Localized Cutaneous Nodular Chromoblastomycosis Caused by *Diaporthe phaseolorum*; A Case Report and Literature Review

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ABSTRACT:

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We report an unusual case of localized cutaneous nodular chromoblastomycosis caused by *Diaporthe phaseolorum* in a diabetic patient with previous kidney transplantation. Clinical presentation showing a group of multiple cutaneous brownish nodules located on unilateral leg was initially suspicious of subcutaneous phaeohyphomycosis. Diagnosis was confirmed by histological evaluation, mycological culture and molecular identification of causative organism. This was the first case presentation of chromoblastomycosis caused by *Diaporthe phaseolorum*. We encourage that the combination of clinical suspicion, skin biopsy, tissue culture and molecular diagnosis are important and remain the mainstay for making a diagnosis of the atypical cutaneous fungal infection especially from the uncommon causative fungi.

Key words: Chromoblastomycosis, phaeohyphomycosis, *Diaporthe phaseolorum*

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Introduction

Dematiaceous fungi are heterogenous groups of molds containing brown melanin or melanin-like pigment in the cell wall. Skin and soft tissue infection caused by dematiaceous fungi can be present in several diseases such as phaeohyphomycosis, chromoblastomycosis and eumycotic mycetoma which can occur in both immunocompromised and immunocompetent human hosts[1]. A nodular type of chromoblastomycosis shows clinical distinction of erythematous-violaceous nodules with smooth or hyperkeratotic skin surface which can be occasional present admixed with the common verrucous chromoblastomycosis[2].

Here we report a case of nodular chromoblastomycosis caused by an unusual fungal pathogen "*Diaporthe phaseolorum*" in a diabetic patient who had undergone kidney transplantation. Furthermore, we did the literature review and summarized the previous reported cases of skin and soft tissue infection caused by *Diaporthe phaseolorum*.

Case presentation

A 68-year-old Thai male presented with one-month history of multiple slow-enlarging, nontender nodules on the left lower leg. He was currently a retired government officer who denied previous history of trauma to the lesional skin. He had underlying diseases of diabetes mellitus, hypertension, and chronic kidney disease post kidney transplantation for one year. His daily medication was oral tacrolimus 6 g/day and oral prednisolone 10 mg/day as prescribed for a post-transplantation immunosuppressive regimen.

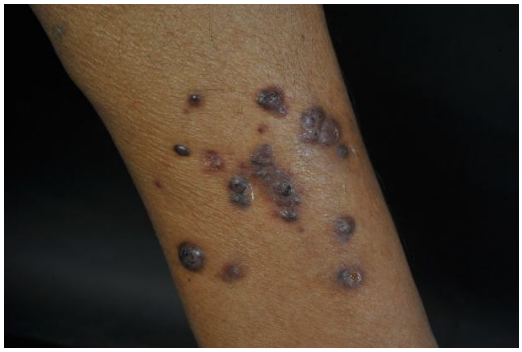

Figure 1 A group of multiple brownish nodules on the medial aspect of the left lower leg

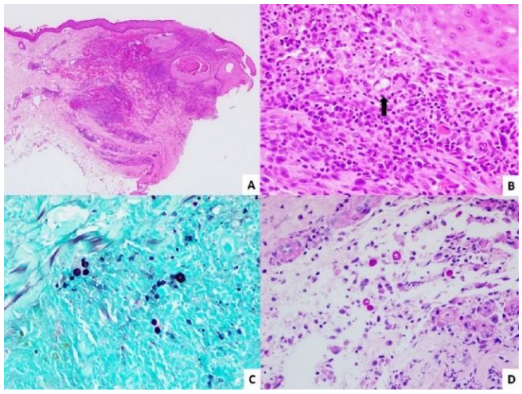

Figure 2

A,B) Pseudoepitheliomatous hyperplasia with mixed-cell granuloma and scattered Medlar bodies (arrow) (A; H&EX40, B; H&EX400).

C) Grocott-Gomori's Methenamine Silver (GMS) and

D) Periodic acid-Schiff (PAS) stains showed yeast-like fungi.

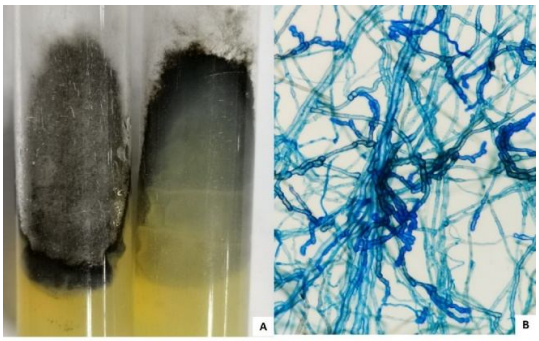

Figure 3 A) Black cottony fungal colony with a black reverse, B) Microscopic morphology showed dematiaceous septate hyphae without conidiation.

