

A case of disseminated subcutaneous phaeohyphomycosis caused by *Exserohilum rostratum* with *CARD9* mutation

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Abstract

Phaeohyphomycosis is a rare cutaneous and subcutaneous fungal infection caused by dematiaceous fungi. They have a widespread global distribution occasionally affecting humans. A 26-year-old woman presented with multiple skin lesions over her face and extremities for last 7 years, unresponsive to systemic amphotericin B and itraconazole. Further investigations revealed *CARD9* mutation and phaeohyphomycosis caused by the pigmented fungus *Exserohilum rostratum*. Lesions subsequently improved with oral flucytosine and itraconazole.

Key words: *Exserohilum rostratum*, phaeohyphomycosis, *CARD9*

Introduction

The term phaeohyphomycosis, coined by Ajello *et al.* in 1974,¹ refers to infections caused dematiaceous fungi belonging to a diverse group of organisms found in the soil, plants and organic debris.² The major etiologic agents include *Bipolaris*, *Exophiala*, *Curvularia*, *Exserohilum* and *Wangiella* species. These fungi can infect the skin and subcutaneous tissue along with paranasal sinuses, eyes, bones or central nervous system. These infections usually result from inconspicuous penetrating injuries. The common presentations include a solitary cutaneous nodule, plaque or deep-seated subcutaneous cyst or abscess localized to the exposed areas of body, especially the extremities.²

Susceptibility to fungal infections in otherwise healthy individuals with Mendelian disorders is being increasingly recognized due to widespread genome sequencing. Primary immunodeficiencies, characterized by various genetic defects hinder the proper development of innate and adaptive immunity. Caspase recruitment domain-containing protein 9 (*CARD9*) is an important regulator of innate immunity, present in neutrophils, macrophages and dendritic cells. Thus, mutations involving the

CARD9 gene can lead to severe immunosuppression resulting in severe disseminated infections.³

We report this case of Amphotericin B non-responsive disseminated subcutaneous phaeohyphomycosis caused by *Exserohilum rostratum*, in a patient with novel *CARD9* mutation.

Case Report

A 26-year-old married woman, agriculturist by profession, presented with several skin lesions affecting her face and extremities for the last seven years; gradually increasing in size. There was no past history of known trauma. She was afebrile without any history of significant medical illness. Four years back she was prescribed anti-tubercular drugs (ATD) for nine months without any improvement of her skin lesions. Surgical excision was followed by recurrence of lesions at the same sites and distant places within six months. She also received two cycles of intravenous amphotericin B for 26 days each five months apart along with oral itraconazole, 200 mg twice daily for eight months with minimal improvement.

Cutaneous examination revealed multiple grouped, skin-colored to hyperpigmented, verrucous papules, nodules

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and plaques, diameters ranging from few mm to 6 cm, affecting the bilateral forearm, right knee, left leg and right cheek [Figures 1 and 2]. They were non-tender and soft to firm on palpation. No lymphadenopathy was noted.

Clinically, chromoblastomycosis, phaeohyphomycosis, tuberculosis verrucous cutis and atypical mycobacterial infections were considered as the differentials.

Routine biochemistry including blood sugar and serum electrolytes was within normal limits. Serum was negative for HBV, HCV and HIV viral markers.

Histological examination of a representative papule (right arm) demonstrated pseudo-epitheliomatous hyperplasia with nodular granulomatous infiltrate in the dermis and multiple pigmented septate hyphae [Figure 3].

Tissue for fungal culture yielded growth within seven days on Sabouraud's dextrose agar. Colonies were grey to olive-brown

with cottony texture and black reverse pigmentation. Slide culture showed septate hyphae. The conidiophores were long with multiple septae demonstrating sympodial geniculate growth with knobby, zigzag appearance. The conidia were elliptical with transverse septations and distinct protruding hilum at their base [Figure 4]. All these features were suggestive of the pigmented fungus *Exserohilum rostratum*.

The lymphocyte sub-population analysis and nitro blue tetrazolium test were normal. Her serum IgE was raised (9350 IU/L). Primary immunodeficiency gene panel by next-generation sequencing detected a homozygous non-sense variation in exon 8 of the *CARD9* gene HMZ p.Q370X (c.1108C>T). A whole-body CT scan (brain, chest, abdomen and pelvis) failed to show any systemic involvement.

