



Clinical characteristics of 5 adult patients with rhinofacial entomophthoromycosis in Thailand

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ABSTRACT

Five patients [mean age: 36 years (range: 22–65)] were diagnosed with rhinofacial entomophthoromycosis at our center during the study period. All patients presented with painless cheek and nasal dorsum swelling with nasal obstruction. All pathology reports confirmed rhinofacial entomophthoromycosis, which is characterized by the Splendore-Hoeppli phenomenon. *Conidiobolus coronatus* was identified from fungal culture in all patients. All patients were successfully treated with various antifungals.

1. Introduction

Rhinofacial entomophthoromycosis is an invasive fungal infection of the subcutaneous soft tissue surrounding the nose and face. *Conidiobolus spp.* is a pathogenic organism, which is commonly found in soil and regions with organic compound degradation. Thus, rhinofacial entomophthoromycosis is widespread among tropical farmers [1].

Swelling over the face and dorsum of the nose is the most common symptom. Physical exams frequently reveal non-tender subcutaneous induration and nasal mucosal swelling [2,3]. Soft tissue infiltrative lesions in the inferior nasal turbinate, lateral nasal walls, and face may be detected via computed tomography [4]. To identify the fungal organism, pathologic assessment or fungal culture could be used to provide a definitive diagnosis. In tissue pathology, the Splendore-Hoeppli phenomenon, which is characterized by fungal hyphae surrounded by eosinophils, is a pathognomonic sign [5].

Rhinofacial entomophthoromycosis is a rare condition. There is currently no standard treatment protocol. Medication, surgery, or hyperbaric oxygen treatment could all be used as therapeutic options. Amphotericin B, posaconazole, fluconazole, itraconazole, terbinafine, and potassium iodide are among the medications used (KI) [6]. However, information on proper antifungal selection is scarce.

A series of cases were reported in tropical countries, such as India [7], Brazil [8], the Dominican Republic [9], and France [10,11]. Many cases were reported over different regions in Thailand; 5 Cases from Ramathibodi Hospital, Mahidol University in the central area [12], 3

Cases from Srinagarind Hospital, Khon Kaen University in the north-eastern area [4], and 7 cases from Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University in the north area [13].

With 15 years of experience, this study aims to share a clinicopathologic aspect of rhinofacial entomophthoromycosis cases from Siriraj Hospital, Mahidol University.

This study was approved by the Siriraj Institutional Review Board (Registration no. 707/2564(IRB3)). A fifteen-year retrospective chart review (1st January 2007 to 31st October 2022) was done. All cases of rhinofacial entomophthoromycosis with the following ICD-10 codes: B46 Zygomycosis; B46.3 Cutaneous mucormycosis/subcutaneous mucormycosis; B46.5 Mucormycosis unspecified; and B46.8 Other Zygomycoses/Entomophthoromycosis were included. Finally, the literature review was completed via Pubmed database.

2. Case

There were 5 patients diagnosed with rhinofacial entomophthoromycosis in Siriraj hospital during the past 15 years. The average age was 36 years ranging from 22 to 65 years. Three out of five patients were females. Patients' occupations were farmer (n = 1), steel lathe factory worker (n = 1), laborers (n = 2), and accountant (n = 1). Two patients had human immunodeficiency virus infection with current antiviral medications treatment, whereas three other patients were healthy. All denied history of insect bite or maxillofacial trauma. Table 1 displays thorough information on each patient.

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Table 1
Characteristics of the 5 patients diagnosed with rhinofacial entomophthoromycosis at Siriraj Hospital during 2007–2022.

