

Subcutaneous phaeohyphomycosis caused by *Cladophialophora boppii*

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ABSTRACT

Subcutaneous phaeohyphomycosis is an infection of the skin and subcutaneous tissue, caused by dematiaceous fungi. An adult male presented with a history of multiple reddish nodules over the face and hands. Histopathological examination of the skin biopsies showed a dense granulomatous infiltrate of macrophages, containing intracytoplasmic basophilic bodies throughout the dermis. Gomori methenamine-silver stained sections revealed yeast cells within macrophages. Multiple cultures on Sabouraud's dextrose agar grew *Cladophialophora boppii*. The patient was treated with oral itraconazole for a year and the response monitored with dermal ultrasound. This is the first case report of subcutaneous phaeohyphomycosis caused by *Cl. boppii* in India.

Key words: Phaeohyphomycosis, dematiaceous fungi, *Cladophialophora boppii*, ultrasound biomicroscopy, itraconazole

INTRODUCTION

Dematiaceous fungi are characterized by their dark pigmentation derived from the melanin complex in their cellular wall. The major infection patterns, typically based on histological findings, are grouped into three broad classes: chromoblastomycosis, phaeohyphomycosis, and eumycotic mycetoma. Phaeohyphomycosis is an umbrella term for all those mycoses where the fungus is present in host tissues with melanized filaments, and represents a broad range of primary and opportunistic mycoses by *Fonsecaea*, *Exophiala*, *Cladophialophora* and others.^[1] Subcutaneous phaeohyphomycosis involves skin and subcutaneous tissue. We present this case of subcutaneous phaeohyphomycosis due to the rarity of the etiological agent and the unusual clinical manifestation. This is the first case report of subcutaneous phaeohyphomycosis caused by *Cladophialophora boppii* in India. Also, another interesting aspect of this case is the use of ultrasound biomicroscopy with 50 MHz ultrasound in monitoring the treatment response which helped us to decide the duration of therapy, in the absence of established guidelines for the same.

CASE REPORT

A 23-year-old Indian man, software engineer by occupation, with no medical history, presented with a 2-month history of slowly growing multiple asymptomatic reddish nodules which appeared simultaneously on the face and right hand. He was otherwise well. The patient denied any apparent antecedent trauma, arthropod bite, family history or contact with a person with similar lesions or foreign travel. He had not sought any treatment previously.

Physical examination revealed multiple erythematous, non-tender, firm nodules ranging in size from 0.5 to 0.8 cm on the right lower eyelid [Figure 1a] and right hand, and a tumid plaque about 1 × 1 cm on the chin [Figure 1b]. The nodule on the eyelid showed surface crusting. Regional lymph nodes were not enlarged. There was no thickening of peripheral nerves or loss of sensations. A review of systems revealed no abnormalities.

The clinical differential diagnoses of leprosy, cutaneous leishmaniasis, deep fungal infection and sarcoidosis were considered. Results of the following

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laboratory studies were normal or negative: complete hemogram, blood chemistry analysis, Venereal Disease Research Laboratory (VDRL) test and Human Immunodeficiency Virus (HIV) antibody. Radiography of the chest and skull revealed no abnormality.

An excision biopsy of the hand lesion and punch biopsy from the chin lesion was obtained for histological examination and culture. Histopathological study of hematoxylin and eosin stained sections demonstrated an atrophic epidermis with a dense infiltrate throughout the dermis composed of macrophages, lymphocytes and a few plasma cells; the macrophages showed intracellular basophilic bodies. Acid-fast stained sections for bacilli were negative. Culture and imprint smears were negative for leishmania. Gomori methenamine-silver stained sections showed yeast cells within macrophages [Figure 2]. Cultures on Sabouraud's dextrose agar grew olivaceous-green, woolly fungal colonies which on microscopic examination revealed septate, brown hyphae and long chains of smooth-walled globose conidia suggestive of *Cl. boppii* [Figure 3]. These findings were consistent with subcutaneous phaeohyphomycosis caused by *Cl. boppii*, a dematiaceous fungus.

