Presumably Entomophthoramycosis in an HIV-Infected Patient : The First in Thailand

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Abstract

The authors reported the case of a symptomatic HIV-infected woman with a slowly progressive infiltrative lesion which invaded in and around the nasal cavity over a 6-month period. Physical examination showed erythematous to violaceous plaques at the nasal and malar areas. Swelling of the inferior turbinate was noted in the right nare. Skin biopsy of the involved area revealed multiple nonseptate, broad, thin-walled hyphae within giant cells and granulomata. Entomophthoramycosis was diagnosed based on clinical features and histopathology. She was treated with intravenous amphotericin B for two weeks, followed by oral itraconazole 400 mg daily. At six months there was complete resolution of all lesions.

Key word : Entomophthoramycosis, *Conidiobolus*, Entomophthorales, HIV

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The zygomycoses (phycomycoses) are fungal diseases caused by Zygomycetes; fungi of the order Mucorales and Entomophthorales. The Entomophthorales have two genera, *Conidiobolus* and *Basidiobolus* that are responsible for human disease. Both cause chronic granulomatous inflammation of submucosal and subcutaneous tissue, but involve different parts of the body.

Infections by *Basidiobolus* occur predominantly in children. Those by *Conidiobolus* occur in

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adults[1]. We report a case of rhinoentomophthoramycosis due to *Conidiobolus*. To our knowledge, this is the first reported case in Thailand and in an HIV-infected patient.

CASE REPORT

A 27-year-old Thai female came to Chulalongkorn Hospital with the complaint of slowly progressive infiltrative lesions on her face, starting 6 months prior to admission. She initially noted stuffiness and itching of her right nasal cavity and had received antibiotics and nasal decongestants without improvement. Three months prior to admission, she noted swelling on the right side of her nose extending to the right malar area. She went to a local hospital where computerized axial tomography (CAT) scanning of paranasal sinuses was performed. It revealed a soft tissue mass at her right nasal cavity extending and destroying her right maxillary and ethmoid sinuses. She was then transferred to the Ear-Nose-Throat (ENT) Department of Chulalongkorn, University Hospital. The nasal mass was biopsied, and microscopic examination revealed an inflammatory polyp with foreign body granuloma. She also had a positive blood test for HIV. Oral ciprofloxacin was given without improvement. One month prior to admission, a repeat biopsy was performed. Acute and chronic inflammation was noted but no specific diagnosis was suggested. Three weeks prior to admission, the swelling extended into her left nostril and malar area. She was then transferred to the infectious disease unit for further investigation. Systemic symptoms such as fever and weight loss were absent. Her past medical history was unremarkable except for a history of *Herpes zoster* at her neck one year previously.

Physical examination revealed an oral temperature of 37°C, and normal consciousness. There were infiltrative erythematous to violaceous plaques at the nasal and both malar areas without any signs of inflammation (Fig. 1). Swelling of the right inferior turbinate was noted. No nasal discharge or foreign body was present. Oral candidiasis and hairy leukoplakia were seen. There was no lymph node enlargement, and no hepatosplenomegaly.

A complete blood count showed a hematocrit of 34 per cent, white blood cell count of 3,500 cells/mm^3 with 34 per cent neutrophils, 32 per cent lymphocytes, 12 per cent monocytes, 16 per cent eosinophils and a platelet count of 381,000 cells/mm^3. Other blood chemistry tests were within normal limits. A chest radiograph was normal. Her CD_4+T cell counts was 99 cells/mm^3.

A variety of diseases can present with submucosal and subcutaneous infiltrations of the face. These include malignancies such as non-Hodgkin's lymphoma and chronic infection with mycobacteria or fungi. A repeat biopsy was, therefore, performed at the malar area, and the histological examination revealed diffuse fibrosis and granulomatous infiltration of lymphohistiocytes and multinucleated giant cells. The multiple nonseptate broad thin-walled hyphae within giant cells and granulomata were seen on hematoxylin and eosin staining (H&E) (Fig. 2). However, the hyphae were not as well demonstrated by modified silver staining. The Splendore-Hoeppli phenomenon, eosinophilic material surrounding the hyphae, was also noted.

