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Int J Case Rep Images 2018;9:100930Z01AJ2018.
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A case of subcutaneous phaeohyphomycosis in a cardiac transplant patient

Anil Kumar Jonnalagadda, Maria Rodrigo, Farooq Sheikh, Mark Hofmeyer, Selma Mohammed, Samer Najjar

ABSTRACT

Introduction: Phaeohyphomycosis is a rare mycotic infection, affecting mainly the immunocompromised patients. It has wide clinical spectrum, ranging from subcutaneous cyst to life threatening cerebral abscess. Case Report: A 63-year-old female presented with asymptomatic swelling on the left middle finger that evolved one year after the cardiac transplantation. The diagnosis was based on the histopathological examination and culture of the skin lesion. The pathogen was confirmed as Exophiala species. The patient was successfully treated with surgical resection and oral voriconazole. Conclusion: Asymptomatic swellings in transplant patients should be evaluated carefully to prevent life threatening complications.

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Received: 26 May 2018
Accepted: 18 June 2018
Published: 05 July 2018

Keywords: Exophiala, Pheaeohyphomycosis, Transplant

How to cite this article

Jonnalagadda AK, Rodrigo M, Sheikh F, Hofmeyer M, Mohammed S, Najjar S. A case of subcutaneous phaeohyphomycosis in a cardiac transplant patient. Int J Case Rep Images 2018;9:100930Z01AJ2018.

Article ID: 100930Z01AJ2018

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doi: 10.5348/100930Z01AJ2018CR

INTRODUCTION

Phaeohyphomycosis (PHM) is a chronic mycotic infection caused by a group of black-colored fungi called "Dematiaceous Fungi" first described in 1947 [1–3]. It commonly occurs in immunocompromised patients like transplant recipients or human immunodeficiency virus (HIV) patients, patients with breast cancer, or other chronic illnesses [1, 4, 5]. Severo et al., [6] reported that solid organ transplantation is the most common risk factor for PHM (38.8%). The incidence of such infections is increasing along with the growing number of transplant recipients and widespread use of immunosuppressive medications [7–10]. Exophiala species are the most common causative organisms of the skin, and subcutaneous PHM in transplant patients [11–13]. Exophiala species are the most common causative organisms of the skin, and subcutaneous PHM in transplant patients [11–13]. Herein, we present a case of Exophiala-associated PHM in a cardiac transplant recipient.

CASE REPORT

A 63-year-old female heart transplant recipient presented to the transplant clinic, with swelling of the left middle finger that evolved one year after the transplant. The swelling worsened over the past month, with no associated pain, tenderness, fever, or chills. She denied any history of trauma at the site of the swelling. She was on tacrolimus, mycophenolate and prednisone for immunosuppression. Physical examination revealed a 4 cm mass along the left middle metacarpophalangeal joint, extending to the dorsum of the hand. There were no notable systemic signs of infection.

An X-ray scan showed a soft tissue mass along the left third metacarpophalangeal joint. Computed tomography (CT) showed a multilobulated mass proximal to the third metacarpophalangeal joint (MCP), closely attached to the tendons as shown in Figure 1 (A and B). Giant cell tumor was suspected, and the patient was referred to the orthopedic clinic. Fluid aspiration was performed, revealing a purulent material. She was admitted to hospital for further evaluation. Incision of the swelling revealed a large brown-tan colored cyst attached to the tendon. Debridement was done as much as possible without damaging tendons/nerves. The specimen was sent for culture, and vancomycin (1 gm iv daily) was started emperically. Three days later, preliminary culture results reported yeast infection. Vancomycin was stopped and Amphotericin B (320 mg iv daily) was started. The patient developed acute kidney injury due to Amphotericin B and was switched to voriconazole (loading dose of 300 mgiv twice daily for one week, followed by 200mg oral twice daily). Direct microscopic examination revealed brown-colored hyphae among a multinucleated giant cell infiltration as shown in Figure 2(A–C), and the diagnosis of Phaeohyphomycosis was made. Subsequent fungal cultures grew Exophiala species. Chest CT and brain Magnetic resonance imaging (MRI) showed no evidence of systemic infection. The patient underwent a radical synovectomy and amputation of the left third digit. Subsequent re-exploration of the wound was performed a week later; no abnormality was found, only minor swelling was found along ulnar surface of the left index finger, for which she underwent incision and drainage. Unfortunately, repeat cultures also grew Exophiala species; however, as the site was debrided well, conservative management with oral voriconazole was continued. MRI of hand three months post-debridement did not show any evidence of recurrence. She was closely followed through the Infectious Disease and Orthopedic clinics every three months. The patient successfully completed a one year course with voriconazole. No evidence of recurrence was found, during a follow-up visit 1 month after completion of the voriconazole.

