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Onset of disseminated cutaneous nodules following toe amputation in heart transplant patient

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Abstract

Alternaria spp. infections are rare, but organ transplant recipients and immunosuppressed patients are particularly at risk of developing cutaneous alternariosis. Although cutaneous alternariosis is well-defined, instances of disseminated infection are exceedingly rare. We report a case of disseminated *Alternaria* infection in an immunocompromised patient from a primary focus of unguis phaeohyphomycosis.

Keywords: alternariosis, disseminated mycosis

Introduction

Alternaria species are plant pathogens that are associated with infections by dematiaceous fungi (phaeohyphomycosis), [3]. We recently encountered a heart transplant patient with disseminated phaeohyphomycosis caused by *Alternaria alternata*. *Alternaria* spp. infections are rare, but immunosuppressed patients are at risk for cutaneous alternariosis, usually following a traumatic inoculation [1-5]. Prolonged corticosteroid treatment is a specific risk factor and the resulting skin fragility may play a role in predisposing patients to inoculation [2, 4, 5]. Disseminated disease can manifest as cutaneous papules or nodules with or without ulceration [5].

Case Synopsis

A 64-year-old woman with history of non-ischemic cardiomyopathy status post heart transplant ten

months prior to admission was admitted with neutropenic fever. During her admission, she developed multiple tender nodules on the right and left proximal arms and right distal leg. Her antirejection medications included mycophenolate mofetil, prednisone, and tacrolimus. Additional medical history included end-stage renal disease requiring hemodialysis, *Clostridium difficile* colitis, recurrent urinary tract infections, amputation of the left finger eight months prior, and amputation of two toes three weeks prior.

Six weeks before dermatologic consultation, the patient was admitted with urinary tract infection, *Clostridium difficile* colitis, and non-ambulatory status secondary to painful necrotic ulcerations confined to the toes of her right and left feet. Three weeks into her hospital stay, the decision to perform partial right hallux and left third toe amputation was made owing to "excessive granulation tissue" in an attempt to improve the patient's ambulatory status and quality of life. Pathology reports from the amputations showed pseudoepitheliomatous epidermal hyperplasia overlying suppurative granulomatous inflammation. No special stains were obtained and infection was not mentioned in the report.

On subsequent admission with neutropenic fever (three weeks following the amputations), the patient developed cutaneous nodules on the legs and arms and dermatology consultation was requested. Physical examination revealed a crusted sessile nodule of the right distal leg, crusted erythematous nodules, plaques, and palpable subcutaneous nodules of the proximal arms (**Figure 1A**). Portions