She was administered a combination therapy of oral itraconazole 200 mg twice daily with oral flucytosine 500 mg four times daily resulting in significant improvement of her



Figure 1: Well-defined, erythematous plaque on the right cheek extending to nose and chin



Figure 2: Multiple grouped, verrucous, papules, nodules and plaques on bilateral forearm, right knee and left leg

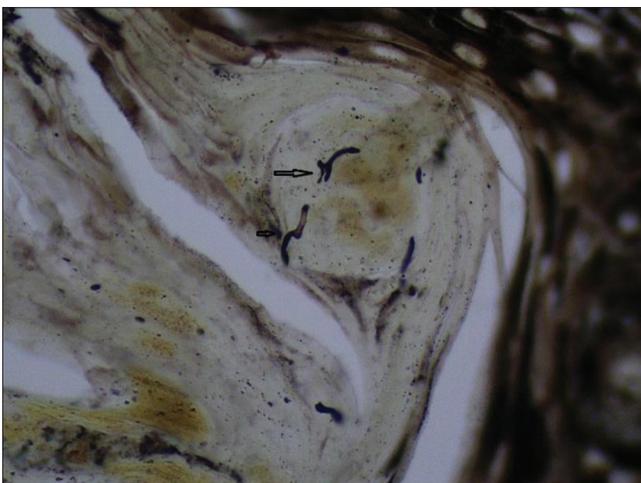


Figure 3: Pigmented, septate hyphae in the stratum corneum (Gomori methenamine-silver nitrate stain GMS stain, x100)



Figure 4: Conidia with protruding hilum (arrow) (Lactophenol cotton blue stain LCB, x100)

lesions within one month. [Figure 5]. Notably she failed to respond to intravenous Amphotericin B previously. We advised regular follow-up to assess the long-term therapeutic response.

Discussion

Phaeoid fungi can cause a diverse group of infections including chromoblastomycosis (characteristic sclerotic bodies in tissue), eumycetoma (secretion of black coloured grains from the lesions) and hence, phaeohyphomycosis is a term used for other clinical presentations caused by dematiaceous fungi which form yeast-like cells, pseudohyphae, hyphae or a combination of these in the infected tissues.⁴

CARD9 deficiency is an autosomal-recessive disorder. Mutations in *CARD9* (a key regulator of innate immunity) lead to impaired synthesis of pro-inflammatory cytokines resulting in depressed Th17- and Th22-associated anti-fungal response.⁵ Till now, 24 different genetic alterations in *CARD9* have been described in 60 patients with fungal infections like candidiasis, dermatophytosis, phaeohyphomycosis and invasive aspergillosis resulting in *CARD9* deficiency.³ This is the first Indian case of phaeohyphomycosis with a novel genetic alteration in the *CARD9* gene.

The treatment of phaeohyphomycosis varies depending on their clinical presentation. Localized lesions respond to surgical excision and cryotherapy. Itraconazole and voriconazole demonstrate the most consistent *in vitro* activity against dematiaceous fungi while fluconazole has no role. Amphotericin B has good *in vitro* activity against most clinically important dematiaceous fungi. However, *in vitro* resistance and therapeutic failures have been reported with this drug. Flucytosine has a unique mechanism of action, inhibiting DNA and RNA synthesis. Combination therapy is often useful for refractory cases.⁶

Therapeutic success depends on the time of diagnosis, extent of lesions, comorbidities, the choice of anti-fungal drug and host immune status. Patients with *CARD9* deficiency are often recalcitrant to conventional antifungal therapy.⁵ The use of sub-cutaneous granulocyte colony-stimulating factor as adjunctive immunomodulator in *CARD9*-deficient patients with CNS infection by *Candida* species has been described.⁷

In a review of 48 cases of phaeohyphomycosis caused by *Exserohilum*, immunosuppression (27.2%) was the commonest underlying condition followed by trauma (16.6%) and atopy (12.5%). Systemic involvement was reported in 73% patients while cutaneous (25%), corneal (16.7%) and subcutaneous (10.4%) infection were also recorded.⁸ There are two prior reports of subcutaneous phaeohyphomycosis due to *Exserohilum rostratum* from India.^{9,10}

The underlying immunological mechanisms, particularly *CARD9* mutation needs to be investigated in such apparently healthy patients with atypical, disseminated and refractory fungal infections. A multidisciplinary approach involving



Figure 5: Significant improvement after 1 month of treatment

immunologists, microbiologists and dermatologists is necessary to gain newer insights into host immune response against fungi which may facilitate the development of newer and effective therapeutic strategies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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