# Rhinofacial Conidiobolomycosis due to *Conidiobolus coronatus*: A case report and update of the disease in Asia

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**ABSTRACT**

**Introduction:** Rhinofacial entomophthoromycosis, is a rare subcutaneous mycosis, caused by *Conidiobolus coronatus* affecting the upper respiratory mucosa and adjacent subcutaneous tissues. Herein, we report a case of rhinofacial entomophthoromycosis in a farmer from Bidnapur, West Bengal, India and present the review of literature of cases published so far from Asia. **Case Report:** A 55-year old male presented with slowly progressive swollen nose with bilateral nasal obstruction. Also, the swelling involved the cheek and forehead. Contrast Enhanced Computed Tomography scan of the paranasal sinuses showed bilateral soft tissue thickening in the nasal cavities suggestive of polypoidal or granulomatous lesion and the involvement of the left maxillary sinus. The biopsy from the left nasal cavity revealed ill-defined epitheloid cell granuloma and chronic granulation tissue. However, the nasal skin biopsy specimen on culture grew multiple white colonies on Sabouraud glucose agar after 3 days of incubation at $28^0$C. The isolate was identified as *Conidiobolus coronatus* by Internal Transcribed Spacer and D1/D2 region of ribosomal subunit of rDNA. The patient was treated with oral itraconazole 400mg/day and 10 drops three times in day of saturated solution of potassium iodide. After 8 weeks of this treatment, marked clinical improvement, as evidenced by regression of facial swelling and relief from symptoms were observed. **Conclusion:** Conidiobolomycosis is endemic in Asia but is under reported due to lack of clinical suspicion and mycological facilities in health care setups.

**Keywords:** Asia**,** Conidiobolomycosis, Entomophthorales, Mycology

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## INTRODUCTION

Rhinofacial entomophthoromycosis is a rare subcutaneous mycosis caused by *Conidiobolus coronatus*. The three species of the order Entomophthorales that cause conidiobolomycosis in humans and animals are *C. coronatus*, *C. incongruus* and *C. lamprauges*. The fungus primarily affects the upper respiratory mucosa and adjacent subcutaneous tissues, inducing a granulomatous reaction in which the hyphae are encapsulated in amorphous eosinophilic material. This phenomenon is known as Splendore-Hoeppli and typically manifests as the development of hard nodules in the subcutaneous tissue of the face, nasal congestion, and epistaxis.[1] Conidiobolomycosis has been reported largely from tropical regions of Africa, South and Central America and Asia mainly from India, particularly among adult men who engage in outdoor activities professionally.[2-4] The diagnosis is based on histopathological examination and culture of biopsies of skin lesions. We report a case of rhinofacial entomophthoromycosis in a 55-year, old-male, farmer from Bidnapur, West Bengal, who presented with a slowly progressive swollen nose. The diagnosis was based on isolation of *C. coronatus* in culture which was confirmed by direct DNA sequencing of internal transcribed spacer (ITS) region of rDNA. We also discuss the difficulties in diagnosing this condition and present the review of literature of cases published so far from Asia.

## CASE HISTORY

A 55-years old male farmer from Bidnapur, West Bengal, India, presented with a slowly progressive swollen nose in March 2012. He developed nasal obstruction 2 years back which was initially left sided but progressively increased and became bilateral. The swelling later progressed and involved the cheek and forehead (Figure 1).

