CASE REPORT

Phaehyphomycosis or Eumycetoma: A Case Report of a Diagnostic Dilemma

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ABSTRACT

We reported a case of recurrent subcutaneous swelling on the left foot of a diabetic patient. Two different organisms, *Cladosporium spp.* and *Phaeoacremonium krajdenii* were isolated, both of which are associated with phaeohyphomycosis and eumycetoma. The cure was achieved through surgical excision of the lesion and a course of antifungal therapy. The diagnosis was uncertain since clinical manifestations and laboratory results were insufficient to distinguish the two diseases.
Malaysian Journal of Medicine and Health Sciences (2024) 20(1):392-394. doi:10.47836/mjmhs.20.1.50

Keywords: Phaeohyphomycosis, Madura foot, eumycetoma, *Phaeoacremonium krajdenii*

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INTRODUCTION

Phaeohyphomycosis refers to fungal infections caused by large heterogenous group of black pigmented or dematiaceous fungi. Its clinical presentation varies from superficial cutaneous infections to deep or systemic infections, with subcutaneous phaeohyphomycosis being rare (1). They are sometimes indistinguishable from a condition called mycetoma also known as "Madura foot". Mycetoma is a localized chronic, suppurative infection affecting skin, subcutaneous tissue, and bones caused by either bacteria (actinomycetomas) or fungi (eumycetomas) (2). Dematiaceous fungi are heterogeneous group of melanized fungi found ubiquitously in the environment (1). *Exophiala, Alternaria, Phialophora*, and *Curvularia* were the most common dematiaceous fungi identified in patients with phaeohyphomycosis and mycetoma. *Phaeoacremonium* and *Cladosporium* species were rarely associated with the disease but had been reported in some geographical area. Appropriate and timely diagnosis remain dilemma due to the similarity in the clinical presentations and laboratory findings between these two fungal infections.

CASE REPORT

A-75-year-old man with diabetes mellitus presented with a recurrent history of a nodule on the dorsum of right foot that slowly grew in size until it resembled a tumour. It was painless, no visible sinus or discharge on the skin's surface. In January 2020, he was admitted to a hospital due to four months history of swelling on his right foot, which was getting bigger, where an excision biopsy was performed. Six months post excision, a nodule appeared on the scar and became infected. He is an office driver, but he spends his free time doing farming. He did not recall prior foot injury or trauma. Pus for fungal culture yielded *Cladosporium* spp. colonies which grew after seven days of incubation on Sabouraud dextrose agar at 30°C (Fig. 1). He was treated with oral itraconazole for one month. After a few months, a recurrent swelling appeared and grew in size.. Examination of the right foot revealed a tumour-like swelling over the dorsum measuring 10cm x 8cm x 5cm (Fig. 2). It was multilobulated with soft to firm in consistency with no sinuses or discharge was present. Upon further examination, he was noted to have right inguinal lymphadenopathy. Right foot radiograph and magnetic resonance imaging (MRI) performed excluded any bone involvement. He underwent a wide local resection of the soft tissue tumour of his right foot. A 7cm x 4cm mass extending to plantar aspect of the big

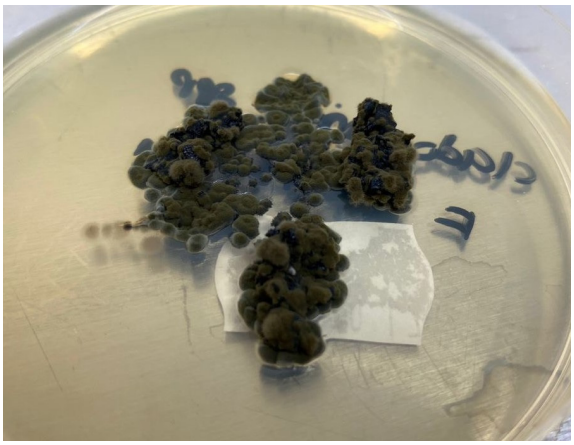

Figure 1: Olivaceous blackish-brown colonies of *Cladosporium* spp on Sabouraud's dextrose agar

