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Subcutaneous phaeohyphomycosis from *Medicopsis romeroi* in a diabetic patient

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ABSTRACT

Dematiaceous fungi can cause subcutaneous phaeohyphomycosis, an uncommon fungal infection of the dermis and subcutaneous tissues. *Medicopsis romeroi* is an emerging organism that can infect patients with subcutaneous phaeohyphomycosis, especially immunocompromised patients. The present case involved subcutaneous phaeohyphomycosis caused by *Medicopsis romeroi* in an 80-year-old Thai male with poorly controlled diabetes, for whom the lesion underwent spontaneous remission after his glycemic control was improved. Furthermore, cases of subcutaneous phaeohyphomycosis for the last 10 years were reviewed.

1. Introduction

Subcutaneous phaeohyphomycosis is not a common fungal infection of the dermis and subcutaneous tissues. It is caused by dematiaceous fungi, and it is believed to result from the traumatic implantation of the fungi into the subcutaneous tissue [1,2]. This form of infection is common in tropical countries and has been reported mainly in immunocompromised hosts. The common causative fungi are *Exophiala jeanselmei*, *Exophiala dermatitidis*, *Phialophora spp.* and *Cladophialophora spp.* [2,3]. The typical clinical presentation is an asymptomatic single nodule, or a cyst, or an abscess at the site of previous trauma, commonly on the extremities.

Medicopsis romeroi is allocated to phylum Ascomycota according to National Center for Biotechnology Information. It produces brown-colored, septate, hyphae without conidia [4]. These organisms are widely distributed in the soil and plants, and they are able to infect people by direct inoculation [4].

Medicopsis romeroi is an emerging fungus causing subcutaneous phaeohyphomycosis. Recent case reports have demonstrated that most patients with subcutaneous phaeohyphomycosis arising from *Medicopsis romeroi* have impaired immune systems [4–8], including patients with type 2 diabetes mellitus who have poor glycemic control [9,10]. Total surgical excision and debridement are the other options for eradicating the infection [1,2]. In this case, we demonstrated the case of subcutaneous phaeohyphomycosis caused by *Medicopsis romeroi* in a poorly controlled diabetic patient who achieved disease improvement through better glycemic control.

2. Case

An 80-year-old Thai male presented to the hospital (day 0) with 1-year of a single nodule on the medial aspect of his right foot (day −360). The lesion had gradually progressed to a size of around 1 cm. No pain or itching was found. He did not have fever, chronic cough, weight loss, or any other abnormal systemic symptoms. He denied having had previous trauma or working-contact with the soil or plants.

For 5 years (day −1800), the patient had had diabetes mellitus, which was poorly controlled (HbA1c 10%). However, he did not have retinopathy nor nephropathy. His current medications were metformin (1.5 g/day), glipizide (10 mg/day), and (aspirin 81 mg/day). He denied using any herbal drugs or other immunosuppressive drugs.

An examination revealed a single, firm, well-defined, erythematous nodule on the medial aspect of the right foot, but without lymphadenopathy (Fig. 1). All other physical examination findings were normal. A laboratory investigation showed normal blood cell counts and serum creatinine of 1.22 mg/dL (estimated glomerular filtration rate 41.0 ml/min/1.73 m^2).

An incisional biopsy was undertaken (day 0) for histopathology, mycobacterium and fungal cultures, and fungal identification. The hematoxylin-and-eosin-stained histological sections revealed a nodular infiltrate of aggregates of epithelioid histiocytes with a mixed inflammatory infiltrate composed of numerous neutrophils, eosinophils,