Bacteriologic and mycologic culture of the biopsy specimen was performed but there was no growth. A diagnosis of entomophthoramycosis conidiobolae was made on the basis of clinical fea-

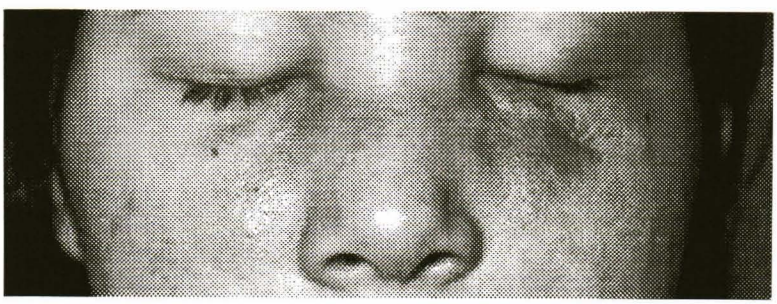
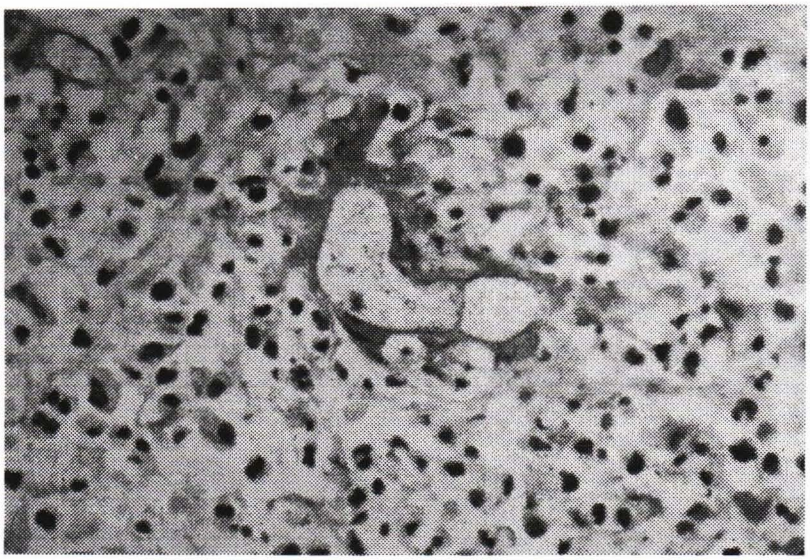


Fig. 1. The face of the patient at the first presentation showed infiltrative erythematous to violaceous plaques at the nasal and both malar areas.



This picture is representative of the true picture due to inability to find the tissue section.

Fig. 2. The nonseptate, broad, thin-walled hypha was demonstrated on hematoxylin and eosin staining (H&E).

tures, the sequence of tissue involvement and the microscopic documentation of tissue invasion by morphologically typical hyphae of this genus. The patient was initially treated with intravenous amphotericin B for two weeks and then discharged from the hospital on oral itraconazole 400 mg daily. The swelling of her face and nose gradually improved. She was seen for the last time six months later with complete resolution of all the involved areas. She decided to take only co-trimoxazole 960 mg and itraconazole 400 mg once daily without antiretroviral medication due to financial problems. Her CD_4 cells count at the time of examination was 29 cells/mm^3. Her general condition was good and without any symptoms and signs of opportunistic infections.

DISCUSSION

Entomophthoramycosis is a rare disease caused by fungi of the order Entomophthorales. Two genera are responsible for human disease: *Basidiobolus* and *Conidiobolus*. Entomophthoramycosis has been subdivided into entomophthoramycosis conidiobolae and entomophthoramycosis basidiobolae based on anatomic localization of the disease and the fungal genus. The former involves the head and face and the latter usually the trunk and arms. However, reports of disseminated infection caused by *Conidiobolus* have been published[2]. *Conidiobolus* are normal inhabitants of soil throughout the world. However, most reports came from tropical countries. In 1962, Bridges first reported *Conidiobolus* infection as the etiologic agent of nasal polyps in horses[3]. Three years later, the first human case was reported from Jamaica[4]. Since then, almost 100 cases have been described[1-5], the majority came from West Africa, with a few reports from the Americas and some parts of Asia. Many were from India[6]. Surprisingly, in tropical South East Asia, there was only one report from Malaysia[7]. To our knowledge, this is the first reported case in Thailand and also in the first patient with AIDS.