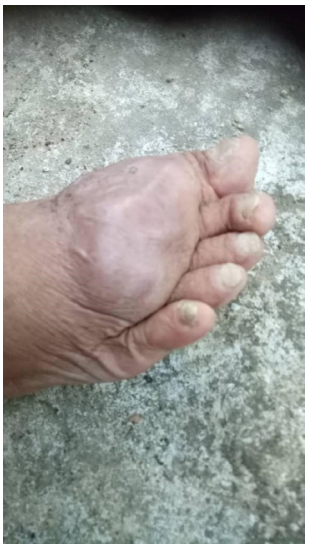

Figure 2: Clinical picture of patient showed a tumour like swelling over right foot dorsum

toe through first webspace was removed. There were no classical sinuses seen. Surrounding tissues and bone were healthy. Microscopy of haematoxylin and eosin (H&E) stain from the tissue showed necrotising granulomatous inflammation evidence by extensively fibrotic areas and granuloma formed by histiocytes admixed with lymphocytes with scattered giant cells (Fig. 3). Tissue culture grew an olivaceous mould colonies after ten days of incubation at 30° Celcius on Sabouraud's dextrose agar (Fig. 4a). Microscopic findings on Lactophenol cotton blue (LPCB) mount showing septate hyphae, mono- and polyphialides of cylindrical shapes with ellipsoidal to allantoid conidia (Fig. 4b). Further genotypic identification of the organism was performed by extraction of DNA from the isolate followed by PCR for ITS1/ITS4 regions followed by sequencing and was identified as *Phaeoacremonium krajdenii*. He was treated with itraconazole for a period of six weeks.

DISCUSSION

Phaeoacremonium spp. is one of the dematiaceous fungi. Cutaneous and subcutaneous lesions are the most common presentations despite reported cases of onychomycosis, endophthalmitis, central nervous system involvement, endocarditis, and disseminated disease (fungemia). *Phaeoacremonium krajdenii* was among the species recognized causing human infection especially in subcutaneous type. The first case was reported from India in 2006, presented with white grain eumycetoma of the foot (3). *Phaeoacremonium krajdenii* is a slow growing fungus where the colonies became visible after eight to ten days and slowly turned into olivaceous brown. Microscopic picture reveals black septate hyphae either singly or in bundles of fascicles. The classic morphologic characters are short and unbranched conidiophore, cylindrical phialides

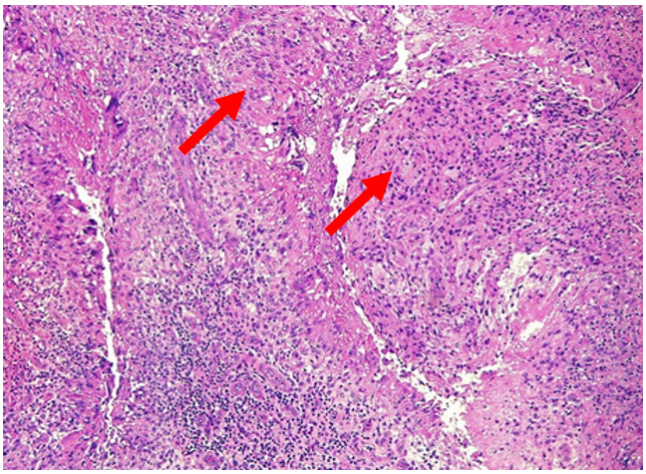

Figure 3: Granulomas (red arrows) formed by histiocytes admixed with lymphocytes with scattered giant cells (H&E, X 100)

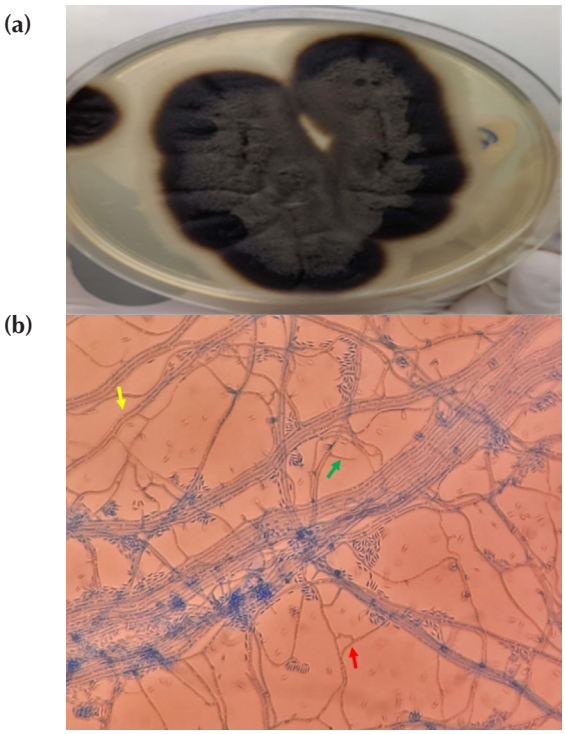

Figure 4: (a) Olivaceous colonies of *Phaeacremonium krajdenii* on Sabouraud's dextrose agar. (b) Microscopic features showing septate hyphae (yellow arrow), mono- (green arrow) and polyphialides (red arrow) of cylindrical shapes with ellipsoidal to allantoid conidia. (LPCB, X 40)

