CASE REPORT

Iatrogenic Phaeohyphomycosis: A Rare and Underrecognized Disease

Mong Wayne Lim, *MRCP*, Abdul Rahman Che Abdul Rahim, *MRCP*, Rajalingam Ramalingam, *AdvMDerm*

Department of Dermatology, Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia

Summary
Phaeohyphomycosis refers to a heterogenous group of mycotic infections caused by dematiaceous fungi where unintentional traumatic inoculation accounts for majority of the cases. Herein, we are reporting a rare case of iatrogenic subcutaneous phaeohyphomycosis which is secondary to intravenous cannula placement.

Key Words: *Iatrogenic; Phaehyphomycosis; Dematiaceous fungi*

Introduction
Phaeohyphomycosis is a group of fungal infections caused by dematiaceous fungi in tissue.[1] More than 150 species have been described as causal agents which includes *Exophiala*, *Wangiella*, *Phialophora* and *Cladosporium* among others.[2] There is a large variety of clinical presentations which includes superficial cutaneous, subcutaneous disease, cerebral and disseminated disease.[3] The subcutaneous infection typically occurs at exposed areas of the body from traumatic inoculation. We report this case of iatrogenic phaeohyphomycosis for its unusual mode of inoculation by intravenous cannula placement which is perceived to be a clean and sterile procedure.

Case Report
HS, a 70-year-old gentleman with type II diabetes mellitus, hypertension and end stage renal failure on haemodialysis, presented with slowly enlarging, asymptomatic nodules over the dorsum of both hands for the past one month. He reported that they started at previous sites of intravenous cannula insertion during his hospital stay one month ago. He did not notice any prior traumatic injury and was otherwise well.

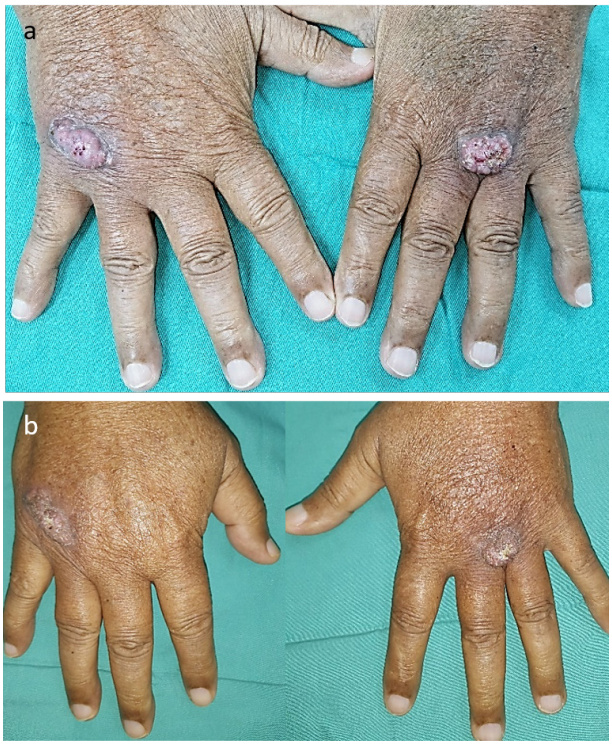
Physical examination revealed an erythematous plaque with verrucous surface measuring 1 x

Corresponding Author
Dr Lim Mong Wayne,
Department of Dermatology,
Hospital Tengku Ampuan Afzan,
25000 Kuantan, Pahang, Malaysia
Email: limmongwayne@gmail.com

1cm, over the dorsum of his right hand. Another erythematous plaque with verrucous surface and minimal surface erosions, measuring 2.5cm x 1.5cm, was located over the dorsum of his left hand. There was no regional lymphadenopathy and examination of other systems was unremarkable.

We considered several differential diagnoses, including iatrogenic fixed cutaneous sporotrichosis, chromoblastomycosis, tuberculosis verrucosa cutis and non-tuberculous mycobacterial infection.