Year	Age (years)	Gender	Job	Underlying disease (s)	Duration of onset (months)	Presenting symptom(s)	Physical examination	Computed tomography	Pathology	Fungal culture	Treatment	Response
2007	28	F	Labor	HIV on GPO-VIR	3	Swelling right cheek & right nasal dorsum	Infiltrative mass right cheek, nasal dorsum, gingivobuccal sulcus, and nasal septum	Infiltrative mass right nasal cavity, soft tissue infiltration up to nasal bridge, deviated nasal septum due to pressure effect to left side	Transnasal biopsy: Splendore-Hoepli phenomenon	<i>Conidiobolus coronatus</i>	Amphotericin B (2 weeks) → Cr rising → switch to itraconazole → drug allergy (SJS) → SSKI (0.6 mg/ml) 1 ml PO tid (2 years)	Complete resolution
2011	36	F	Labor	HIV on D4T/3TC/IDV; Allergy to trimethoprim/sulfamethoxazole	6	Nasal obstruction	Swelling septal mucosa, necrotic septal cartilage	Enhancing soft tissue at septum with bony destruction	Transnasal biopsy: Splendore-Hoepli phenomenon	<i>Conidiobolus coronatus</i>	SSKI 1 ml tid, (3 months)	Recurrent disease after 9 years
2015	22	F	Factory worker	None	12	Right nasal obstruction & swelling right cheek	Infiltrative mass right nasal valve, swelling nasal septum, swelling right cheek	Enhancing soft tissue lesion at skin and subcutaneous soft tissue	Transnasal biopsy: Splendore-Hoepli phenomenon	<i>Conidiobolus coronatus</i>	Amphotericin B 40 mg (2 weeks) → itraconazole solution 20 ml bid, terbinafine (250) 1 tabs bid (2 years)	Complete resolution
2020	65	M	Farmer	None	6	Right nasal obstruction & swelling nasal dorsum	Induration over nasal dorsum, swelling right nasal vestibule	Abnormal thickening right nasal vestibule	Transcutaneous incisional biopsy: Splendore-Hoepli phenomenon	<i>Conidiobolus coronatus</i>	Itraconazole (100) 2 tabs tid with SSKI 1 ml bid (2 months) → itraconazole (100) 2 tabs bid with SSKI 1 ml OD (10 months)	Complete resolution
2022	30	M	Accountant	None	5	Left nasal obstruction & swelling nasal dorsum and cheek	Infiltrative ill-defined mass over bilateral frontal and maxillary area	Infiltrative enhancing mass involving skin -subcutaneous extending from frontal region, upper to lower face with pressure effect to both anterior nasal cavities	Sublabial incisional biopsy: Splendore-Hoepli phenomenon	<i>Conidiobolus coronatus</i>	Itraconazole (100) 2 tabs tid with SSKI 1.5 ml tid (3 days) → itraconazole (100) 2 tabs bid with SSKI 1.5 ml tid (10 months)	Complete resolution

Abbreviations: F, female; M, male; HIV, human immunodeficiency virus; D4T, stavudine; 3 TC, lamivudine; IDV, indinavir; CT, computed tomography; Cr, creatinine; SJS, Steven-Johnson syndrome; SSKI, saturated solution of potassium iodide; PO, oral administration; tid, three times per day; bid, two times per day.

All patients presented with painless swelling of the cheek and dorsum of the nose and nasal obstruction. The onset of symptoms ranges from 3 to 12 months. The patients also complained about rhinorrhea and recurrent epistaxis. Physical examinations demonstrated infiltrative mass at the cheek, dorsum of the nose, and gingivobuccal sulcus. The nasal telescope revealed mucosal swelling over various parts of the nasal cavities including nasal vestibule, nasal turbinates, and nasal septum in all patients (Fig. 1). Interestingly, one patient had septal perforation with necrotic septal cartilage which was an uncommon finding in rhinofacial entomophthoromycosis.

Computerized tomography of the paranasal sinus and facial soft tissue showed enhancing infiltrative mass over the facial subcutaneous soft tissue including the cheek up to the nasal bridge as well as abnormal thickening of the nasal vestibule, turbinate, and septum (Fig. 2). Detailed information on each patient is presented in Table 1.

The tissue samplings for diagnosis were done via nasal endoscopic biopsy in three patients, transcutaneous incisional biopsy of the swelling of dorsum of the nose in one patient, and sublabial incisional biopsy in another patient. All pathological reports confirmed rhinofacial entomophthoromycosis which is characterized by hyphal fungal elements surrounded by eosinophils, so-call the Splendore-Hoepli phenomenon (Fig. 3). The GMS staining demonstrated non-septate broad fungal hyphae (Fig. 4). *Conidiobolus Coronatus* was identified from the fungal culture in all five patients.

Antifungals including amphotericin B, itraconazole, terbinafine, and a saturated solution of potassium iodide (SSKI) were used to treat the patients. Table 1 provides detailed information regarding each patient.