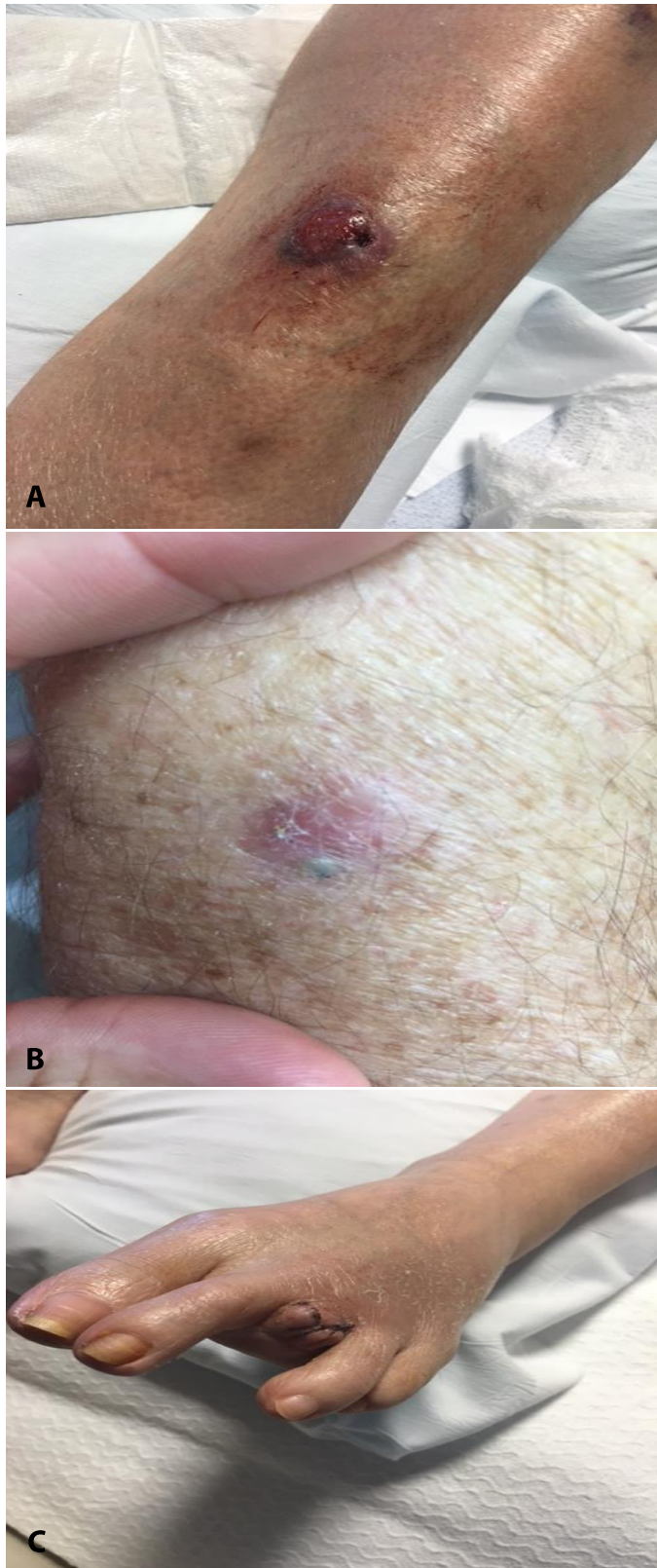


Figure 1. Clinical images. **A)** Erythematous crusted plaque and nodules of right upper arm. **B)** Nodule on the left upper arm. Note the area of pigmentation at the inferior aspect. **C)** Complete amputation of third toe on left foot.

of the nodules were pigmented (**Figure 1B**). Amputation sites appeared well-healed (**Figure 1C**).

Biopsies from the cutaneous nodules were obtained for histology and for fungal, bacterial, and mycobacterial tissue cultures. The biopsies revealed suppurative granulomatous inflammation and multinucleate histiocytes containing many fungal forms (**Figure 2A, B**). Mycobacterial and bacterial tissue cultures were negative, as were blood and sputum cultures. Chest X-ray was within normal limits. *Aspergillus* galactomannan and (1,3)- β -D-glucan assays were negative. Fungal tissue culture grew *Alternaria alternata*. Subsequent review of the patient's previous pathology from the amputated toes revealed numerous fungal hyphae (**Figures 2C, D**). The patient was treated with posaconazole 300mg daily for six months for disseminated *Alternaria alternata* infection and remains disease free one year later.

Case Discussion

We report a case of disseminated *Alternaria* infection in an immunocompromised patient. We postulate dissemination of *Alternaria* from a primary focus of unguis phaeohyphomycosis given the number and distribution of cutaneous and subcutaneous lesions observed three weeks following partial right hallux and left third toe amputations. Pathology from the amputated toes was reviewed and demonstrated numerous fungal hyphae.

It is well known that *Alternaria alternata* is a pigment-producing fungus that has been implicated in the development of fungal melanonychia. Although cutaneous alternariosis is well-defined, occurrences are rare and instances of disseminated infection are exceedingly rare [3, 5, 6]. Among these are two reports of simultaneous involvement of skin and nails in immunosuppressed patients [1, 6]. Organ transplant and immunosuppression are considered significant risk factors for the development of alternariosis infection (**Table 1**).