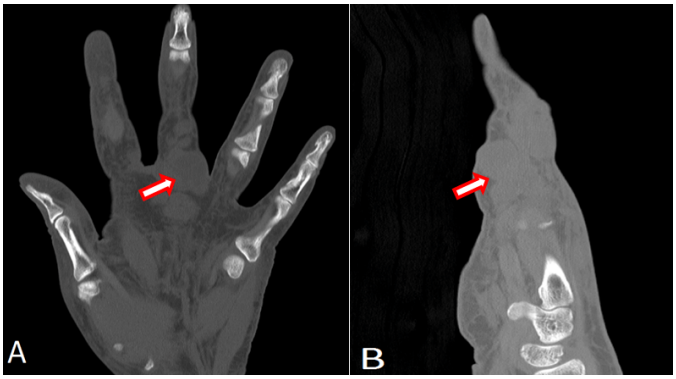

Figure 1(A and B): Coronal (A) and sagittal (B) views of CT of hand showing hypodense deposition around third metacarpophalangeal joint (arrows).

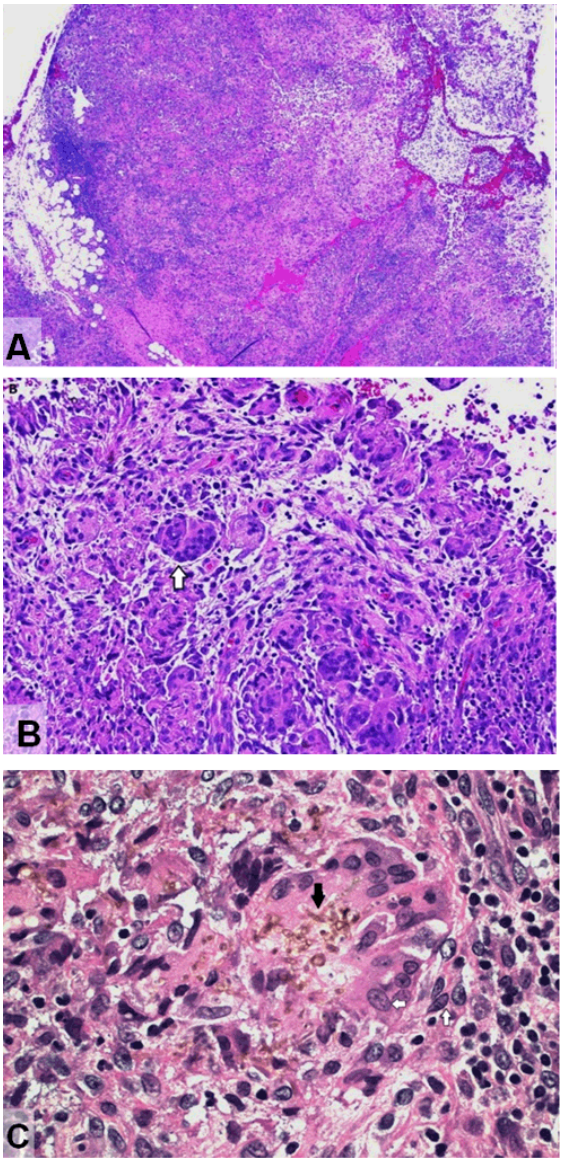

Figure 2(A–C): (A) Hematoxylin and Eosin (H&E) staining shows infiltration of inflammatory cells such as lymphocytes, and neutrophils. (B) Histopathological examination of Hematoxylin and Eosine (H&E) stain shows granulomas with multinucleated giant cells (white arrow). (C) Showed multinucleated giant cell infiltration (white arrows), Brown spindle-shaped hyphae are seen inside the giant cells (black arrow).

