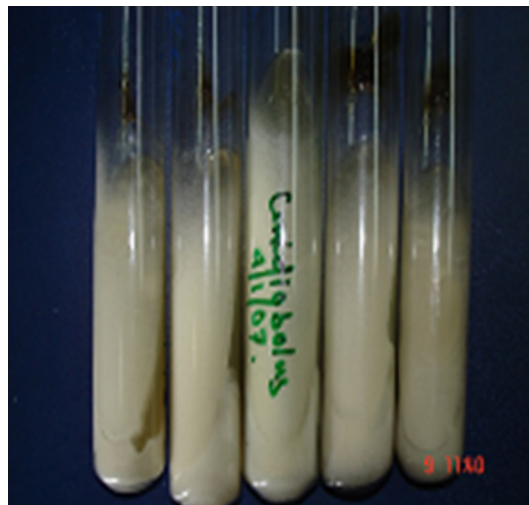


Fig. 9 *Conidiobolus coronatus* culture in Sabouraud dextrose agar

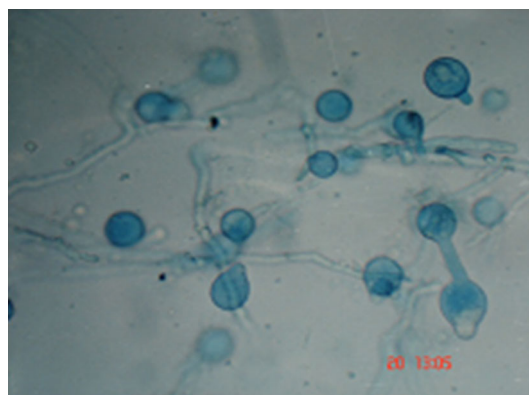


Fig. 10 High power magnification lactophenol cotton blue (LPCB) stained smear showing several conidiophores with spherical conidia

occurs first, followed by a diffuse erythematous infiltration with thickening of the skin on the nose and face. Later it causes discomfort and restriction of movement of the face and upper lip [14]. Development of subcutaneous nodules in the eyebrows, upper lip and cheeks may give the patient the appearance of hippopotamus [15]. In the more advanced cases, the lesions can also affect the nasopharynx, oropharynx, palate and laryngopharynx [16, 17]. It rarely extends to the intracranium, mediastinum or lungs [18, 19]. All of our patients complained of unilateral or bilateral nasal obstruction. They showed swelling either in the ala or inferior turbinate of nose along with swelling of dorsum of nose, cheek (nasolabial and nasofacial region), upper lip or glabella. One case had developed swelling of palate. The lesion is occasionally misdiagnosed clinically as cellulitis, rhinoscleroma, lymphoma, lymphoedema, Kimura disease, angiolymphoid hyperplasia with eosinophilia and sarcoma [7, 14]. On histopathological examination hyphae of *Conidiobolus coronatus* are difficult to

Table 1 Distribution of patients according to age, sex, habitat and occupation

Serial no	Age (in years)	Sex	Habitat	Occupation
1	18	Male	Rural	Student
2	44	Male	Rural	Farmer
3	36	Male	Rural	Farmer
4	43	Male	Rural	Farmer
5	37	Female	Rural	Housewife
6	39	Male	Rural	Farmer

find as they are outnumbered by numerous commensal fungi. Hyphae of *Conidiobolus coronatus* are short and broad with conspicuous septation. They are ensheathed by amorphous eosinophilic Splendore-Hoepli material, which is believed to be an antigen–antibody precipitate. The adjacent stroma consists of granulation tissue that is rich in eosinophils [8]. Only 15% of Conidiobolomycosis are positive on mycological culture from clinical specimens [20, 21] as hyphae are often damaged and become non-viable during biopsy procedure or by chopping up or grinding processes in the laboratory. Their growth is also superseded by commensal fungi [22–24]. Only one patient (16.67%) in our study had positive culture. Conidia are forcibly discharged and stick to the walls of the culture container forming waxy to powdery colonies completely clouding the view of the culture with time [1]. On microscopy, broad septate hyphae with unbranched short, erect conidiophores are seen [1]. Various treatment protocol have been tried with mixed results. Medications used to treat Conidiobolomycosis include SSKI, ketoconazole (200–400 mg/day), itraconazole (200–400 mg/day), fluconazole (100–200 mg/day), miconazole, voriconazole, terbinafine, amphotericin B, clotrimazole and hyperbaric oxygen [3, 25, 26]. Of these, itraconazole and fluconazole are both effective and relatively safe [6]. SSKI (1 gm/ml) is

useful for patients in developing countries, because of its ease of administration and low cost. It is initiated in a dose of 5 drops/day (diluted in water, milk or fruit juice) and gradually increased up to a maximum of 40–50 drops per day, as tolerated [27]. The exact mechanism of its action is not known. Iodide perhaps facilitates phagocytic killing by promoting the respiratory burst associated with superoxide formulation in phagolysosomes [28]. Iododerma, acneiform eruption, gastric intolerance, increased salivation and lacrimation, unpleasant brassy taste, hypothyroidism etc. are the usual side effects [8]. Combination therapy with oral potassium iodide and oral azoles give rapid and lasting results [8]. We found good result with topical therapy similar to a report by Haruna et al. [29]. We also got acceptable result with intranasal use of topical nystatin, which is actually prescribed for mycotic keratitis [30]. Relapse is common, even after successful treatment [7, 8]. In such cases systemic steroid is used. Steroids probably act as adjuvant to inhibit deposition of a barrier eosinophilic immune complex around the fungus thereby ensuring availability of antifungal drugs to the target site [31]. Two patients of our study had recurrence. One of them was cured with treatment after initial course of oral steroid. Others were completely cured. Treatment should be continued for at least 3 months after the lesions have cleared [8]. Surgical resection is seldom helpful and it may hasten the spread of infection.

Conclusion

Conidiobolomycosis should be brought into mind as differential diagnosis of subcutaneous swelling in the rhinofacial region especially in adult male agricultural workers. Look of the patient is the mainstay of diagnosis. Excessive tissue damage has to be avoided during biopsy. Similarly teasing and processing of the specimen should be gentle to

Table 2 Distribution of patients according to symptoms and signs

Serial no.	Symptoms	Signs
1	Bilateral nasal obstruction for 4 months, swelling of nose for 3 months	Generalized swelling of ala and dorsum of nose
2	Left nasal obstruction for 3 months, swelling of left side of dorsum of nose and left cheek for 2 months	Swelling of left inferior turbinate, left side of dorsum of nose and left cheek
3	Right nasal obstruction for 5 months, swelling of nose for 4 months	Swelling of right ala and dorsum of nose
4	Left nasal obstruction for 4 months, swelling of left side of dorsum of nose and left cheek for 3 months	Swelling of left inferior turbinate, left side of dorsum of nose and cheek
5	Left nasal obstruction for 4 months, swelling of nose, cheek and glabella for 3 months	Swelling of right ala, dorsum of nose, bilateral cheek and glabella
6	Left nasal obstruction for 4 months, swelling of left side of dorsum of nose, left cheek and upper lip for 2 months	Swelling of left inferior turbinate, left side of dorsum of nose and upper lip

avoid damage to the hyphae during culture. Fungal hyphae are to be searched meticulously under microscope as they are outnumbered by commensal fungi. Treatment should be started on the basis of histopathological report as culture is often negative. No treatment is standardized yet worldwide. Treatment should be continued for at least 3 months after complete resolution. With increasing awareness of the disease and expansion of mycological diagnostic facilities, we can expect more frequent reporting of the disease.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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