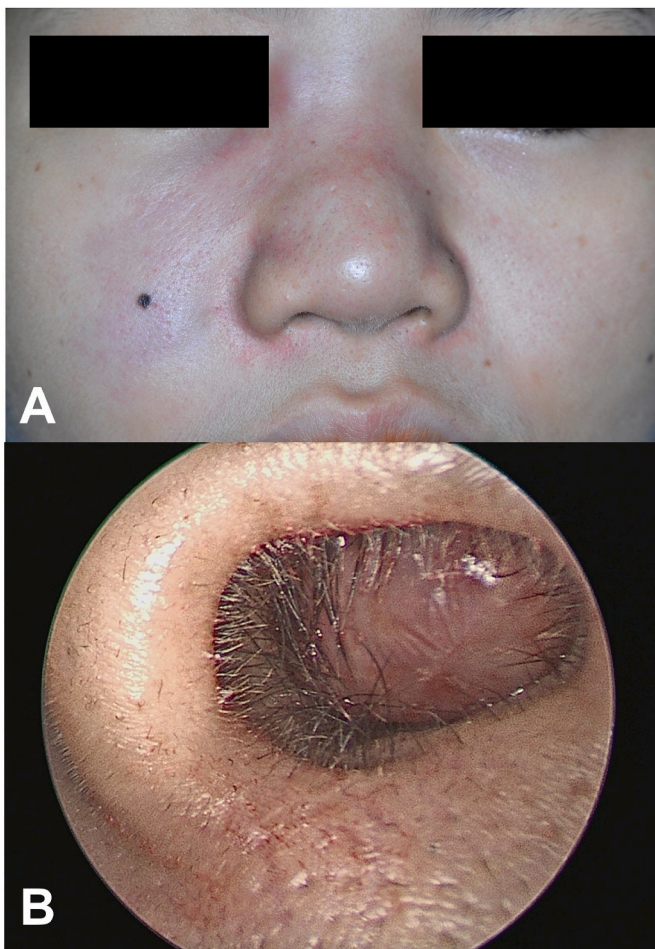


Fig. 1. (a) Physical examinations demonstrated infiltrative mass at the cheek, nasal dorsum, and gingivobuccal sulcus. (b) The nasal telescope revealed swelling nasal vestibule and nasal septum.



Fig. 2. Computerized tomography of the paranasal sinus and facial soft tissue showed enhancing infiltrative mass over the facial subcutaneous soft tissue.

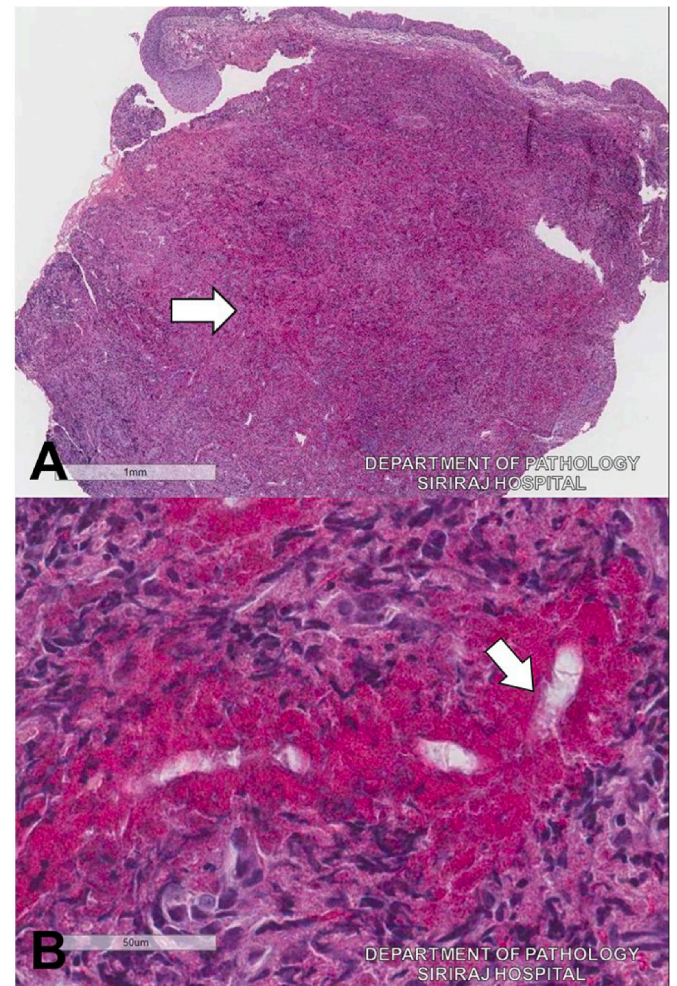


Fig. 3. Pathological reports confirmed rhinofacial entomophthoromycosis which is characterized by hyphal fungal elements surrounded by eosinophils, so-call the Splendore-Hoepli phenomenon.

All of them had a dramatic response to the treatment. After 9 years of follow-up, one HIV patient developed recurrent disease.

The Pubmed database search identified 63 case reports or case series with 128 participants included. The reports were from 19 countries including India, Cameroon, Nigeria, Spain, Brazil, French, Madagascar, Thailand, Colombia, the US, South Africa, Switzerland, Portugal, Germany, China, Dominican, Sri Lanka, United Arab Emirates, and Mexico. Histopathology and fungal culture were used to identify the organisms.



Fig. 4. The GMS staining demonstrated non-septate broad fungal hyphae.