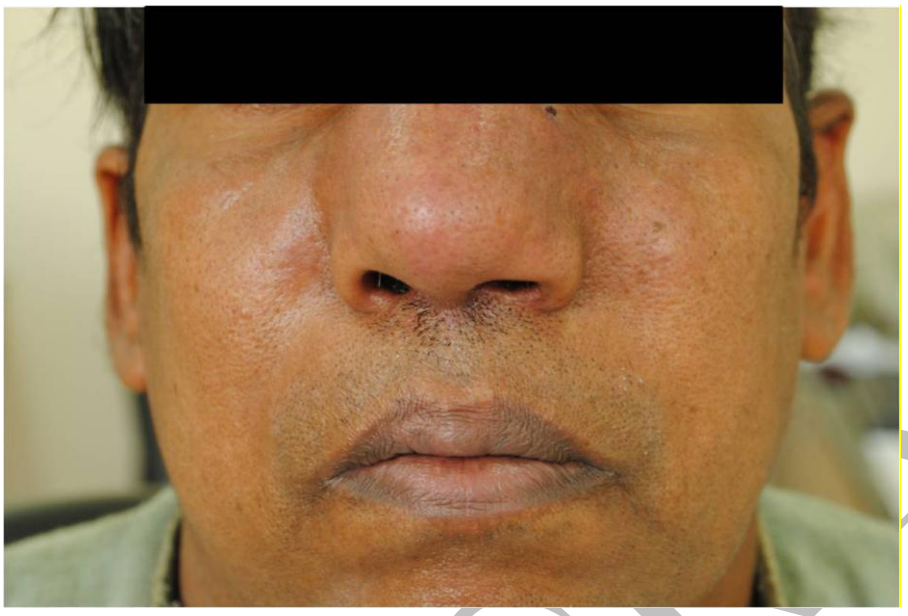

**Figure 1:** Facial features of the patient with rhinoentomophthoromycosis, showing swelling and enlargement of the nose and medial cheeks.

He also complained of anosmia but had no history of epistaxis. The patient could not recollect history of local trauma. He was a non-diabetic, non-alcoholic, and HIV antibodies were negative. He had underwent a left sided nasal surgery in his hometown one year ago and the nasal secretions/lavage which were sent for culture did not yield any bacterial or fungal pathogens and the histopathology report was also inconclusive. Several biopsies of the paranasal region were performed in the following year, which exhibited only granulomatosis and no microbial agents were observed. Also, the cultures were repeatedly negative for pyogenic bacteria, mycobacteria, and fungi. His symptoms were not relieved and his nasal swelling progressed.

He presented to Delhi, in a private hospital, almost two years later. On local examination, the right nasal cavity showed highly deviated nasal septum while on nasal endoscopy on the left side the endoscope could not be reached beyond 2-3cms due to severe scarring between medial and lateral walls. The nasal dorsum showed a diffuse, mildly tender, erythematous, non-pitting, bilateral swelling. Contrast Enhanced Computed

Tomography (CECT) scan of the paranasal sinuses showed bilateral soft tissue thickening in the nasal cavities suggestive of polypoidal or granulomatous lesion. It also showed involvement of the left maxillary sinus.

The biopsy from the left nasal cavity revealed ill-defined epithelioid cell granuloma and chronic granulation tissue. No acid fast bacilli were seen on Ziehl-Neelsen staining and Periodic Acid Schiff staining was negative. As no conclusive diagnosis was achieved, finally a nasal skin biopsy from the distal part was collected and referred to our institute for investigation of a possible fungal etiology.

The nasal skin biopsy specimen on culture revealed multiple white colonies on Sabouraud glucose agar (SGA) supplemented with chloramphenicol and gentamicin, after 3 days of incubation at $28^0$C. The colonies were flat, slightly powdery and glabrous becoming tan brown with age (Figure 2).

**Figure 2**: Culture plate showing growth of *Conidiobolus coronatus* after 3 days of incubation at $28^o$C.

Restricted growth of the same fungus was also observed on the lid of the culture plate which suggests the forceful discharge of conidia from the primary culture. Slide cultures on potato dextrose agar revealed large septate hyphae with numerous short slender conidiophores and globose conidia with a basal papilla (Figure 3). The same fungus also grew at $37^0$C. In addition, few villose conidia typical of *C. coronatus* were also present.

