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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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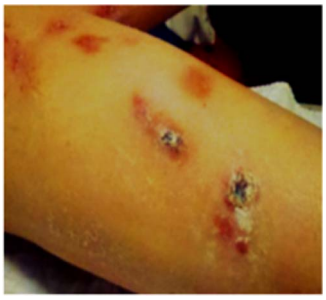

Fig. 1. Violaceous indurated nodules and ulcers on right lower extremity.

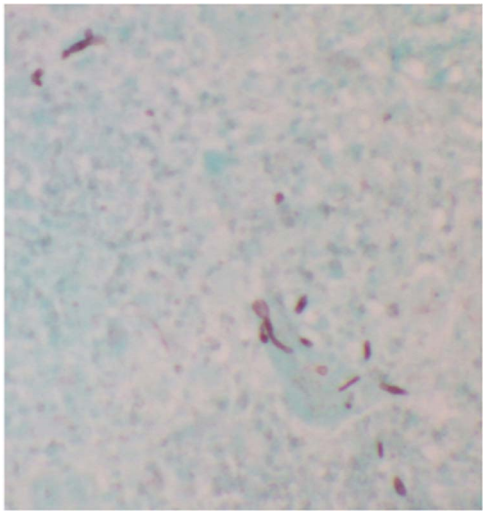

Fig. 2. Skin biopsy showing fungal hyphae with occasional branching (Gomori Methenamine stain, 200× original magnification).

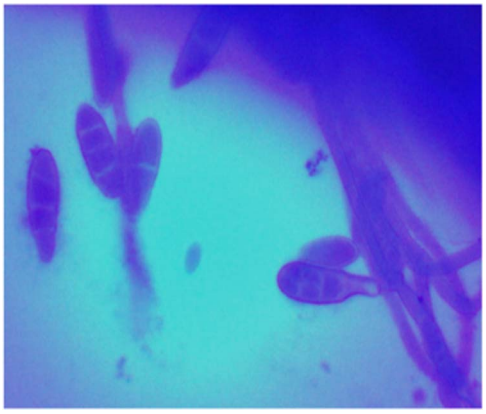

Fig. 3. Multicellular ovoid macroconidia arising on septate hyphae (Lactophenol Cotton Blue mount, 400× original magnification).

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.

Table 1
Published cases of cutaneous Alternariosis from 2008–2016.