and oblong-ellipsoidal conidia (3). Based on culture and microscopic characteristics, identification might be just at the genus level which is *Phaeoacremonium* spp. The definitive species identification is facilitated by genomic sequencing.

Phaeohyphomycosis and eumycetoma are the common melanized fungal infections. Unlike the other fungal infections, these dematiaceous fungi infection have an indolent course and varied clinical presentation therefore making the diagnosis difficult (4). In majority of cases, fungal infection was not considered as the initial diagnosis because it resembles soft tissue tumour. Majority were treated as a soft tissue tumour until histopathological findings and culture results were available. The fungi are usually implanted into the skin after a direct penetration by a plant or a soiled-contaminated object acquired via barefoot or through pre-existing abrasions. Despite no history of trauma was found in our case, localization of the lesion and working as a part time farmer might suggest the possible risk factor and organism point of entry. In both phaeohyphomycosis and eumycetoma, most of the cases were associated with poor general health and underlying immunosuppressive conditions such as diabetes, renal transplant, rheumatoid arthritis, and corticosteroid therapy (1,2,4).

Clinical presentations for both vary. The typical lesions of subcutaneous phaeohyphomycosis are nodules or abscesses with a small tendency towards lymphatic dissemination. Sometimes the lesions may coalesce and form a single large cavity, which later surrounded by a capsule and thus giving a cyst like appearance. Classical triad of painless subcutaneous mass, sinuses, and a discharge containing granules is pathognomonic for Madura foot or mycetoma (2). Atypical mycetoma presentations may have absence of sinuses and granules (5). In non-classical presentation, clinical diagnosis is challenging. One of the rapid tools for diagnosis is by radiographic imaging such as plain radiograph, ultrasound and MRI which can assess the presence and extent of soft tissue and bone. A diagnosis of eumycetoma can be established by an MRI showing the classical "Dot In Circle" sign (5). Although laboratory diagnosis may take a longer time, histology and culture can prompt to a definitive diagnosis. In eumycetoma, direct macroscopic examination of the purulent discharge admixed with black granules is helpful in giving a rapid provisional identification of the etiological agent. Mold colonies may be isolated in both cases when culture on Sabourauds Dextrose agar and incubate at 30° Celcius. In most cases, molecular technique was applied to ascertain the fungal species. HPE may highlight the presence of fungal bodies by using special stains like PAS and GMS. In eumycotic mycetoma, histology of tissue showed multiple micro abscessess with intradermal mycetoma consist of a necrotic core where palisading histiocytes and eosinophilic hyaline material surrounded the fungal colonies referred as "Splendore-Hoeppli" reaction (2-4). Focal giant cell reaction with reactive fibrosis and chronic inflammatory response surrounding the micro abscess may also be seen in the outermost layer. There will be absence of "Splendore-Hoeppli" phenomenon in phaeohyphomycosis and histology revealed a dense fibrous tissue associated with a granulomatous inflammation comprise of abundant giant cells, necrosis and septate hyphae (1,4). Radiology and histology clinched the diagnosis of eumycetoma based on "Dot In Circle" sign and "Splendore-Hoeppli" phenomenon. There is no established treatment for phaeohyphomycosis. Choice of surgery and length of antifungal therapy is primarily based on clinical presentation and the initial response. In cases with large soft tissue lesion, surgical excision helps to reduce fungi burden and shortened antifungal treatment for complete eradication.

CONCLUSION

Diagnosis is a dilemma for this case. Considering the clinical presentations with the findings from multimodal diagnostic tools including radiological, microbiological, and histological favour towards diagnosis of phaeohyphomycosis. Since these fungal infections are subclinical in presentation, the importance of imaging and histology should be emphasized to achieve appropriate treatment, prevent recurrence, and avoid functional and aesthetical impairments.

ACKNOWLEDGEMENTS

We would like to thank the patient who gave us permission for the publication of this case report.

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