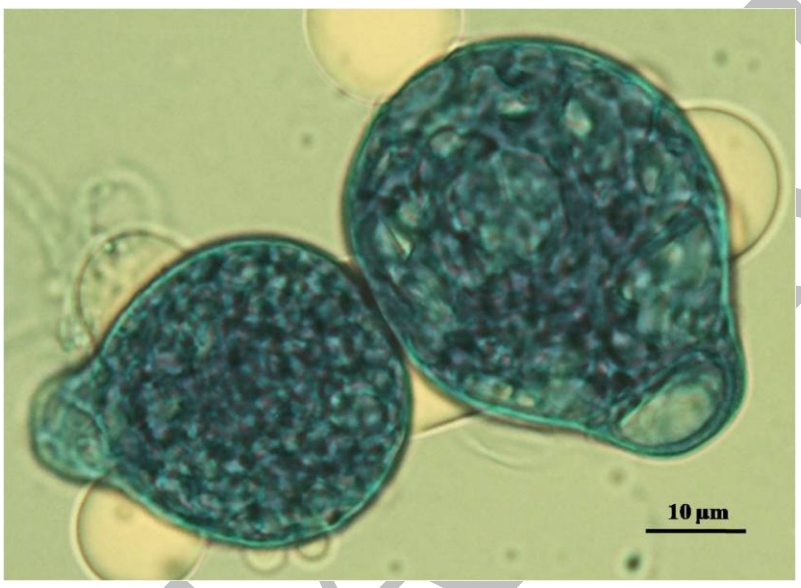


**Figure 3:** Slide culture of *Conidiobolus coronatus* showing papillate conidium, lactophenol cotton blue (LCB) mount X 1000.

The molecular identification of the isolate was done by DNA sequencing of internally transcribed spacer (ITS) region of small ribosomal unit (SSU) of rDNA and D1/D2 region of large ribosomal unit (LSU) of rDNA. The DNA was extracted by phenol chloroform isoamyl extraction method.[5] The desired ITS and D1/D2 region of rDNA were amplified using panfungal primers ITS1, ITS2 and NL1, NL4.[6,7] The amplicons were purified (Wizard SV Gel and PCR Clean-up System; Promega, Fitchburg, WI, USA) and sequenced. The sequencing reactions were done using the cycle sequencing kit (BigDye Terminator v3.1 cycle sequencing kit RR100; Applied Biosystems, Foster City, CA, USA) and sequenced on an ABI 3130xL Genetic analyzer (Applied Biosystems). For final identification of the

isolate, the nucleotide sequence of ITS and D1/D2 region were used for GenBank BLAST (basic local alignment search tool) searches (http://www.ncbi.nlm.nih.gov/Blast.cgi). BLAST result of ITS and D1/D2 regions showed 99% identity with *C. coronatus* (accession no. FN421422, HQ602777, AB 363771 and DQ364203).

The patient was treated with oral itraconazole (ITC) 400mg/day and 10 drops t.d.s. of saturated solution of potassium iodide (SSKI). After 8 weeks of this treatment, the patient experienced marked clinical improvement, as evidenced by regression of facial swelling and relief from symptoms. He was followed up till 6 months of continued therapy and reported no ill effects or drug toxicity.

## DISCUSSION

Fungal infections caused by species of the order Entomophthorales typically occur in immunocompetent patients, residing in subtropical and tropical climate.[8,9] The taxonomy of order Entomophthorales has been revised by Hibbett *et al*., in 2007 and the order Entomophthorales, which traditionally belonged to class Zygomycetes, phylum Zygomycota has been reclassified based on phylogenetic studies of multiple genes, including rRNA genes. A new subphylum, called Entomophthoromycotina, was described in the class Glomeromycetes (phylum Glomerales) and includes the order Entomophthorales.[10] *Conidiobolus coronatus* is a saprophyte and is known intestinal pathogen or colonizer of insects, amphibians, reptiles, and bats. The environmental niches include tropical rain forests, soil, rotting vegetation, and the gastrointestinal tract of insectivorous animals.[11]

The inhalation of spores and the traumatic inoculation of the intranasal mucosa are the probable routes of infection for *Conidiobolus* species.[12] This route is supported by the meta analysis of published case reports by Choon *et al.*, which revealed upper respiratory tract (nose and/or sinuses) involvement in 95% of cases and the lower respiratory tract involvement in all cases of systemic conidiobolomycosis.[13]

A definitive diagnosis of rhinofacial entomophthoromycosis requires histopathologic demonstration of the etiologic agent and its isolation in culture.[14,15] In the present case patient underwent many repeated biopsies but

could not be diagnosed due to lack of clinical suspicion and mycological expertise. Therefore, clinical awareness and diagnostic mycological facilities are required to ascertain an early diagnosis and institution of appropriate antifungal therapy.