Year	Author	Sex	Age	Underlying Condition[a]	Species	Primary Therapy[b]	Outcome for Primary therapy[c]
2008	C Williams [25]	M	85	None	*Alternaria spp.*	ITZ	Cure
2008	J Brasch [26]	M	68	Renal Tx	*Alternaria infectoria*	ITZ	Cure
2008	L Podda [27]	M	24	ALL	*Alternaria infectoria*	Vori	Cure
2008	G Calabro [28]	M	53	Renal Tx	*Alternaria alternata*	ITZ	Cure
2009	S Segner [29]	M	73	Renal Tx	*Alternaria infectoria*	ITZ	Improved
2010	RD Boyce [30]	F	45	Cardiac Tx	*Alternaria spp.*	Sx+CSP+ITZ	Failure
2010	RD Boyce [30]	M	62	Cardiac Tx	*Alternaria spp.*	Sx+Vori	Cure
2010	RD Boyce [30]	M	51	Renal & Pancreas Tx	*Alternaria spp.*	ITZ	Failure
2010	RD Boyce [30]	F	60	Lung & Renal Tx	*Alternaria spp.*	Sx+Vori	Improved
2010	RD Boyce [30]	M	41	Renal & Pancreas Tx	*Alternaria spp.*	Sx	Failure
2010	RD Boyce [30]	M	36	Renal Tx	*Alternaria spp.*	ITZ	Failure
2010	RD Boyce [30]	M	40	Renal & Pan Tx	*Alternaria spp.*	Sx+ITZ	Cure
2010	RD Boyce [30]	F	63	Pancreas Tx	*Alternaria spp.*	Sx+ITZ	Cure
2010	AM Morales [31]	M	63	Cardiac Tx	*Alternaria spp.*	Cryotherapy+ITZ	Cure
2010	F Santiago [32]	M	55	Renal Tx	*Alternaria alternata*	ITZ	Failure
2010	SEM Vermeire [21]	F	51	Renal Tx	*Alternaria alternata*	Sx+Vori	Cure
2010	TR Leahy [19]	F	14	AML	*Alternaria infectoria*	LamB+Vori	Cure
2010	M Yasui [33]	M	68	None	*Alternaria alternata*	Thermotherapy	Cure
2010	DR Matson [34]	M	17	None	*Alternaria spp.*	ITZ	Improved
2011	GW Osmond [35]	M	57	Cardiac Tx	*Alternaria spp.*	Sx+Vori	Improved
2011	DS Kpodzo [6]	M	58	CLL	*Alternaria alternata*	Sx+Posa	Cure
2012	T Robert [36]	F	73	DM	*Alternaria infectoria*	ITZ	Improved
2012	T Robert [36]	M	54	Renal Tx	*Alternaria infectoria*	FLU	Improved
2012	T Robert [36]	F	75	Renal Tx	*Alternaria infectoria*	Vori	Died of unrelated cause
2012	T Robert [36]	M	56	Cardiac & Lung Tx	*Alternaria infectoria*	Sx+Vori	Improved
2012	T Robert [36]	M	77	CMML	*Alternaria infectoria*	ITZ	Died of unrelated cause
2012	T Robert [36]	F	41	None	*Alternaria infectoria*	ITZ	Failure
2012	D Cunha [37]	M	53	Renal Tx	*Alternaria infectoria*	ITZ	Cure
2012	B Rammaert [38]	F	64	Cardiac Tx	*Alternaria infectoria*	ITZ	Failure
2012	D Tambasco [39]	F	64	Renal Tx	*Alternaria infectoria*	Terb	Cure
2012	RA Lavergne [40]	M	63	Cardiac Tx	*Alternaria alternata*	Vori	Improved
2012	L Rudnicka [41]	M	13	Alopecia areata	*Alternaria chlamydospora*	Unknown	Outcome not known
2012	VSM Saegeman [5]	F	52	Lung Tx	*Alternaria infectoria*	Sx+Vori	Improved
2012	F Seyfarth [42]	F	65	Renal Tx	*Alternaria infectoria*	Ciclo+Vori	Failure
2013	B Sharifkashani [43]	M	37	Heart Tx	*Alternaria spp.*	Vori	Cure
2013	L Lopes [4]	M	61	Renal Tx	*Alternaria infectoria*	ITZ	Cure
2013	L Lopes [4]	M	63	Renal Tx	*Alternaria infectoria*	Cryotherapy+Posa	Improved
2013	L Lopes [4]	M	56	Renal Tx	*Alternaria infectoria*	Sx+ITZ	Cure
2013	B Kleker [44]	M	55	ALL	*Alternaria alternata*	Vori	Failure
2013	N Alhmali [45]	F	65	Liver Tx	*Alternaria infectoria*	Ciclo+FLU	Cure
2013	C Dessinioti [46]	M	58	None	*Alternaria alternata*	BIF+ITZ	Failure
2013	Z Secnikova [3]	M	60	Heart Tx	*Alternaria alternata*	Sx+Vori	Improved
2013	MC Gonzalez-Vela [47]	M	60	Lung Tx	*Alternaria triticina*	ITZ	Improved
2014	N Essabbah [48]	F	33	Renal Tx	*Alternaria tenuissima*	decrease IS	Improved
2014	M Michelon [49]	M	70	Renal Tx	*Alternaria spp.*	ITZ	Improved
2014	E Coussens [50]	M	65	Liver Tx	*Alternaria infectoria*	FLU	Cure
2014	D Daglar [51]	M	33	Renal Tx	*Alternaria infectoria*	ITZ	Failure
2014	SH Sohng [52]	M	76	None	*Alternaria alternata*	KET	Improved
2015	M Demirci [53]	F	32	Renal Tx	*Alternaria spp.*	ITZ	Cure
2015	W Hu [54]	M	28	None	*Alternaria arborescens*	ITZ+LamB	Cure
2015	CC Hsu [55]	M	61	Renal Tx	*Alternaria spp.*	ITZ	Failure
2015	S Bras [56]	M	65	Liver Tx	*Alternaria alternata+Alternaria infectoria*	Sx+ITZ	Cure
2016	CL Simpson [57]	M	60's	Heart Tx	*Alternaria spp.*	ITZ	Failure
2016	RC Patel [58]	M	13	None	*Alternaria spp.*	econazole+ITZ	Cure
2016	C O'Meara [59]	M	80	MDS	*Alternaria spp.*	silver chloride gel	Cure