Immunofluorescence, RT-PCR, and DNA sequencing were also used. KI and amphotericin B were the most used as first-line antifungals with treatment failure. Triazoles, such as itraconazole, fluconazole, and voriconazole, are the most used as curative antifungals. The treatment extended an average duration of 6 months, ranging from 7 weeks to 18 months. Further detailed information was provided in a supplementary document.

3. Discussion

Zygomycota phylum are fungi that include species from the orders Mucorales and Entomophthorales. In comparison to Mucorales, Entomophthorales infection has distinct epidemiological characteristics, clinical presentations, and pathological findings. Several clinical patterns were shown, including limb and trunk subcutaneous entomophthoromycosis, mucocutaneous rhinofacial entomophthoromycosis, and visceral organ infection [6].

Entomophthoromycosis refers to illnesses caused by Entomophthorales, which can be divided into *Basidiobolomycosis* and *Conidiobolomycosis* based on the pathogens involved. Human pathogenic species include *Basidiobolus ranarum*, *Conidiobolus coronatus*, and *Conidiobolus incongruus*. *In vitro*, the organisms produce several enzymes, including elastase, esterase, collagenase, and lipase, which may play a role in pathogenicity.

Conidiobolus entomophthoromycosis is a chronic inflammatory disease that primarily affects the submucosal soft tissue of the face and nasal cavity and is characterized by a palpable submucosal bulge. Most cases were documented in tropical areas. The infection is spread by inhaling fungal spores into the torn nasal mucosa or by autoinoculation from a soiled hand. Slow progressive nasal obstruction, nasal granulomas, and subcutaneous infiltrative mass over the perinasal-facial regions leading to facial disfigurement were among the symptoms. Almost all cases have unilateral involvement, but the disease can spread bilaterally.

Conidiobolomycosis is often diagnosed based on both clinical manifestations and laboratory investigations, including histopathology and organism isolation from tissue culture. Previous research found that mycological culture could only be verified in 15 % of rhinofacial *Conidiobolomycosis* cases [14]. *Basidiobolus* and *Conidiobolus* serologic immunodiffusion assays are highly sensitive and specific. Fresh samples should be refrigerated or otherwise put in a specific transport medium that allows transportation and storage at room temperature. It could be considered as an alternative to assist with the diagnosis. However, the technique is not extensively used in the real world [15]. Even though common microbiology laboratories are capable of performing several

first-line procedures such as microscopy and culture, access to these tests is still restricted in many nations throughout the world especially low and middle-income countries (LMIC) according to the WHO fungal pathogen priority list (FPPL). Some publications have mentioned fungus detection utilizing light cycler real-time fluorescence PCR [16,17]. Recently, pathogenic fungi could have been confirmed and identified using the direct DNA sequencing of the internal transcribed spacer (ITS) region of rDNA [18].

The Splendor-Hoepli phenomenon is a sign observed in tissue pathology [5]. This phenomenon is characterized by various species of microorganisms radiated with eosinophilic elements [19]. The eosinophilic reaction was thought to be an immune complex deposition caused by the host's immune response to the inflammation caused by the pathogenic organisms [19]. It is most frequent in entomophthoromycosis, however, it is not limited to the condition. Kimura disease; which is a rare chronic eosinophilic granulomatous inflammatory disorder of unknown etiology; and other conditions with eosinophilic tissue infiltration should be considered in the differential diagnosis [4].

Medical treatment and surgical treatment are the two main treatment modalities for *conidiobolomycosis*. Previous studies regularly reference antifungal drug administration as part of medical treatment, either as a monotherapy or as a combination treatment. Antifungal medications available include SSKI, fluconazole, itraconazole, ketoconazole, terbinafine, and trimethoprim/sulfamethoxazole (TMP/SMX). However, Guarro et al. studied *Conidiobolus* *in vitro* antifungal susceptibility and discovered that *Conidiobolus* possessed high minimum inhibitory concentration (MIC) values to all antifungals tested, including amphotericin B, ketoconazole, miconazole, itraconazole, fluconazole, and flucytosine [20]. Most case reports recommended antifungal treatment for 2–18 months, depending on the severity of the lesions and the clinical response of each patient. The surgical treatment aims to remove the diseased mucosa and reconstruct the deformation caused by the infection. It could be beneficial in the case of extensive disease.

Rhinofacial entomophthoromycosis is a rare disease. No standard treatment regimen is available at the moment. Multiple treatment modalities could be introduced depending on the extent of the lesions and the clinical response of each patient. The surgical treatment might be useful for extensive disease. A further study focusing on antifungal selection is recommended.

Ethical form

This was an unfunded study. The authors have obtained written and signed consent to publish the case report from the patient or legal guardians.

Declaration of competing interest

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

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