A dermatological examination revealed multiple brownish nodules, varying in size from 0.5 – 1.0 cm, localized on the medial aspect of the left leg (Figure 1). Some nodules showed smooth surface with some others were crusted and slightly verrucous. No regional superficial lymphadenopathy was detected. Physical examination of the other system and laboratory investigation were unremarkable. X-ray imaging was not performed. The clinical differential diagnosis included non-tuberculous mycobacterial infection and subcutaneous fungal infection. A skin biopsy was performed and histological examination with hematoxylin and eosin stain (H&E) demonstrated pseudoepitheliomatous hyperplasia with mixed-cell granulomatous inflammation in dermis and scattered faint-brown yeast-like bodies (Medlar bodies) among the dermal inflammation. Grocott-Gomori Methenamine Silver (GMS) and Periodic acid-Schiff (PAS) stains highlighted Medlar bodies in the tissue without fungal hyphae (Figure 2). Ziehl-Neelsen stain was negative for acid-fast bacilli. Mycological culture from the tissue showed initially brown-to-black cottony fungal colony that turned to entirely black color after 7 days of incubation. Reverse was also dark black in color. Microscopic morphology revealed dematiaceous septate hyphae without conidiation (Figure 3). Sequence analysis was performed and the internal transcribed spacer region of ribosomal DNA was amplified and sequenced. BLAST sequence identity searched with NCBI Blast sequence database showed 99.7% identity with *Diaporthe phaseolorum* and 99.699% similarity when search with CBS database.

Based on overall investigated data, a diagnosis of chromoblastomycosis caused by *Diaporthe phaseolorum* was finalized. The patient was treated with oral itraconazole 200 mg/day with oral terbinafine 250 mg/day. After 5 months of treatment, the patient showed significant improvement of the cutaneous lesions. Surgical removal of the residual lesions had been advised and was denied by the patient due to his personal reason. Later on, the patient was lost to the follow-up visit at our granuloma clinic, the Dermatology Department. We were then

informed by the patient's family that he had recently passed away from severe pneumonia of unknown etiology at his primary-care hospital.

Discussion

Dematiaceous fungal infection leads to several diseases such as chromoblastomycosis, phaeohyphomycosis and eumycetoma. There are many tissue forms of pathogenic fungi in phaeohyphomycosis such as yeast-like cell, pseudohyphae, septate hyphae, or any combination of these forms. On the other hand, chromoblastomycosis showed a distinctive round, thick-wall, brown cells called Medlar bodies, muriform cells or sclerotic bodies in the tissue. Etiologic pathogens of phaeohyphomycosis and chromoblastomycosis are different but some agents can be the cause of both diseases. Organisms causing phaeohyphomycosis include up to 100 different fungal species from 60 genera. Some fungi are detected worldwide while some have a restricted geographical distribution. Most frequent causative fungi of subcutaneous phaeohyphomycosis include *Exophiala jeanselmei*, *Phialophora* spp., *Bipolaris* spp., and *Wangiella* (*Exophiala*) *dermatitidis*. Chromoblastomycosis is most commonly caused by *Fonsecaea pedrosoi*, while less common causes are *Phialophora verrucose*, *Fonsecaea compacta*, *Cladophialophora carrionii* and *Rhinocladiella aquaspersa*. Both diseases are usually asymptomatic and occur at trauma-prone areas. Lesions of phaeohyphomycosis are usually painless cystic cold abscesses, while chromoblastomycosis can initially appear as a painless papule or nodule then slowly grow into hyperkeratotic verrucous fibrotic nodules, plaques, tumoral or cicatricial atrophic lesions[1,2].

Despite our case was initially suspicious of phaeohyphomycosis due to nodular cutaneous lesions, the histopathology supported chromoblastomycosis according to the presence of marked epidermal hyperplasia with Medlar bodies surrounded by granuloma. Furthermore, the fungal culture and molecular study demonstrated *Diaporthe phaseolorum* as the causative pathogen.