The patient was treated orally with itraconazole 200 mg and 30 drops of supersaturated solution of potassium iodide per day. The hand lesion did not recur following excision. At 4 months of therapy, the chin lesion was excised due to absence of clinical improvement; however, histology and cultures were negative for *Cl. boppii*. The potassium iodide was discontinued and oral itraconazole continued. At 9 months of therapy, there was noticeable reduction of the eyelid swelling with minimal erythema and post-inflammatory hyperpigmentation. The chin lesion did not recur following excision. However, ultrasound biomicroscopy in the region of the affected eyelid using a 50 MHz probe revealed a normal epidermal entry echo, a well-defined oval hypoechoic mass lesion (granuloma) measuring 2.5 × 1.5 mm in the dermis with normal underlying subcutaneous tissue [Figure 4].

Hence, therapy was continued to a total duration of 1 year at the end of which the lesion healed with post-inflammatory hyperpigmentation [Figure 5], and a repeat ultrasound biomicroscopy showed healing of the dermal granulomas. Five months after completion of the therapy, there was no recurrence of lesions.

DISCUSSION

Dematiaceous fungi are characterized by their dark pigmentation derived from the melanin complex in their cellular wall. They are ubiquitous in nature, found mostly in soil and vegetation. Infection is probably introduced by traumatic inoculation or inhalation of the etiologic agent. Trivial unnoticed trauma may be responsible for initiating infection in this case. Chromoblastomycosis, eumycetoma and phaeohyphomycosis are the distinct clinical syndromes.^[1-4]

Phaeohyphomycosis is a rare infection caused by dematiaceous fungi, involving the skin and subcutis, paranasal sinuses, eyes, bones or central nervous system. Skin and subcutaneous tissue involvement is termed subcutaneous phaeohyphomycosis, and is characterized by papulonodules, verrucous, hyperkeratotic or ulcerated plaques, cysts, abscesses, pyogranuloma, non-healing ulcers or sinuses. In India, commonly associated genera are *Exophiala*, *Phialophora*, *Cladosporium*, *Curvularia*, *Fonsecaea* and *Alternaria* [Table 1].^[1,2]

Laboratory diagnosis includes isolation of fungal hyphae on potassium hydroxide mounts and culture on Sabouraud's dextrose agar.^[4] Histopathologically, the lesions show brown-walled septate hyphae or yeast or a combination of both in tissue. The Fontana-Masson stain (specific for melanin), periodic acid-Schiff and Gomori methenamine-silver stains can be used to confirm the diagnosis.^[4,5]

Cladophialophora spp. may cause phaeohyphomycosis, chromoblastomycosis, and mycetoma. *Cl. boppii* has been isolated from cases of chromoblastomycosis, phaeohyphomycosis and lung infections. Species identification is important in cases of phaeohyphomycosis as other species such as *Cladophialophora bantiana* are neurotropic, causing brain abscess which is frequently fatal. *Cladophialophora* colonies are powdery to woolly with olivaceous-green to black on the obverse and black on the reverse. *Cl. boppii* produces unbranched, very long chains of smooth-walled globose conidia. No shield cells are observed and the conidia directly emerge from the conidiophores.^[6]

Local infection may be cured with excision or cryotherapy alone, or in combination with

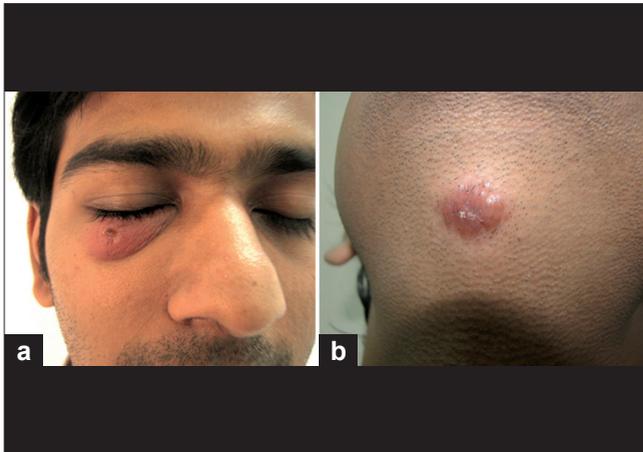


Figure 1: (a) Erythematous nodule on right lower eyelid; (b) erythematous plaque on chin