Figure 1. (a). Clinical presentation of the patient, showing erythematous nodule with verrucous surface on the bilateral aspect of both hand with minimal erosion; (b) After one month on itracomazole



Blood investigations were unremarkable apart from mild hypochromic microcytic anaemia and high urea and creatinine, in keeping with his underlying renal disease. Histopathological examination of the plaques revealed pseudoepitheliomatous epidermal hyperplasia with moderate lymphoplasmacytic infiltration with foci of neutrophilic microabscesses. No granulomas were appreciated. While Ziehl Neelsen and periodic acid Schiff (PAS) stains did not demonstrate any fungus, tissue culture, however, isolated *Exophiala* species.

Hence, a diagnosis of iatrogenic subcutaneous phaeohyphomycosis caused by *Exophiala* species was made and he was promptly treated with oral itraconazole. His lesions improved dramatically after one month of treatment and subsequently successfully cleared after 4 months of treatment.

Discussion

The infections caused by dematiaceous fungi, are classified into three groups which include phaeohyphomycosis, chromoblastomycosis and eumycotic mycetoma.[1-3] This variety of dematiaceous fungi develops in infected tissue as darkly pigmented yeast-like cells, pseudohyphae-like elements, hyphae, or in any combination of these forms.[3-4] Phaeohyphomycosis should be distinguished from other infectious syndrome also caused by dematiaceous fungi which include chromoblastomycosis and eumycetoma.

There are many different clinical syndromes for phaeohyphomycosis.[1-4] One of the more extensive clinical syndrome classifications divides it into nine groups, which includes: (1) superficial (including black piedra & tinea nigra); (2) onychomycosis; (3) subcutaneous; (4) corneal or mycotic keratitis; (5) allergic fungal sinusitis; (6) allergic fungal bronchopulmonary mycosis; (7) pneumonia; (8) brain abscess; and (9) disseminated disease.[4] Phaeohyphomycosis is caused by more than 150 species of fungi, which includes *Exophiala*, *Phialophora*, *Alternaria*, *Cladosporium*, *Scytalidium*, *Drechslera*, *Curvularia* and *Wangiella* species. The most common species are *E. jeanselmi* and *E. dermatitidis*.[1-3]

Subcutaneous phaeohyphomycosis lesions most commonly occur on exposed area of body such as hands, arms, feet and legs.[1] Traumatic inoculation accounts for majority of the cause of subcutaneous phaeohyphomycosis, however cases are being reported which has no prior recollection of traumatic injury.[3] There are also reports on iatrogenic phaeohyphomycosis.

This includes report of subcutaneous phaeohyphomycosis in association with intravenous cannula insertion and report demonstrating osteoarticular infection secondary to contaminated methylprednisolone injections.[2,6]

The immune status of the host plays a major role in the clinical presentation of the patient. Typically, majority of cases of phaeohyphomycosis has been associated with an immunocompromised state, this includes human immunodeficiency virus patients, malignancies, transplant recipients, systemic lupus, vasculitis, primary immunodeficiency syndromes, debilitating chronic diseases and diabetes among others.[1,3] In addition to that, immunocompromised states are also at risk of cerebral and systemic phaeohyphomycosis. Despite that, cases in immunocompetent patients are on the rise.[3] As for subcutaneous phaeohyphomycosis, this typically presents as papulonodules, verrucous, hyperkeratotic or ulcerated plaques, cysts, abscesses, pyogranuloma, non-healing ulcers or sinuses.[1,7]

For the diagnosis of phaeohyphomycosis, histopathologically, the lesions show brown-walled septate hyphae or yeast-like cells, or both in tissue. In order to help differentiate it from eumycetoma and chromoblastomycosis which are also caused by dematiaceous fungi, eumycetoma is characterized by the presence of mycotic granules in draining sinus tract while chromoblastomycosis is a typically verrucous hyperplastic cutaneous infection characterized by the presence of medlar bodies (sclerotic bodies).[2,3] All dematiaceous fungi are similar in morphology and cannot be differentiated in tissue. Hence, it can only be differentiated by cultures.