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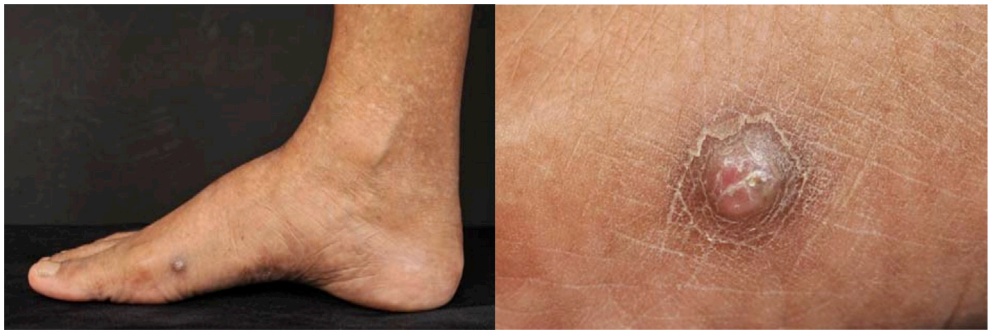

Fig. 1. Clinical pictures of the patient demonstrated a single, firm, well-defined erythematous nodule on the medial aspect of the right foot.

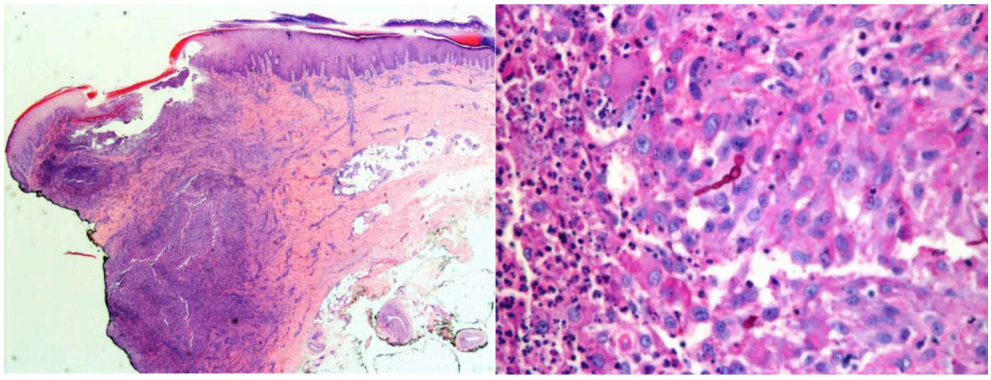

Fig. 2. The Periodic acid–Schiff stain showed mixed-cell granulomas with intracellular, brownish, septate hyphae, pseudohyphae, and yeast-like organisms.

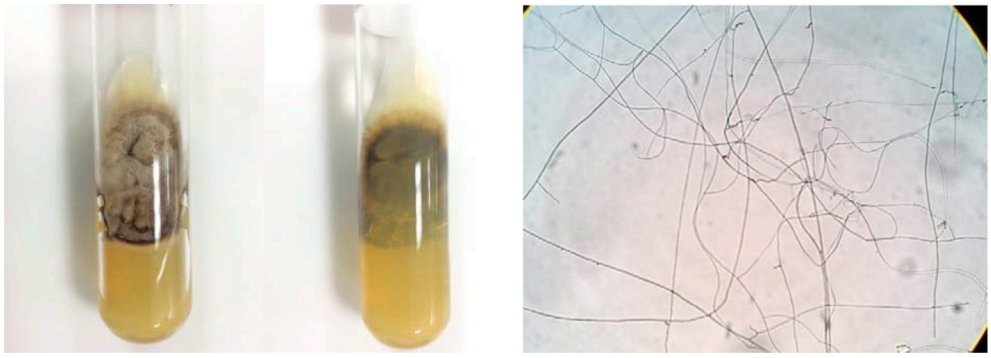

Fig. 3. A fungal culture of the tissue biopsy demonstrated dematiaceous molds. Microscopic examination of the culture found broad, septate, branched, dark brown hyphae. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Polymerase chain reaction (PCR) protocol using sequencing of international transcribed spacer (ITS) region.