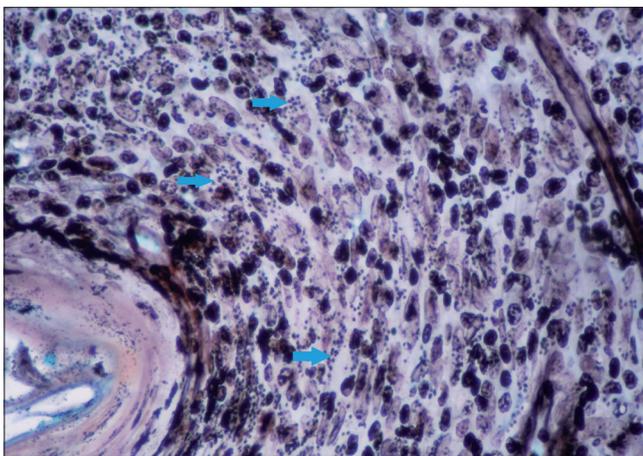


Figure 2: Yeast cells within macrophages (Gomori methenamine silver, x40)

antifungals.^[2] Dematiaceous fungi are most susceptible to itraconazole, voriconazole and posaconazole. Ketoconazole and fluconazole have limited activity. Amphotericin-B and 5-flucytosine may be used. Systemic disease is often refractory to therapy.^[4,7] The precise duration of therapy is not established, and it may range from 1 to 48 months. Hence, non-invasive techniques like ultrasound biomicroscopy can be useful in delineating the dermal lesions and monitoring response to therapy.

Ultrasound biomicroscopy (UBM) is high frequency ultrasonography performed using a 50-MHz probe (resolution of 40 μm and depth of penetration 4 mm). Dermatological ultrasound is usually performed



Figure 3: *Cl. boppii* showing unbranched, very long chains of smooth-walled globose conidia (slide culture of tissue on Sabouraud's dextrose agar)



Figure 4: UBM image of lesional skin showing a hypoechoic mass (arrow) measuring 2.5 x 1.5 mm in the dermis



Figure 5: Resolution of the lesion with post-inflammatory hyperpigmentation at 1 year of therapy

Table 1: Subcutaneous phaeohyphomycosis in India

Report	Patient	Sex	Isolate	Site affected	Lesion
1	1	M	<i>Phialophora dermatitidis</i>	Disseminated	Warty and cystic
2	2	M	Not known	Not known	Abscess
3	3	M	Not known	Not known	Abscess
4	4	M	<i>Cladosporium bantianum</i>	Foot	Nodule
5	5	M	<i>P. dermatitidis</i>	Leg	Chronic ulcer
	6	M	<i>P. dermatitidis</i>	Leg	Chronic ulcer
	7	M	<i>P. dermatitidis</i>	Leg	Chronic ulcer
6	8	F	<i>Exophiala jeanselmei</i>	Disseminated	Cysts, warty plaques
7	9	F	<i>E. jeanselmei</i>	Disseminated	Papuloplaques
8	10	M	<i>Cladosporium cladosporoides</i>	Arm	Warty plaques
9	11	F	<i>Phialophora gougerotii</i>	Arm	Cysts
10	12	M	<i>Alternaria alternate</i>	Toe and nail	Scaly and dystrophic
	13	F	<i>Alternaria chlamyospora</i>	Disseminated	Scaly
11	14	F	<i>Cl. cladosporoides</i>	Foot	Verrucous growth
12	15	F	<i>Phialophora richardsiae</i>	Waist and buttock	Keratotic, macerated
	16	F	<i>P. richardsiae</i>	Waist and buttock	Keratotic, macerated
13	17	M	<i>Fonsecaea compactum</i>	Below mandible	Sinuses
14	18	M	<i>Curvularia pallescens</i>	Below feet and thigh	Ulcer
	19	M	<i>Cu. pallescens</i>	Left thumb	Ulcer
15	20	M	<i>Curvularia lunata</i>	Leg	Nodule
16	21	F	<i>Phialophora verrucosa</i>	Shin	Ulcer
17	22	F	<i>Nattrassia mangiferae</i>	Hand	Scaly lesion
18	23	F	<i>Fonsecaea pedrosoi</i>	Waist	Ulcerated plaque
	24 (present case)	M	<i>Cl. boppii</i>	Face and hand	Nodules

using a 20-MHz probe (resolution of 80 μm and depth penetration 8–10 mm). However, UBM gives a much superior resolution of the dermis and epidermis, compared with lower-frequency probes. It can be used to measure skin thickness, axial and lateral extension of tumors and inflammatory processes.^[8]

In our case, the duration of treatment was decided based on ultrasound findings in spite of apparent clinical resolution. As there are no conclusive guidelines regarding duration of antifungal therapy which may range widely, UBM can be a useful tool to guide duration of therapy.

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