Treatment of systemic *alternaria* infection requires systemic antifungal agents. Posaconazole has been shown to effectively treat cases of cutaneous

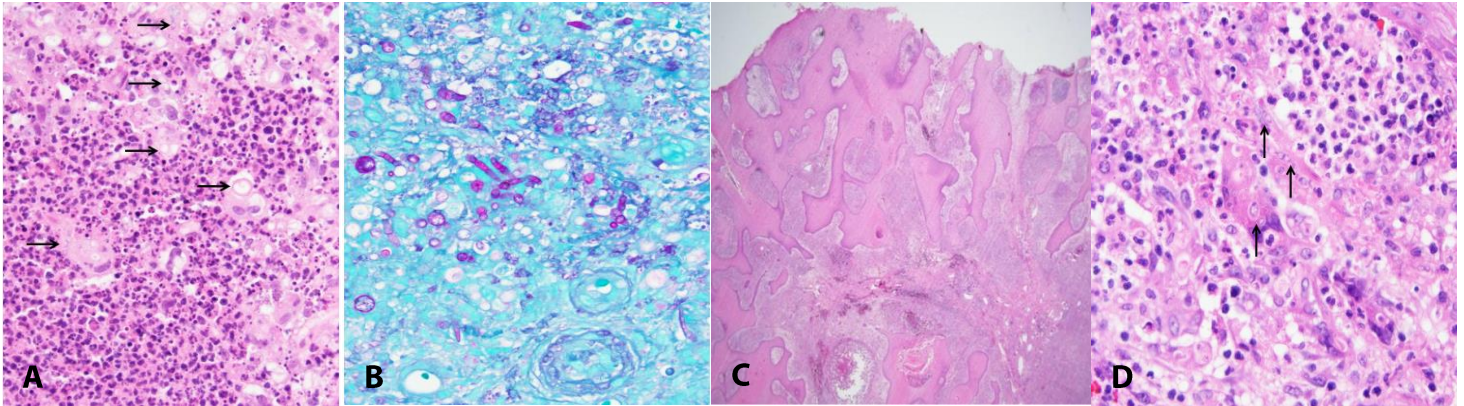


Figure 2. Histopathology. **A)** Suppurative granulomatous inflammation and multinucleate histiocytes. H&E, 200 \times . **B)** H&E (200 \times) PAS highlights many fungal forms. **C)** Toe amputation showing pseudoepitheliomatous hyperplasia. H&E, 40 \times . **D)** Higher power (400 \times) demonstrating numerous fungal forms.

alternariosis and was utilized effectively in our patient [1].

Conclusion

Our case highlights the potential significance of saprophytic unguinal infections in immunosuppressed

patients. Timely and appropriate therapy may prevent disseminated mycosis.

Potential conflicts of interest

The authors declare no conflicts of interests.

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Table 1. Clinical Features of Cutaneous Alternariosis in Transplant Recipients.