Step	Temp.(°C)	Time (sec.)	Round
Pre-denature	94	60	1
Denature	94	30	35
Annealing	48	30	
Extension	68	60	
Final extension	68	300	1
Hold at	4	α	

lymphocytes, and plasma cells. A Periodic acid–Schiff stain showed scattered multinucleated giant cells containing intracellular brownish septate hyphae, pseudohyphae and yeast-like organisms (Fig. 2). The fungal culture of the tissue biopsy demonstrated dematiaceous molds (day +90) (Fig. 3). A microscopic examination of the culture found broad, septate, branched, and dark brown hyphae. Molecular identification of the fungal species revealed *Medicopsis romeroi* (day +90). Molecular diagnosis is performed by sequencing of international transcribed spacer (ITS) region using primer sequence for ITS1 (5′-TCC GTA GGT GAA CCT GCG G-3′). The accession number of closest hit was JX088727.1 with 100% identification of maximal score of 852. The length of analyzed sequence was 477. The detail of polymerase chain reaction (PCR) protocol was demonstrated in Table 1. The bacterial and mycobacterial cultures of the tissue biopsy were negative (day +90). The diagnosis was subcutaneous phaeohyphomycosis caused by *Medicopsis romeroi*. After the histopathological diagnosis was established, an X-ray of the right foot was performed, but there was no evidence of an osteolytic lesion (day +50). A magnetic resonance imaging (MRI) study of the right foot was subsequently conducted (day +120). It found a small, diffuse, infiltrative region of abnormal signal intensity of the skin and subcutaneous tissues of the plantar surface of the foot, adjacent to the head of the first metatarsal bone and measuring about 2.4 x 0.9 × 2.5 cm (antero-posterior x width x height). No abnormality in signal intensity was observed in the bony structure or marrow. However, the imaging revealed that there were residual infiltrative lesions. While the patient was waiting for total excisional surgery, he succeeded in

Table 2
Clinical settings and treatment outcomes of reviewed phaeohyphomycosis from *Medicopsis romeroi* patients.

Report from	Age	Sex	Setting	Lesion	Site	Treatment and outcomes	Ref.
India	45	Female	Healthy	Subcutaneous nodule, cystic consistency	Right forearm	Surgical excision without oral anti-fungal treatment; then, completely cured, with no recurrence over 1 year	[11]
India	47	Female	ALL on prednisolone. methotrexate, vincristine, 6-MP	Subcutaneous nodule, cystic consistency	Right index finger	Aspirate pus and drainage; then, subsided gradually over 2 months without oral anti-fungal treatment	[4]
Taiwan	78	Male	Asthma on long-term prednisolone	Multiple papulopustular lesion	Right dorsum of hand and elbow	Amphotericin B for 3 weeks improved the lesion, with no recurrence over 6 months	[8]
Britain	88	Male	Leprosy and Bell's palsy on prednisolone	Discrete keratotic lesion	Dorsum of right hand	N/A	[7]
India	61	Female	RA on prednisolone, DMARD, methotrexate	Soft to firm mass	Proximal phalanx of right index finger	Itraconazole (200 mg/day) for 3 months; then, lesion improved, and no recurrence over 6 months	[6]
India	43	Male	KT on prednisolone, mycophenolate mofetil, tacrolimus	Multiple nodular lesion	Left thigh and calf	Itraconazole and then terbinafine; then, there were new lesions and were treated with excision and voriconazole	[5]
China	55	Male	KT on prednisolone, mycophenolate mofetil, cyclosporin	Nodule	Left posterior thigh	Surgical excision with long-term itraconazole	[15]
Africa	66	Male	KT on prednisolone, mycophenolate mofetil, tacrolimus	Hyperkeratotic nodule	Left heel	Surgical excision without oral anti-fungal treatment; then, completely cured, with no recurrence over 9 months	[14]
France	47	Female	DM type 2 for 3 years (BS 413 g/dL)	Firm mass	Radius of right foot	I&D without antifungal; then, clinical improvement	[9]
India	48	Male	DM type 2 (FBS 320 mg/dL), LL with ENL on dapsone, rifampicin	Subcutaneous nodule, cystic consistency	Lateral aspect of left foot	I&D plus itraconazole; then, lost to follow-up	[16]
India	50	Female	DM type 2 for 5 years with poor compliance (random BS 413 g/dl)	Soft to firm mass	Left foot	I&D plus itraconazole (200 mg/day) for 2 weeks; then, swelling resolved completely	[10]