There is no uniform treatment approach for the treatment of these infections. The length of therapy and choice of treatment are primarily based on clinical presentation, underlying immune status of the host and the initial response to treatment.[8] Literature shows surgical excision of the lesion has been successfully applied in some cases.[9-13] Adding on antifungal monotherapy or combination therapy is also preferred to avoid local spread and to treat subclinical lesions.[3] Broad-spectrum azoles are currently the mainstay of therapy, with itraconazole historically the most commonly used agent that demonstrates good activity against the vast majority of melanized fungi. Voriconazole is becoming more popular with preferable side effect profile and is available in intravenous formulation.[3] However, it is not available in our local setting for this patient. Other systemic agents used successfully include amphotericin B, flucytosine & posaconazole.[3] Fluconazole and ketoconazole have essentially no role in invasive disease cause by dematiaceous fungi. Terbinafine was also reported to be less effective, especially in serious systemic infection.[2]

Conclusion

To the best of our limited knowledge, this is the second reported case of iatrogenic subcutaneous phaeohyphomycosis secondary to intravenous cannula insertion. While it is uncommon for a clean procedure as a source of inoculation to cause subcutaneous phaeohyphomycosis, clinicians should have a high index of suspicion and be aware of this infection. This is to avoid any delay in treatment so as to avoid further complications.

Conflict of Interest Declaration

The authors have no conflict of interest.

Acknowledgement

We thank the staff of departments of Dermatology and Pathology of Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia for their support in this article. We would also like to thank the Director General of Health, Malaysia, for his permission to publish this article.

References

1. Chintagunta S, Arakkal G, Damarla SV, Vodapalli AK. Subcutaneous phaeohyphomycosis in an immunocompetent Individual: A case report. Indian Dermatol Online J 2017;8:29-31.

2. Arcobello JT, Revankar SG. Phaeohyphomycosis. Semin Respir Crit Care Med 2020;41:131-40.
3. Ramalingam R. The clinical spectrum of cutaneous phaeohyphomycosis in three immunocompetent patients and a review of literature. Malaysian J Dermatol 2019;42:33-8.
4. Prieto-Granada CN, Lobo AZ, Mihm MC Jr, Kradin RL. Skin infections: Diagnostic Pathology of Infectious Disease. 2nd edition. Philadelphia: Elsevier;2018. p.542-7.
5. Espanhol CM, Recuero JK, Pagani DM, Ribeiro AC, Vettorato G, Duquia RP et al. Cutaneous phaeohyphomycosis caused by *Exophiala xenobiotica*: A case report. Med Mycol Case Rep 2019;27:39-41.
6. Abdolrasouli A, Gonzalo X, Jatan A, McArthur GJ, Francis N, Azadian BS et al. Subcutaneous phaeohyphomycosis cyst associated with *Medicopsis romeroi* in an immunocompromised host. Mycopathologia 2016;181:717-21.
7. Shirbur S, Telkar S, Goudar B, Mathew T. Recurrent phaeohyphomycosis: a case report. J Clin Diagn Res 2013;7:2015-6.
8. Chowdhary A, Meis JF, Guarro J, de Hoog GS, Kathuria S, Arendrup MC et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. Clin Microbiol Infect 2014;20:47-75.
9. Girard C, Dereure O, Rispail P, Durand L, Guilhou JJ. Subcutaneous phaeohyphomycosis due to *Pyrenochaeta romeroi* in a patient with leprosy. Acta Derm Venereol 2004;84:154-5.
10. Ferrer C, Pérez-Santonja JJ, Rodríguez AE, Colom MF, Gené J, Alio JL et al. New pyrenochaeta species causing keratitis. J Clin Microbiol 2009;47:1596-8.
11. Badali H, Najafzadeh MJ, van Esbroeck M, van den Enden E, Tarazooie B, Meis JF et al. The clinical spectrum of *Exophiala jeanselmei*, with a case report and in vitro antifungal susceptibility of the species. Med Mycol 2010;48:318-27.
12. Verkley GJ, Gené J, Guarro J, Pérez-Santonja JJ, Rodríguez AE, Colom MF et al. Pyrenochaeta keratinophila sp. Nov., isolated from an ocular infection in Spain. Rev Iberoam Micol. 2010;27:22-4.
13. Khan Z, Ahmad S, Kapila K, Ramaswamy NV, Alath P, Joseph L et al. *Pyrenochaeta romeroi*: a causative agent of phaeohyphomycotic cyst. J Med Microbiol 2011;60:842-6.