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Cutaneous alternariosis in a renal transplant patient successfully treated with posaconazole: Case report and literature review

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ABSTRACT

Cutaneous alternariosis is an uncommon fungal infection that most commonly presents in organ transplant patients on immunosuppressive therapy. There are no clinical trials or guidelines to guide treatment of this condition, however itraconazole is the most commonly used antifungal in published cases. Here we report on a case of cutaneous alternariosis in a renal transplant recipient treated with a newer antifungal, posaconazole. A review of published reports of cutaneous alternariosis since 2008 is also discussed.

1. Introduction

Skin lesions are common in organ transplant recipients who are on immunosuppressive therapy. Almost all cases require a biopsy to confirm the etiology, as there are a variety of infectious and non-infectious causes of the skin lesions in this patient population. We recently saw a pancreatic-renal transplant patient who presented with cutaneous alternariosis. Infection with *Alternaria* spp. is relatively uncommon and has been primarily described in case reports and small case series, with the last major review reported in 2008 [1]. Therefore, in this report we summarize the clinical findings from reports since 2008. Further, there are no randomized trials that address treatment of cutaneous alternariosis. Although itraconazole has been used most commonly, there have been case reports of failure or relapse with that agent [2]. Newer antifungal agents have started to gain popularity in treating cutaneous alternariosis [3–6], including our case which was successfully treated with posaconazole.

2. Case

A 56 year old male with end stage renal disease secondary to type 1 diabetes mellitus (DM) and history of renal and pancreatic transplant presented to the clinic (day 0) with complaints of multiple non-pruritic lesions on his lower extremities. The patient stated that he first noticed the lesion three weeks prior to presentation as a single lesion on his left ankle with then progressed and spread to both lower extremities. The patient had undergone a cadaveric renal and pancreatic transplant five months prior to presentation. The transplanted kidney underwent acute rejection and was removed four months prior to presentation, necessitating reinstitution of hemodialysis. He was continued on his immunosuppressive therapy because of well-functioning pancreatic transplant. His immunosuppressive regimen included tacrolimus 2 mg in morning and 3 mg in evening, mycophenolate mofetil 540 mg twice daily and prednisone 5 mg daily. He was also on trimethoprim-sulfamethoxazole double-strength tablet three times a week as prophylaxis against opportunistic infections. Other medications included metoprolol for hypertension and erythropoietin injections for anemia.

On the day of presentation to the clinic, the patient's physical examination was only remarkable for onychomycosis involving the toenails and multiple nodular, violaceous mildly tender skin lesions on both lower extremities up to the level of his knees. Some of these lesions had scabs associated with them (Fig. 1). Laboratory findings on day 0 revealed a white blood cell count of 3600/mm^3 with a normal differential, a hemoglobin of 11.2 g/dL, a platelet count of 145,000/mm^3, a creatinine of 5.4 mg/dL, a blood urea nitrogen of 21.1 mg/dL, normal liver function tests, and an erythrocyte sedimentation rate of 26 mm/h. His HIV serology was negative. A chest X-ray revealed clear lung fields.

One of the lesions was biopsied and the histopathology revealed a few fungal hyphae. Routine, fungal and mycobacterial cultures were requested. Fungal culture grew *Alternaria* that was not speciated (Figs. 2 and 3). As there was no evidence of systemic infection, a diagnosis of cutaneous alternariosis was made on day 14, and antifungal treatment was initiated with posaconazole 200 mg three times a day. By week 6, follow up visit revealed significant improve-

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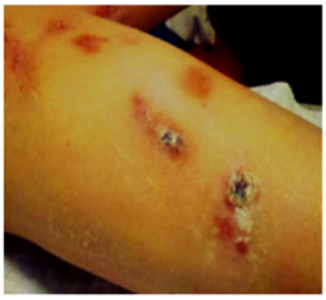

Fig. 1. Violaceous indurated nodules and ulcers on right lower extremity.

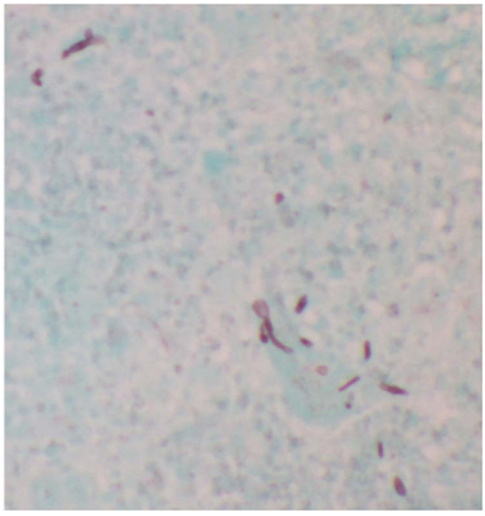

Fig. 2. Skin biopsy showing fungal hyphae with occasional branching (Gomori Methenamine stain, 200× original magnification).