DISCUSSION

PHM is a rare cutaneous disease, caused by dematiaceous fungi [1, 8]. It is more prevalent in tropical and sub-tropical regions, and is classified into four main categories, depending on the distribution of the disease: superficial, cutaneous, subcutaneous, and systemic infection [1, 2, 14]. Clinical symptoms include subcutaneous nodules, cysts, and abscesses [1, 12]. Claudia et al. [2] reported that the skin is the organ most commonly affected by PHM, and 9% of transplant patients experience such infections within few years after the transplant. Schieffelin et al. [14] conducted a retrospective study between 1928 and 2008 of 3441 patients who received transplants, and 27 were proven to have PHM, 9% of them underwent cardiac transplant surgery, the average time between the surgery and PHM was 20 months. Exophiala PHM is mostly seen in immunocompromised patients such as those post-transplant, or with HIV, diabetes, cancer [1, 4]. Exophiala species are saprobes, widely distributed in soil, wood, and plants [1]. Infection with this organism can usually be traced to a traumatic inoculation. The injury may be as simple as a splinter or a prick from a thorn, and it may have occurred months or years before the lesion appears. Our patient doesn't remember any trauma at site of swelling. Other methods of inoculation include contaminated wounds, inhalation of spores, contagious spread and hematogenous dissemination. Lymph node involvement or dissemination is rare. Cases of PHM involving eyes, paranasal sinuses, joints, lungs, liver and brain were reported. Cerebral PHM is very rare but has poor prognosis with survival rates at two years being less than fifty percent [15]. Most common presentation of exophiala species is slowly enlarging cutaneous and subcutaneous nodules that may be confused with ganglion cysts, epidermal inclusion cysts, or foreign body granulomas [16].

Diagnosis is usually made through the direct microscopy and culture [10, 13]. Microscopic examination shows infiltration of inflammatory cells such as leukocytes, lymphocytes, and multinucleated giant cells [1]. The diagnosis is confirmed in culture specimens by the visualization of dark-walled hyphae or pseudo-hyphae [10]. Arakaki et al. [12] mentioned that CT and non-invasive ultrasonography may also serve as a good diagnostic tool.

At present, there are no clinical trials to guide the management of phaeohyphomycosis due to rarity of this condition. Most data come from isolated case reports and small series. The accepted treatment of choice is surgical excision. In addition, antifungal therapy is recommended for recurrent cases and for immunocompromised patients, but there are no standards in terms of agents or duration of therapy. In vitro, the most effective agents are itraconazole, voriconazole, and amphotericin B. Fluconazole is ineffective, and ketoconazole is associated with side effects. Usual duration of treatment is anywhere between 6 months to 2 years [10, 16].

Reviewing the literature, 12 case reports of PHM in cardiac transplant patients were identified, 11 of which identified Exophiala as the causative species as shown in Table 1 [2, 7, 10, 11, 17–22]. The symptoms described in those cases included subcutaneous nodules and swellings on the extremities. Most of the cases improved upon surgical removal alone or in combination with antifungal drugs. In a few cases, the symptoms relapsed, requiring long-term antifungal medications or further surgical resection.

Table 1: Summary of the findings of published case reports about subcutaneous phaeohyphomycosis in cardiac transplant patients.