Systematic studies on the prevalence of rhinofacial conidiobolomycosis in Asia are lacking. The available information is based upon sporadic case reports and the cases of conidiobolomycosis so far reported from Asia are presented in Table 1. About two third of the cases are reported from India (74%) followed by Thailand (13%). The remaining cases are from Malaysia, China, Taiwan, Japan, Sri Lanka and Singapore. Notably in Asia the male:female ration in cases of rhinofacial entomophthoromycosis is 3:1. This preponderance of males in the cases in Asia is similar to the gender predisposition (male:female ratio of 8:1) of the disease reported globally.[3,12] Though, preponderance of males is much less pronounced in Asia. Barring one case, which may have involvement of lung in a 3-year female child, all other cases due to *C. coronatus* had involvement of rhinofacial region.[14]

In a recent meta-analysis of globally published case reports and series of conidiobolomycosis to determine clinical, pathologic, mycologic, and treatment factors on prognosis revealed that the majority of patients (91%, 181/199) presented with stereotypical rhinoentomophthoramycosis defined as chronic nasal symptoms, nasal tumor, and/or facial swelling in otherwise healthy individuals. The causative or suspected agent was *C. coronatus* in 97% and *C. incongruus* in 0.5% (1/181).

Furthermore, the authors reported that severe infections were significantly associated with nonstereotypical presentation (e.g., orbital cellulitis), visceral infection, presence of comorbidities (eg, immunosuppression, hematolymphoid malignancy), and infection with *C. incongruus* or *C. lamprauges* but not with *C. coronatus*.[13]

The efficacy of different types of treatments for conidiobolomycosis has not been studied [9]. Several case reports describe treatment using SSKI, ketoconazole (400 mg/d), ITC (300 mg/d), or fluconazole (300 mg/d) for 6 months and amphotericin B. Other treatments include 5- flucytosine,

trimethoprim/sulfamethoxazole, and terbinafine (TRB).[16-19]

In the present case the patient responded to therapy with ITC for 6 months. Majority of case series from developing countries report usage of SSKI because of its ease of administration and low cost.[16] According to Fisher *et al*., patient with rhinofacial *C. coronatus* infection was successfully treated with the combination therapy of ITC and TRB, although the isolate showed resistance towards ITC and TRB by *in vitro* susceptibility testing. Since such combination therapy is successful in some cases, systematic synergy studies in future may be undertaken.[20]

There is no consensus about the duration of treatment, but it must be continued for long periods until a negative mycological examination and a good clinical response is achieved. Furthermore, routine culture and susceptibility testing is required to define the efficacy of these therapeutic agents.

## CONCLUSION

Conidiobolomycosis can affect not only the immunocompromised, but immunocompetent hosts also. The disease is predominantly seen in tropical and subtropical regions. The diagnosis of conidiobolomycosis requires familiarity with the clinical presentation and awareness among the clinicians. Also, a thorough support from the microbiologists and histopathologists is mandatory for clinching the diagnosis. Finally, conidiobolomycosis in Asia is a significant clinical entity, which may be under reported due to lack of clinical suspicion and paucity of mycology facilities in many health care setups.