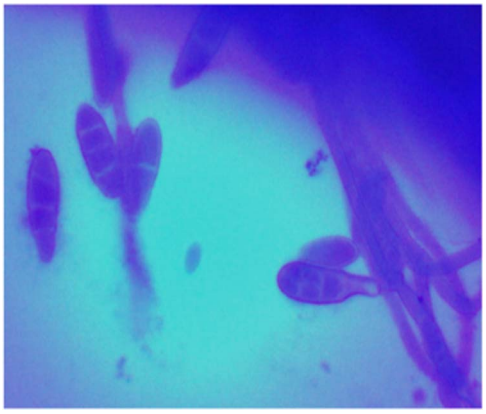

Fig. 3. Multicellular ovoid macroconidia arising on septate hyphae (Lactophenol Cotton Blue mount, 400× original magnification).

ment, with complete resolution by week 14. The patient was continued on posaconazole due to continued immunosuppression for the functioning pancreatic graft. The patient died 18 months after the diagnosis of cutaneous alternariosis because of unrelated causes without relapse of cutaneous fungal infection.

3. Discussion

Alternaria spp. are dematiaceous fungi, which are ubiquitous in nature. They infrequently cause human infection in immunocompetent patients [7]. However, as the number of immunocompromised patients has increased, so has the reported cases of alternariosis [8,9]. Since the first case report in 1933 [10], over 200 cases have been reported in the literature. Cutaneous infections represent the overwhelming majority of cases [1,11].

We have reviewed the literature published in English from 2008 to 2016 for case reports or case series on cutaneous alternariosis. Our search yielded 55 cases that are summarized in Table 1. This will supplement the comprehensive reviews of cases published by Lyke et al. in 2001 and Pastor and Guarro in 2008 [1,2]. In our review there are 15 females and 40 males with ages ranging from 13 to 85 years. Consistent with previous reports [1,2], cutaneous alternariosis of the extremities was the most common site of involvement.

3.1. Agent

The genus *Alternaria* is comprised of over 80 species. *A. alternata*, *A. infectoria*, *A. tenuissima* and *A. chartarum* cause the majority of infections. *Alternaria alternata* (59/156, 38%) followed by *A. tenuissima* (23/156, 15%) were the most frequent isolates described in a previous review (Pastor, 2008), however, in 55/156 (35%) cases a speciation was not performed. In our review of 55 cases since 2008, species determination was done in 36/55 (65%) cases with *Alternaria infectoria* implicated in 22/55 (40%) followed by *Alternaria alternata* in 11/55 (20%) and *Alternaria tenuissima* in 1/55 (1.8%) of cases, suggesting a possible shift in prevalence of each species over the past decade.

3.2. Risk factors

Most patients with cutaneous alternariosis have an immunocompromising condition, such as transplantation [12], collagen vascular disease (e.g. systemic lupus erythematous (SLE)) [13], hematological malignancy [2], endogenous hypercortisolism and diabetes [2,12]. Rare cases have been described in hosts with no known immunocompromising conditions [14].

In our review of cases from 2008 to present, 39/55 (71%) patients had an organ transplant and were on multiple immunosuppressive agents when lesion/lesions occurred, six (11%) patients had hematological malignancies, and several had other conditions affecting the immune system. In seven (13%) patients no obvious immunosuppression was noted. This is in contrast to cases earlier than 2008, where only 51 out of 156 (33%) cases had an organ transplant, potentially due to the increasing number of organ transplant patients living today leading to a greater percentage of infected patients falling into this category.

3.3. Mode of acquisition and clinical features

Alternaria spp. are ubiquitous in distribution and are common soil saprophytes. The mode of acquisition is not always established, although minor skin trauma and subsequent inoculation appears to be a plausible route of entry [15]. The most common presentation is skin lesions [1,11]. Cutaneous alternariosis exists in two forms: epidermal type or dermal type depending on the depth of fungal invasion. In both types, the lesion usually appears on the exposed sites such as the dorsum of hands, forearms, knees and legs. Scaly infiltrated erythematous or ulcerative are seen with the epidermal type. The dermal type has been described as plaques with papules, pustules, crusts, and with the surface being more or less granular and atrophic. In some cases, pain is associated with the lesions [16]. Less common clinical syndromes reported with alternariosis include allergic sinusitis, hypersensitivity pneumonitis, osteomyelitis, keratitis, endophthalmitis, rhinosinusitis, onychomycosis, and peritonitis [1,2,7,17].

3.4. Diagnosis

The establishment of *Alternaria* spp. infection requires demonstration of fungal tissue invasion or recovery of the fungi from a sterile site.