The Mucorales, another order of the same class of Zygomycetes as the Entomophthorales, are opportunistic fungi known to provoke infection in diabetics and immunocompromised patients[8,9]. In contrast to mucormycosis, entomophthoramycosis occurs mostly in otherwise healthy individuals.

However, entomophthoramycosis conidiobolae was recently reported in a renal transplant patient[10]. To the best of our knowledge, this is the first reported case in a patient with AIDS.

In the present case, the disease initially began with nasal obstruction due to infiltration of the submucosa of the nostril and subsequent extension into the right maxillary sinus and subcutaneous tissues. Malignancies and infectious processes were excluded[11]. Infection with *Sporothrix schenckii*, *Mycobacterium tuberculosis* or other non-tuberculous mycobacteria (NTM) can also mimic entomophthoramycosis. Biopsy and microscopic evaluation is necessary for diagnosis. Previous reports did not describe a substantial difference of yield for identification of the typical hyphae between submucosal or subcutaneous biopsy specimens. Previous submucosal biopsy specimens did not demonstrate the fungi in our case but the subcutaneous one did. A diagnosis of entomophthoramycosis conidiobolae can be made on the basis of clinical features, course and microscopic documentation of nonseptate, broad, thin-walled hyphae surrounded by an eosinophilic material (the Splendore-Hoeppli phenomenon)[1,12]. The hyphae are readily visible on H&E staining, but in contrast to most other fungi, are not as well demonstrated by modified silver staining. The absence of invasion of blood vessels by the fungi in our biopsy specimen also distinguished entomophthoramycosis from the other agents of mucormycosis. Unfortunately, we could not identify the species of *Conidiobolus* due to a negative culture attempt.

There are two species of *Conidiobolus*, *C. incongruans* and *C. coronatus*, which can cause disease in humans. The former causes a very rare disease, characterized by multiorgan dissemination. The latter causes a localized disease involving the nose and face. Thus, *C. coronatus* should be the responsible pathogen in our patient.

The natural history of untreated entomophthoramycosis is unknown, but appears to be benign as in our patient. Therapeutic recommendations for this disease can be made only on the basis of empirical observations due to the small number of patients reported. Medications reported useful are potassium iodide, cotrimoxazole, imidazoles, triazoles and amphotericin B[13-15]. *In vitro* susceptibility testing is not reliable, and has an uncertain place in guiding therapeutic decisions[5]. Failure of treatment with azoles and amphotericin B have been reported. Amphotericin B has been used in only a small number of patients, usually with life-threatening complications or when other drugs have failed. Thus, amphotericin B was selected for our patient for the first two weeks. Itraconazole was then prescribed until complete resolution was noted after six months of therapy. We can not be certain that the improvement resulted from antifungal therapy or was due to spontaneous resolution after 6 months. This disease may resolve spontaneously in some cases[16]. Currently, there is no consensus regarding duration of treatment. Most reports recommend that therapy should be given until complete resolution of all lesions.

The mechanisms and host response against this invasive fungus are unknown. However, innate immunity may play a role, given the low incidence of this disease. Maintenance therapy with oral itraconazole was considered but not given after complete resolution of the disease. However, in order to minimize recurrence of the disease, one should recommend avoidance of prolonged exposure to soil or decaying vegetation. Entrance of the fungal spores *via* inhalation or direct inoculation has been postulated.

In summary, the authors reported the first case of entomophthoramycosis conidiobolae in Thailand, in an HIV-infected patient.