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| Country | No. of cases | Sex/Age | Sites involved | Histopath | Etiologic agent | Therapy and outcome | Reference |
|---|---|---|---|---|---|---|---|
| India | 46* | 55/M | Nasal/paranasal sinus | _ | *Conidiobolus coronatus* | ITC 400mg/day and 10 drops tds of SSKI. Reduction in the swelling after 8 weeks | Present case |
| | | 20/M | Left nostril and left maxillary sinus | + | *Conidiobolus coronatus* | Oral ITC 200 mg BD. Reduction in the size of swelling within a week. | [21] |
| | | 56/M | Glabellar region | + | Not mentioned | Not mentioned | [22] |
| | | 3/F | Right upper lobe of lung | + | Not mentioned | Not mentioned | [14] |
| | | 30/M | Right nasal cavity and right side of hard palate | + | Not mentioned | Not mentioned | |
| | | 50/M | Nasal Cavity and upper lips | + | Not mentioned | ITC 200 mg twice daily, SSKI 5 drops in fruit juice three times daily. | [23] |
| Thailand | 8 | 44/M | Right nasal cavity and the right ethmoid sinus | + | *Conidiobolus coronatus* | SSKI and T/S for 12 week | [24] |
| | | 20/M | Left nasal canal | + | *Conidiobolus coronatus* | AmB for 10 weeks | |
| | | 66/M | Nasal and paranasal areas | + | *Conidiobolus coronatus* | SSKI and T/S for 12 weeks | |
| | | 65/M | Right nasal and paranasal areas | + | *Conidiobolus coronatus* | ITC and SSKI for 3 months | |
| | | 30/M | Left inferior nasal turbinate | + | *Conidiobolus coronatus* | SSKI for 12 weeks | |
| | | 9 month/F | Right lacrimal sac | + | *Conidiobolus* sp. | Intravenous AmB gradually increased to the dose of 1 mg/kg/day, for a cumulative dose of 924 mg. On day 4 after AmB administration, oral ITC was added (10mg/kg/day) | [25] |
| | | 26/F | Nasal inferior turbinate mass | | *Conidiobolus coronatus* | __ | [26] |
| | | 39/F | Nasal inferior turbinate mass | | *Conidiobolus coronatus* | __ | |
| Malaysia | 2 | 21/F | Upper lip, nose and bridge of nose, and medial cheeks | + | *Conidiobolus coronatus* | AmB 1 mg/kg/d and oral FLU 200 mg once daily. AmB was discontinued due to renal impairment and oral ITC 200 mg was added. FLU 400 mg for 12 weeks. | [13] |
| | | 42/M | Nose & lips | | *Conidiobolus coronatus* | __ | [27] |
| Taiwan | 1 | 37/M | Nasopharynx oropharynx and hypopharynx | + | Not Mentioned | Endoscopic surgical wide excision of tumor. 200 mg of ITC once daily, tapered to 100 mg once daily for the next 9 months. | [28] |
| Sri Lanka | 1 | 32/M | Nasal cavity and maxillary area | ND | *Conidiobolus coronatus* | KI, ITC and CLZ for six months | [29] |
| Japan | 1 | 61/M | Disseminted: ling, kidney & spleen (post-mortem | | *Conidiobolus lamprauges* | MFG, AmB, VRC | [30] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | autopsy) | | | | |
| China | 1 | 36/M | Right antrum maxillae, the antrum ethmoidale and the superior-middle nasal meatus | - | *Conididiobolus coronatus* | Oral SSKI (0.1 g/ml) 10 ml t.i.d. and sulfamethoxazole 200 mg, sulfadiazine 200 mg and trimethoprim 80 mg ITC 200 b.i.d. After 2 months oral terbinafine 250 mg/day intravenous ITC at a dosage of 200 mg/day for 6 months. | [31] |
| Singapore | 1 | 20/M | Left main stem bronchus | ND | *Conidiobolus coronatus* | CFG | [32] |

Abbreviations: ITC, Itraconazole; KI, Potassium Iodide; CLZ, Clotrimazole; MFG, Micafungin; SSKI, saturated solution of potassium iodide; T/S, trimethoprim/sulfamethoxazole; AMB, Amphotericin B; CFG, Caspofungin; FLU, Fluconazole; VRC, voriconazole. *Includes 40 cases reviewed by Chowdhary et al. in 2010. [15]

**Table:** Distribution of the cases of conidiobolomycosis caused by *Conidiobolus* sp. reported from Asia.