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Journal

Dermatology Online Journal, 20(7)

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Publication Date

2014

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Case Presentation

Multifocal cutaneous alternariosis in a 70-year-old Kenyan renal transplant patient

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Dermatology Online Journal 20 (7): 11

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Abstract

Alternaria species are a group of dematiaceous fungi that are ubiquitous in nature and are becoming an increasingly important cause of disease in immunocompromised patients. We present a case of a 70 year old renal transplant recipient with multiple areas of cutaneous Alternaria infections likely introduced during local trauma. Treatment has required a combination of systemic therapy and surgical excision. This case illustrates the importance of recognizing fungal infections with cutaneous manifestations, such as alternariosis, in immunosuppressed patients.

Keywords: Alternaria, cutaneous alternariosis, phaeohyphomycosis

Introduction

Immunosuppressive treatment is necessary in transplant recipients to prevent graft rejection but also makes these patients vulnerable to a variety of complications including cutaneous diseases [1, 2]. Among cutaneous manifestations of immunosuppression, infections are among the most common [1-3]. The risk of opportunistic infections is generally higher in the first one to six months after organ transplantation. Beyond 6 months post-transplantation, infections with opportunistic organisms become less common, except for those with a strong environmental exposure [4].

Alternariosis is an uncommon cause of infection overall, but is becoming an increasingly important cause of infections in immunocompromised patients [5-7]. Often presenting with cutaneous involvement, the clinical appearance can be subtle and varied. Clinical diagnosis can be challenging and often requires biopsy and/or culture for confirmation. No treatment guidelines currently exist and may consist of oral antifungal therapy, surgical intervention, or a combination of both.

Case synopsis

A 70-year-old man with a history of renal transplantation in 2009 presented with nodules on the extremities, first noted while visiting his native country, Kenya, 6 months earlier. During his stay, he enjoyed gardening and recalled sustaining scratches and