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REFERENCES

1. Segura JJ, Gonzalez K, Berrocal J, Marin G. Rhinoentomophthoromycosis: Report of the first two cases observed in Costa Rica (Central America), and review of the literture. Am J Trop Med Hyg 1981; 30: 1078-84.
2. Walsh TJ, Renshaw G, Andrews J, et al. Invasive zygomycosis due to *Conidiobolus incongruus*. Clin Infect Dis 1994; 19: 423-30.
3. Bridges CH. Phycomycosis of horses caused by *Entomopthora coronata*. J Am Vet M Assoc 1962; 140: 673-7.
4. Bras G, Gordon CC, Emmons CW, et al. A case of phycomycosis observed in Jamaica; Infection with *Entomophthora coronata*. Am J Trop Med Hyg 1965; 14: 141-5.
5. Taylor GD, Sekhon AS, Tyrrell DLJ, Goldsand G. Rhinofacial zygomycosis caused by *Conidiobolus coronatus*: A case report including *in vitro* sensitivity to antimycotic agents. Am J Trop Med Hyg 1987; 36: 398-401.
6. Krishnan SG, Sentamilselvi G, Kamalam A, et al. Entomophthoromycosis in India-a 4-year study. Mycoses 1998; 41: 55-8.
7. Ng KH, Chin CS, Jalleh RD, et al. Nasofacial zygomycosis. Oral Surg Oral Med Oral Pathol 1991; 72: 685-8.
8. McBride RA, Carson JM, Dommin GJ. Mucormycosis: Two cases of disseminated disease with cultural identification of *Rhizopus*: Review of the literature. Am J Med 1960; 28: 832-46.
9. Dworzack DL, Pollock AS, Hodges GR, et al. Zygomycosis of the maxillary sinus and palate caused by *Basidiobolus haptosporus*. Arch Intern Med 1978; 138: 1274-6.
10. Walker SD, Clark RV, King CT, et al. Fatal disseminated *Conidiobolus coronatus* infection in a renal transplant patient. Am J Clin Pathol 1992; 98: 559-64.
11. Akpanonu BE, Ansel G, Karurich JD, et al. Zygomycosis mimicking paranasal malignancy. Am J Trop Med Hyg 1991; 45: 390-8.
12. Nathan MD, Keller AP, Lerner CJ, Davis JC. Entomophthorales infection of the maxillofacial region. Laryngoscope 1982; 92: 767-9.
13. Towersey L, Wanke B, Estrela RR, et al. *Conidiobolus coronatus* infection treated with ketoconazole. Arch Dermatol 1988; 124: 1392-6.
14. de Castro e Souza Filho LG, Nico MM, Salebian A, et al. Rhinofacial entomophthoromycosis due to *Conidiobolus coronatus*. A report of a case treated successfully with fluconazole. Rev Inst Med Trop Sao Paulo 1992; 34: 483-7.
15. Foss NT, Rocha MRO, Lima VT, et al. Entomophthoramycosis: Therapeutic success by using amphotericin B and terbinafine. Dermatology 1996; 193: 258-60.
16. Fromentin H, Ravisse P. Les entomophthoromycoses tropicales. Acta Trop 1977; 334: 375-94.

การติดเชื้อ Entomophthoramycosis ในผู้ป่วยติดเชื้อเอ็ชไอวี : รายงานแรกของประเทศไทย

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ได้รายงานผู้ป่วยหญิง 1 รายที่เป็น symptomatic HIV infection มาโรงพยาบาลด้วยเรื่อง slowly progressive infiltrative lesion โดยเริ่มจากในรูจมูก แล้วลามออกไปที่ผิวหนังข้างเคียงในเวลารวม 6 เดือน โดยไม่มีอาการทางระบบอื่น การตรวจร่างกายพบผื่นที่หน้ามีลักษณะเป็น infiltrative erythematous to violaceous plaque บริเวณจมูกและโหนกแก้ม 2 ข้าง inferior turbinate ของรูจมูกข้างขวาหนาและบวมแดง ได้ทำการตัดชิ้นเนื้อผิวหนังบริเวณแก้มเพื่อดูลักษณะทางพยาธิวิทยา พบมี multiple broad non-septate thin walled hyphae within giant cells and granulomata ซึ่งจากอาการทางคลินิก การดำเนินโรค และผลการตรวจทางพยาธิวิทยา เข้าได้กับการติดเชื้อราในกลุ่ม entomophthoromycosis จากเชื้อ *Conidiobolus coronatus* ได้ให้การรักษาโดยให้ amphotericin B ทางหลอดเลือดดำ ขนาด 50 มิลลิกรัมต่อวัน นาน 2 สัปดาห์ และได้เปลี่ยนเป็นให้ itraconazole รับประทาน 400 มิลลิกรัมต่อวัน ผื่นที่หน้าหายไปหลังจากได้รับการรักษาเป็นเวลานาน 6 เดือน

คำสำคัญ : การติดเชื้อรา Entomophthorales, เชื้อรา *Conidiobolus*, เชื้อรา Entomophthorales, การติดเชื้อเอ็ชไอวี

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