Abbreviations: 6-MP, 6-Mercaptopurine; ALL, acute myelocytic leukemia; BS, blood sugar; DM, diabetic mellitus; DMARD, disease-modifying anti-rheumatic drugs; ENL, erythema nodosum leprosum; FBS, fasting blood sugar; KT, kidney transplantation; LL, lepromatous leprosy; RA, rheumatoid arthritis.

bringing his glycemic level under control, with his HbA1C value falling to below 7% (day +270). Because no mass was found on examination, a second MRI study of the right foot was performed (day +390). The MRI showed normal findings, with the disappearance of the small, diffuse, infiltrative region that had been found in the previous MRI study.

In other words, the lesions of the subcutaneous phaeohyphomycosis were cured within 9 months (day +270), without the need for any systemic antifungal drug administration.

3. Discussion

Medicopsis romeroi is an emerging fungus causing subcutaneous phaeohyphomycosis. It has mostly been reported in immunocompromised patients receiving immunosuppressive drugs for hematologic malignancy [4], renal transplantation [5], rheumatoid arthritis [6], leprosy [7], and asthma [8]; however, there has been one report of a healthy, immunocompetent host [11], as shown in Table 2. *Medicopsis romeroi* has also reported in patients with type 2 diabetes mellitus who have poor glycemic control [9,10]. Since phagocytic activity is the main mechanism for anti-fungal infections [12], type 2 diabetes patients with hyperglycemic control have a significant decline in the phagocytic activity of peripheral blood mononuclear cells [13]. This could be why type 2 diabetes patients are susceptible to uncommon, cutaneous, fungal infections like *Medicopsis romeroi*.

In all previous case reports of *Medicopsis romeroi* causing subcutaneous phaeohyphomycosis, the fungus was identified as the causative organism through sequencing of the Internal Transcribe Spacer region and amplification. Fungal identification can guide treatment and inform the prognosis. Complete surgical excision is a curative treatment for phaeohyphomycosis. Systemic antifungal therapy is used in patients with refractory or recurrent infections due to incomplete excision. Information on the antifungal susceptibility of *Medicopsis romeroi* is limited. The few studies that have experimented with its in vitro susceptibilities demonstrated that the most potent drugs are itraconazole, isavuconazole, and posaconazole, each with very low minimum inhibitory concentrations of less than 1 μg/ml [4,11]. By contrast, amphotericin B, voriconazole, and especially fluconazole have been reported to have high minimum inhibitory concentrations [4,11].

Two earlier reports on type 2 diabetes patients had similar settings, namely, the two patients were females aged around 50 years, had a blood sugar level above 400 g/dL, and came to hospital with a firm mass on one side of a foot. In each case, molecular diagnosis identified *Medicopsis romeroi* [9,10]. Both cases demonstrated clinical improvement by surgical incisional and drainage. Although one patient was also prescribed itraconazole (200 mg/day) for 2 weeks, the other did not receive any antifungal drugs. The present patient represented the first case where a lesion regressed spontaneously, not through medical or surgical treatment, but instead by improving glycemic control. This may result from an enhancement of phagocytic activity (measured by using a modified flow cytometry procedure) in patients who have undergone metabolic optimization, as previously reported [13].

Recognition of subcutaneous infections caused by dematiaceous fungi remains challenging because identification is difficult via conventional cultures. The molecular method plays an important role in species identification, thereby aiding the diagnosis of phaeohyphomycosis and the determination of the most appropriate case management plan. Enhancing a patient's immune status may be a useful way to eliminate an infection.

Conflict of interest

There are none.

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