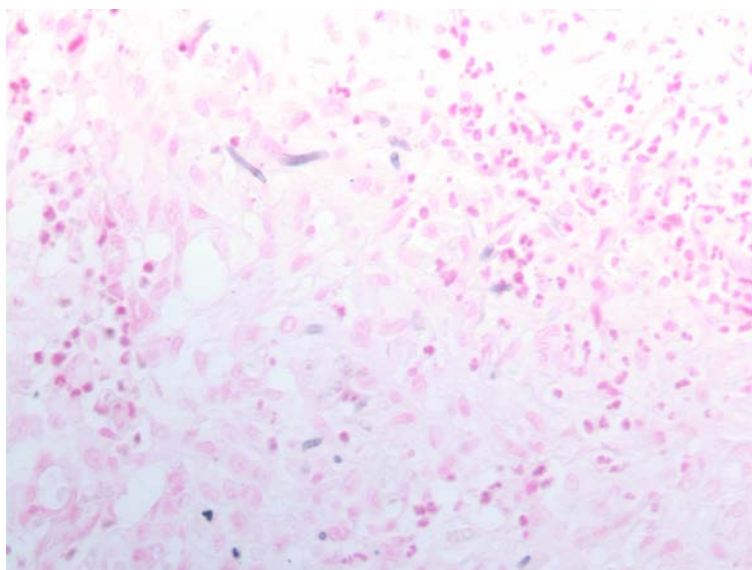
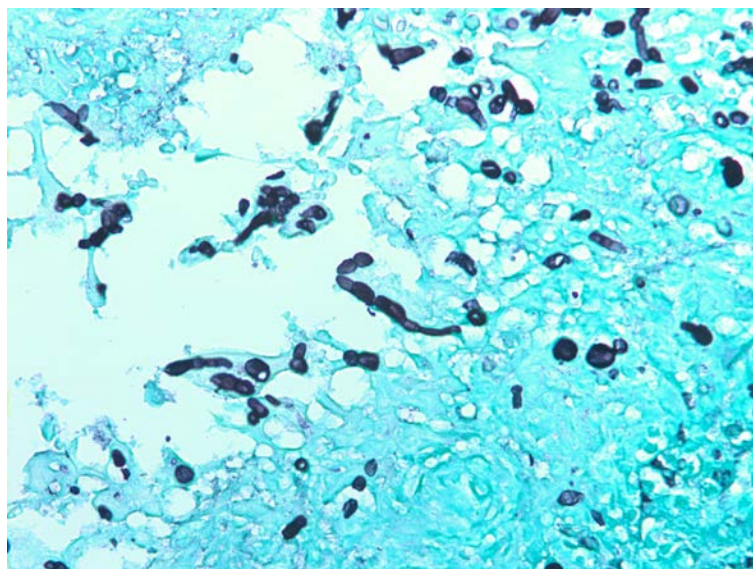
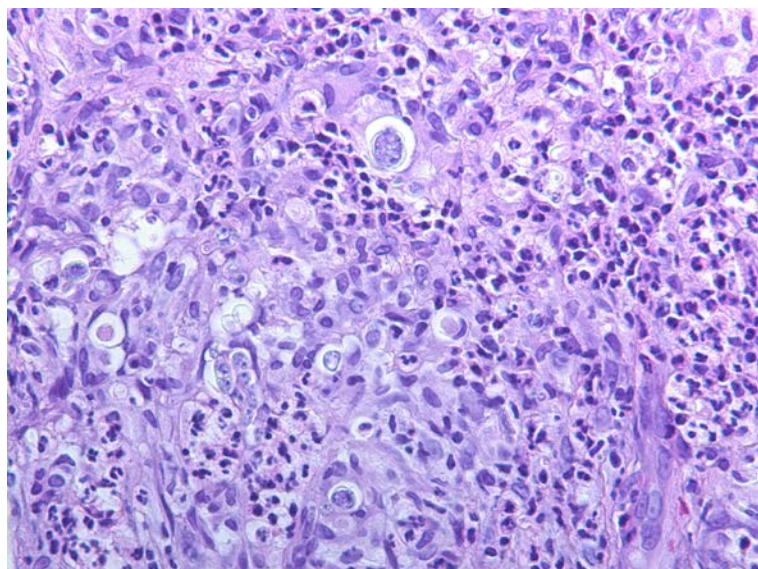
puncture wounds on the extremities from his bougainvillea plants. The lesions began as small cracks in the skin that subsequently enlarged; a few of them ulcerated. He experienced occasional pruritus and discomfort and was able to express some purulent material. Overall, he had been feeling well and denied systemic complaints. His immunosuppressive regimen initially included mycophenolate mofetil 500mg twice daily, tacrolimus 4 mg in the morning and 3 mg in the evening, and prednisone 5 mg daily. Other significant past medical history included insulin-dependent diabetes mellitus. He had no known history of opportunistic infections.

Physical examination revealed multiple firm papules, plaques, and nodules of various sizes over the dorsal aspects of his upper extremities, right lower leg, and right medial plantar arch. Some of them were keloidal, some ulcerated, and one had a verrucous surface (Figures 1a and 1b). Punch biopsies were performed for routine histopathologic analysis and staining (Figure 2).



Figures 1a and b. Keloidal and verrucous plaques

Histological examination demonstrated nodular granulomatous and suppurative inflammation throughout a sclerotic dermis with yeast-like and septated hyphal fungal organisms highlighted by Gomori's methenamine silver (GMS) stain (Figures 2a and 2b). Fontana Masson stain showed scattered positivity indicating melanin production within the fungal cell walls consistent with phaeohyphomycosis (Figure 2c). Tissue culture grew *Alternaria* species.



Figures 2a. yeast-like fungi, **b.** Gomori's methenamine silver (GMS) stain demonstrating septated hyphae, and **c.** Fontana Masson stain shows scattered positivity indicating melanin production within the fungal cell walls.

Treatment

The patient was seen by the infectious disease consultants. Based on minimum inhibitory concentrations and susceptibilities of the *Alternaria* cultures, itraconazole was deemed most appropriate and was initiated at 200mg twice daily. Blood levels of itraconazole were monitored routinely. To reduce immunosuppression and adjust for drug interactions, the patient's tacrolimus dose was decreased, his mycophenolate mofetil was discontinued, and prednisone was continued at the same dose. After eight months of treatment, the itraconazole dose was increased to 300mg twice daily to maintain a therapeutic level. The patient did show some modest improvement in clinical appearance and symptoms as well as a subjective decrease in drainage. Two of the larger nodules eventually required surgical intervention. They were excised with 2 mm margins; the wounds were slow to heal but remained free of clinical signs of infection (Figure 3) at 3 and 6 months of follow-up, respectively. A verrucous plaque on the right fifth digit was debulked through shave biopsy. This was also slow to heal, but has shown significant improvement (Figure 4). Although most of the remaining lesions have become smaller since initiation of systemic antifungal therapy, some, including one on the right instep, continue to be problematic for the patient. However, after 15 months of therapy, the patient showed no obvious signs of active infection and the itraconazole was subsequently discontinued.