Diaporthe phaseolorum (Phomopsis phaseoli) belongs to Diaporthe; a genus of endophytic, saprobic and plant pathogen. It can be pathogenic in human and the other mammals[3]. Literature review showed 7 cases of infected skin and soft tissue infection caused by *Diaporthe phaseolorum* as presented in Table 1. Global distribution had been reported in Brazil, the United States, South America, New Zealand and Asia. Most patients were immunocompromised with history of trauma, gardening and farming. The infected sites were located mostly on extremities. Tissue biopsies showed granulomatous inflammation, dermal abscess, cyst and reactive fibrotic proliferation. Since there was no

standardized treatment for dematiaceous fungal infection to the skin and soft tissue, most cases were treated with combination of systemic antifungal medication and surgical excision which leaded to the satisfying outcomes.

Table 1 Mucocutaneous and soft tissue infection by *Diaporthe phaseolorum* previously reported in humans

Case	Authors. Year (Reference)	Country	Age, Gender	Underlying conditions and previous trauma	Clinical presentation	Histopathology	Diagnosis	Treatment and duration	Outcome
1.	Mandell KJ, et al. 2009[4]	USA	63, M	Healthy, thorn injury while gardening	A recalcitrant corneal ulcer at right eye	N/A	Fungal keratitis	Oral and topical voriconazole and amphotericin B for 5 months, therapeutic keratoplasty, intracameral amphotericin B, topical cyclosporine	Remission
2.	Iriart X, et al. 2011[6]	French Guiana, South America	60, M	HT, HTLV-1, a farmer with barefoot working	Subcutaneous mass with osteomyelitis at left foot for 4 years	Suppurative granuloma with surrounding fibrosis and PAS-positive filamentous fungal grains	Eumycetoma	Itraconazole 400 mg/day, 6 months	Improved
3.	Mattei AS, et al. 2013[7]	Brazil	43, M	ESRD, DM, Post KT, no trauma	Indurated erythematous lesions at right arm and right leg for 2 months	Suppurative granuloma with septated fungal hyphae, and yeast-like cells with a thick wall sometimes in chains	Cutaneous infection	Itraconazole 200mg/day and surgical excision	Remission

Table 1 Mucocutaneous and soft tissue infection by *Diaporthe phaseolorum* previously reported in humans

Case	Authors. Year (Reference)	Country	Age, Gender	Underlying conditions and previous trauma	Clinical presentation	Histopathology	Diagnosis	Treatment and duration	Outcome
4.	Rakita RM, et al. 2016[8]	USA	79, M	Post heart transplant a-tion, outdoor working, gardening and hunting wild animals	Localized swelling at right thigh for 6 months	Biloculated cyst containing fungal elements	Soft tissue infection	Posaconazole, 3 months and surgical excision	Remission
5.	Howard JC, et al. 2019[9]	New Zealand	46, M	DCM, Post heart transplant ation, minor abrasion from playing rugby	A nontender mass on left pretibial area for 1 year	Reactive fibroblastic proliferation and numerous fungal hyphae by PAS	Soft tissue infection	Itraconazole, 7 months and surgical excision	Remission
6.	Laosakul K. et al. 2020[10]	Thailand	66, F	Allergic rhinitis, no trauma	An asymptomatic slow-growing nodule at right hand	Suppurative granuloma with without epithelial sinus tract	Phaeohypho mycosis	Fluconazole 200 mg/day, 2 months and surgical excision	Remission
7.	Our patient	Thailand	68, M	DM, HT, ESRD, Post KT, no trauma	Multiple discrete brownish nodules at left leg	Pseudoepithel iomatous hyperplasia with mixed-cell granuloma and brown yeast-like bodies (Medlar bodies)	Chromoblast omycosis	Itraconazole 400 mg/day with terbinafine 250 mg/day, 5 months	Improved

Abbreviation:

USA: The United States of America, M: Male, F: Female, DM: Diabetes mellitus, HT: Hypertension, HTLV-1: Human T- cell leukemia virus type 1, ESRD: End-stage renal disease, KT: Kidney transplantation, DCM: Dilated cardiomyopathy, Rt.: right, Lt.: left, N/A: Not available, PAS: Periodic acid-Schiff

Our patient had a risk factor of impaired immune function from diabetes mellitus and post-transplantation immunosuppressive medication. Despite lack of the traumatic history, the diagnosis was delivered following tissue biopsy for histological and microbiological studies. After the thorough review of literature and to the best of our knowledge, this is the first case of chromoblastomycosis caused by *Diaporthe phaseolorum* in an immunocompromised patient.

Conclusion

We report the first case of localized cutaneous nodular chromoblastomycosis caused by *Diaporthe phaseolorum* which was clinically resembled subcutaneous phaeohyphomycosis in a diabetic patient with history of renal transplantation. Physicians should be aware of the possibility of subcutaneous or invasive fungal infection caused by unusual pathogens in the patients undergone organ transplantation or immunosuppressed status.

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