Cases	Age(yr)/ sex	Time from transplant to infection	Immuno-suppressive Regimen	Clinical Presentation	Causative Organism	Treatment	Follow up
McGinnis et al. [17]	34/F	6 years	N/A	Painful and erythematous subcutaneous nodules on leg	Exserohilum rostratum	Amphotericin B and Ketoconazole	Cure with the surgical resection with no further follow up.
Sudduth et al. [18]	44/M	22 months	prednisone (20 mg/day) + azathioprine (125 mg/day) + cyclosporine (50 mg twice/day)	Swelling on the ulnar side of the right forearm, erythema to the elbow, and low grade fever	Exophiala-jeanselmei	Incision and drainage + amphotericin B + fluocytosine (1 g) for 6 wks.	No relapse (6 months)
Gold et al. [19]	61/F	3 years	prednisone (10 mg/day) + cyclosporine	Three nodules on the fingers, one on the lateral aspect of the 2nd digit, and other two on the dorsal and medial sides of the 2nd digit	Exophiala-jeanselmei	Surgical excision	No relapse (9 months)

Table 1: *(Continued)*

Cases	Age(yr)/ sex	Time from transplant to infection	Immuno-suppressive Regimen	Clinical Presentation	Causative Organism	Treatment	Follow up
Claudia et al. [2]	64/F	9 months	Prednisone + mycophenolate mofetil + cyclosporine	Nodule on the right elbow	Exophiala species	Surgery	No recurrence (2 years)
Claudia et al. [2]	43/M	16 months	Prednisone + mycophenolate mofetil + tacrolimus	Erythematous plaques on right leg and left hand	Exophiala species	Surgical removal + itraconazole	No recurrence (2 years)
Claudia et al. [2]	42/M	11 months	Prednisone + mycophenolate mofetil + tacrolimus	Tumor on left leg	Exophiala species	Surgical removal + itraconazole (200 mg twice daily for 4 months)	No recurrence (2 years)
Claudia et al. [2]	43/M	2 years	Prednisone + mycophenolate mofetil + cyclosporine	Nodule on left knee	Exophiala species	Surgical excision + itraconazole (200 mg twice daily for 2 months)	No recurrence (2 years)
Liou et al. [7]	62/M	10 months	Cyclosporine + Prednisolone + azathioprine	Plaque on the dorsum of the right hand	Exophiala-jeanselmei	Surgery + itraconazole	No relapse (3 years)
Agger et al. [11]	45/F	N/A	Tacrolimus 5 mg + prednisone, 0.25 mg	Pustule on the 2nd toe of the right foot	Exophiala-jeanselmei	Surgical removal + itraconazole for 4 weeks, followed by amphotericin B + fluorocytosine	Disease progression Itraconazole was maintained for 17 months, then treatment changed to terbinafine for 10 months — no recurrence.
Ronan et al. [20]	64/M	N/A	N/A	Cystic nodule on the left hand	Exophiala-jeanselmei	N/A	N/A
Silva et al. [21]	48/M	N/A	Mycophenolate 3 mg/d + tacrolimus 5 mg/d + prednisone 20 mg/d	Nodular lesion on right lower legs, progressed to ulcers	Exophiala-jeanselmei	Oral itraconazole 200 mg for 3 months then combined with amphotericin B for 4 months	Better Progress with amphotericin B (4 months)
De monbrison et al. [22]	65/F	N/A	Azathioprine 100 mg + prednisone 5 mg + cyclosporine 75 mg	Ulcer on the base of left index	Exophiala-jeanselmei	Surgical excision	Relapse after 15 months, retreated with re-excision with no recurrence for 6 years
Our case	63/F	1 year	Tacrolimus, Cellcept, and prednisone	-Swollen left middle finger - Swelling in left index finger	Exophiala species	Surgical synovectomy and amputation of the left middle digit, and oral voriconazole	no recurrence

N/A: not available, M: Male, F: Female.

CONCLUSION

Although rare, subcutaneous phaeohyphomycosis can spread to brain, especially in immunosuppressed patients and it is a life-threatening condition. Our case signifies that even asymptomatic swellings in transplant patients should be evaluated with great care to prevent life threatening complications.

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Author Contributions

Anil Kumar Jonnalagadda – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Maria Rodrigo – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Farooq Sheikh – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Mark Hofmeyer – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising

it critically for important intellectual content, Final approval of the version to be published
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Samer Najjar – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission
The corresponding author is the guarantor of submission.

Source of Support
None

Consent Statement
Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest
Authors declare no conflict of interest.

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