Figure 3. Left dorsal hand following surgical excision.



Figure 4. Right fifth digit following debulking by shave biopsy.

Discussion

General

Alternaria species, an uncommon cause of infection, belong to the group of dematiaceous fungi that produce melanin pigment within the cell wall and are ubiquitous in nature. An uncommon cause of infection overall, the incidence of *Alternaria* infection appears to be increasing [8], mostly in immunosuppressed patients [5-7].

Clinical Presentation

Dematiaceous fungi are capable of causing a wide range of disease manifestations, including skin and subcutaneous infections, sinusitis, pulmonary disease, central nervous system involvement, and more widespread disease [8]. Among *Alternaria* infections, cutaneous and subcutaneous manifestations are most common and typically occur without signs of systemic involvement [5-7, 9]. Clinically, lesions are typically solitary, but can grouped or even multifocal, as in our patient. Lesions can vary in appearance and include plaques, nodules, pustules, or ulcerations [5, 10], which often occur on exposed areas of skin and limbs in association with previous trauma [7, 8, 10, 11].

Our patient's immunosuppressive regimen most likely played a role in his infection. Tacrolimus, a calcineurin inhibitor, has effects on cell-mediated immunity by inhibiting activated T cells and the expression of pro-inflammatory cytokines [12]. Long term corticosteroid treatment is also thought to play a more direct role in the inoculation process owing to its effect on skin integrity [13]. In our patient, nearly all of his lesions occurred on exposed areas of skin and all were associated with an injury. Inoculation likely occurred during gardening.

Though far outweighed by their immunosuppressive actions, tacrolimus and mycophenolate mofetil also have inherent antifungal activity. They work through inhibition of homologous targets in fungi. Additionally, the combination of immunosuppressants coupled with the antifungals may display synergistic activity against fungal pathogens [14].

Treatment

There is no standard treatment regimen for cutaneous alternariosis. Treatment generally consists of systemic antifungal therapy, surgical excision, or both [5, 6, 9]. There are also case reports of Mohs micrographic surgery (alone and in combination with systemic therapy) used to treat localized cutaneous alternariosis [15, 16]. In one case series, systemic therapy alone was not sufficient and additional surgical treatment was necessary [5]. In another series of 9 transplant recipients with cutaneous alternariosis, treatments were started empirically and included itraconazole (as in our patient), amphotericin B with or without fluocytosin, fluconazole, or terbinafine. Three patients failed initial treatment and required subsequent systemic antifungal medication, surgery, or a combination [10]. Voriconazole has also been shown to be efficacious in cutaneous *Alternaria* infections after treatment failure with itraconazole and amphotericin B [17]. Drug susceptibilities of the organism, if available, can help guide treatment choices, as with our patient. It may also be necessary to adjust immunosuppressive medications, both to allow for healing and to accommodate drug interactions.

When prescribing azole antifungal medications to transplant patients, one must consider potential drug interactions with their immunosuppressive regimen. Itraconazole is a P450 CYP 3A inhibitor and therefore leads to increased levels of tacrolimus, which is metabolized by the CYP3A system when the drugs are given in combination. This increases the risk of toxicity [18]. A study of 40 lung transplant recipients treated with tacrolimus and itraconazole compared tacrolimus doses during treatment with tacrolimus alone and in combination with itraconazole. When itraconazole was discontinued, the patients required 76% higher daily average tacrolimus doses to maintain target blood levels of tacrolimus at the levels achieved when the drugs were taken concurrently [19].

For our patient, we have been able to observe two different treatment approaches simultaneously, systemic therapy alone and in combination with surgery, given that this patient has multiple lesions and not all of them are amenable to surgery. The lesions treated with systemic itraconazole alone have significantly improved and the areas of surgical excisions show well-healed scars without clinical signs of infection.

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