Reported By	Age/ Sex	Transplant Type	Immunosuppressive Treatment/ Duration	Lesion/location/ time of evolution	Systemic Involvement	Culture	Treatment	Outcome
Margheim, et al. (our case)	64/F	Heart	Mycophenolate mofetil, prednisone, tacrolimus/10 months	Nodule/right distal leg; nodules, plaques/proximal arms	No	<i>Alternaria alternata</i>	Posaconazole 300mg/d x 6 months	Disease free one year later
Bajwa et al. [1]	56/M	Pancreatic	Tacrolimus 5 mg/d, mycophenolate mofetil 540mg/12h, prednisone 5 mg/d/5 months	Onychomycosis of the toenails/nodules in bilateral lower extremities/3 weeks	No	<i>Alternaria spp</i>	Posaconazole 200mg TID	Complete resolution by 14 weeks; died 18 months after diagnosis of cutaneous alternariosis due to unrelated causes
Brás et al. [2]	65/M	Liver	Tacrolimus 8mg/d, mycophenolate mofetil 500mg/12h, prednisone 20mg/d/6 months	Nodule/dorsal left hand; nodule/right leg/4 months	No	<i>Alternaria infectoria and Alternaria alternata</i>	Lesions excised followed by Itraconazole 100mg/d x 3 months with adjustment of immunosuppressants	No relapse 5 months after surgery
Gilaberte et al. [3]	27/M	Lung	Methylprednisolone 8 mg/d, tacrolimus 6 mg/d/2 years	Papule, nodule/thighs, leg, arm/3 weeks	No	<i>Alternaria infectoria</i>	Amphotericin B + flucytosine x 1 month; surgery + terbinafine 250mg/d x 6 months	Without lesions; 1.5 years of follow-up; no relapse
Gilaberte et al. [3]	48/M	Liver	Prednisone, cyclosporine, azathioprine/11 months	Papules/left leg	No	<i>Alternaria alternata</i>	Itraconazole 100mg/d x 4 months	Without lesions; died of acute pancreatitis
Gilaberte et al. [3]	66/M	Heart	Prednisone, tacrolimus, azathioprine/2 years	Papules, nodule/lower extremities/2 months (previous trauma)	No	<i>Alternaria infectoria</i>	Itraconazole 200-400mg/d x 8 months; terbinafine 250mg/d x 3 months	Without lesions; 5 months of follow-up; no relapse
Gilaberte et al. [3]	65/M	Kidney	Azathioprine 125 mg/d, prednisolone 30mg/8h/4 years	Cellulitis, ulcers/left leg/1 month	No	<i>Alternaria spp</i>	Amphotericin B liposomal 3 mg/Kg/d x 7d	Died of heart failure
Gilaberte et al. [3]	67/M	Kidney	Prednisone 20mg/d, cyclosporine 0.8	Plaque/right thigh/1.5 years	No	<i>Alternaria spp</i>	Fluconazole 100mg/d x 7 months po;	Improvement. no follow-up

			cc/12h, azathioprine 75 mg/d/2 years	(previous trauma)			fluconazole intralesional	
Gilaberte et al. [3]	63/M	Heart	Cyclosporine 200mg/d, azathioprine 100mg/d, prednisone 10mg/d/2 month	Plaques, papules/lower extremities/2 months	No	<i>Alternaria spp</i>	Fluconazole 100mg/d × 5 months po	Without lesions; 2 months of follow-up; no relapse
Gilaberte et al. [3]	53/M	Kidney	No data available	Plaque/left buttock/1 month	No	<i>Alternaria spp</i>	Itraconazole 200mg/d × 3 months	No data available
Gilaberte et al. [3]	55/M	Kidney	Prednisone 5 mg/d, tacrolimus 500mg/d, mycophenolate mofetil 500mg/d/6 months	Plaque/right knee/4 months	No	<i>Alternaria alternata</i>	Local heat	Without lesions; 1 year of follow-up; no relapse
Gilaberte et al. [3]	67/F	Liver	Tacrolimus, prednisone/11 years	Plaques/foot/2 months	No	<i>Alternaria spp</i>	Terbinafine 100mg/d × 2 months + itraconazole 200mg/d × 2 months	Without lesions
Pastor, et al. [5]	53.9 median age; M>F (64.9% vs. 35.1%)	47/51 cases: solid organ transplant; 4/51 cases: bone marrow transplant	Unspecified regimens for transplant group	Ranging from: erythema, desquamation of skin, red papules that developed to erosion and ulceration, red plaques with central ulceration; multilocular form of disease with papulonodular lesions or cutaneous nodules associated with disseminated alternariosis	No	<i>Alternaria spp</i>	Various antifungals, with Itraconazole used most often	No data available
Baykal, et al. [6]	52/F	Kidney	Cyclosporine A, Methylprednisolone/5 years	Plaque/right hand; + subungual hyperkeratosis, dystrophy, and	No	<i>Alternaria spp</i>	Itraconazole 100mg × 30 days	No improvement; surgical excision planned, but

				discoloration of the nail plate				patient died from acute pancreatitis and disseminated intravascular coagulation 2 months later
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