[a] ALL=acute lymphoblastic leukemia, AML=acute myelogenous leukemia, CLL=chronic lymphoid leukemia, CMML=chronic myelomonocytic leukemia, DM=diabetes mellitus, MDS=myelodysplastic syndrome, Tx=transplant.
[b] BIF=bifonazole, Ciclo=ciclopiroxolamine, CSP=caspofungin, FLU=fluconazole, IS=immunosuppressive therapy, ITZ=itraconazole, KET=ketoconazole, LamB=liposomal amphotericin B, Posa=posaconazole, Sx=surgery, Terb=terbinafine, Vori=voriconazole.
[c] Cure=complete resolution, Improved=Improvement but not complete resolution, Failure=worsening or no improvement.

This is important, as *Alternaria* spp. is ubiquitously present in the environment and thereby could contaminate the culture or could be colonizing, but not infecting, superficial tissue. *Alternaria* spp. usually, but not always, appear dark-walled on standard histopathologic stains. Cell wall melanin may be visible as a brownish-yellow color on hematoxylin-eosin (H & E) stain. If melanin is not evident on H & E stain, it can be identified using the Fontana-Masson method. However, culture is essential for the identification of *Alternaria* spp., since histologic findings are not pathognonic. Morphology of the conidia is used for speciation of *Alternaria spp*. However clinically important species often lose their ability to sporulate and, thus, cannot be identified by microscopic examination. For this reason, molecular techniques are increasingly used to identify *Alternaria spp* [1,18,19].

3.5. Treatment

There are no randomized controlled trials that have assessed the treatment of *Alternaria* spp. infections. In absence of any guidance

from controlled data, multiple therapeutic options have been used. Review of literature has identified itraconazole as the most commonly used antimicrobial. Outcomes appear to be satisfactory. Some series report its efficacy above 90% [2,17]. Doses ranging from 100 mg/day to 600 mg/day have been used, with the duration of therapy usually being in excess of two months. However, there have been reports of failure with itraconazole, even when in vitro data demonstrates susceptibility *in vitro* [2]. Voriconazole [19–21], fluconazole [22], Amphotericin B [16,19], and terbinafine [22] have been used in few cases. Surgery alone has been reported to be successful in the case of localized, superficial lesions [23,24].

In our review, itraconazole was used alone as primary therapy in 20 of 55 patients, with eight of these patients failing therapy and requiring use of additional agents. This 40% failure rate is much higher than previously reported, suggesting a possible increase in resistance to itraconazole [2,17]. The increase in reported failures may, however, be due to a reporting bias because unexpected failures are more likely to be reported than expected cures. In our series, initial combination therapy with itraconazole plus either surgery, cryotherapy, or another antifungal agent resulted in cure in seven of nine patients (78%). Initial use of other azole antifungals, either alone or in combination with other treatment modalities, had generally positive results. Voriconazole monotherapy or in combination with surgery or topical antifungals resulted in cure or improvement in 11 of 14 patients (79%). Fluconazole monotherapy or in combination with topical ciclopiroxolamine led to improvement or cure in all three reported cases. Posaconazole use was reported in two patients, in combination with either surgery or cryotherapy, and led to cure or improvement in both cases. Additionally, in two of the cases that saw initial improvement, but not cure, with voriconazole-based therapy, a change in antifungal to posaconazole yielded improvement in the skin lesions [3,5].

Cutaneous infection with *Alternaria* spp. is a well-described, though still relatively rare, complication in patients on immunosuppressive therapy due to solid organ transplant. Historically, itraconazole has been used most frequently to treat this infection. However it is not universally effective and it has certain disadvantages such as significant drug-drug interactions mediated by inhibition of cytochrome P450 enzymes. Posaconazole is another potential antifungal option that overcomes some of the disadvantages of itraconazole, particularly with regard to drug-drug interactions. Our case demonstrates that posaconazole can be used successfully as a first line treatment of cutaneous alternariosis, however additional clinical data are needed to determine the place in therapy for this agent.

Conflict of interest

There are none.

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