Transplant Infectious Disease . ISSN 1398-2273

Case report

A case of successful treatment of cutaneous *Acanthamoeba* infection in a lung transplant recipient

R. Walia, J.G. Montoya, G.S. Visvesvera, G.C. Booton, R.L. Doyle. A case of successful treatment of cutaneous *Acanthamoeba* infection in a lung transplant recipient.
Transpl Infect Dis 2007: **9:** 51–54. All rights reserved

Abstract: *Acanthamoeba* species are known to cause 2 well-described entities: (1) granulomatous amoebic encephalitis (GAE), which usually affects immunocompromised hosts, and (2) keratitis, which typically follows trauma associated with contamination of water or contact lenses. Less common manifestations include pneumonitis and a subacute granulomatous dermatitis. We describe a case of granulomatous dermatitis secondary to *Acanthamoeba* infection in a lung transplant recipient and a successful outcome following treatment with lipid formulation of amphotericin B and voriconazole. We believe this is the second case report describing disseminated *Acanthamoeba* infection in a lung transplant recipient. We also describe successful outcome with a combination of lipid formulation of amphotericin B and voriconazole, drugs that have not been previously reported to treat *Acanthamoeba*.

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Key words: *Acanthamoeba*; granulomatous dermatitis; lung transplant; amphotericin B; voriconazole

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Received 19 December 2005, revised 13 March 2006, accepted for publication 14 March 2006

DOI: 10.1111/j.1399-3062.2006.00159.x
Transpl Infect Dis 2007: **9:** 51–54

Case report

The patient is a 52-year-old woman with a history of single right lung transplant in 2001 for α-1-anti-trypsin deficiency. She had an uncomplicated course following her transplant, and her immunosuppressive regimen 3 years post transplant consisted of tacrolimus 1 mg twice daily (b.i.d.), mycophenolate 1000 mg b.i.d., and prednisone 6 mg b.i.d. In June 2004, she presented with multiple lesions predominantly on the lower extremity and scattered on the trunk. The lesions were comprised of tender, erythematous nodules ranging from 0.5 to 3.0 cm in diameter (Fig. 1). A review of systems was otherwise negative. Skin biopsy was performed, and pathology was consistent with *Acanthamoeba* infection and granulomatous dermatitis.

She was originally treated by a local physician with itraconazole and metronidazole for about 2 weeks. However, her lesions continued to progress with these oral antibiotics, and she was then transferred to Stanford University Hospital for further management. The lesions were biopsied again at our institution, as we did not have access to the original slides when the patient arrived and specimens were also sent to Centers for Disease Control & Prevention (CDC) in Atlanta. A magnetic resonance imaging (MRI) scan of the brain was performed and lumbar puncture was done to obtain cerebrospinal fluid (CSF). There was no evidence of central nervous system (CNS) involvement clinically or by MRI and CSF studies. MRI also did not show evidence of involvement of the paranasal sinuses. There was no evidence of pulmonary involvement by computed tomography (CT) scan of the chest. *Acanthamoeba* was identified in the skin biopsy section by hematoxylin and eosin (H&E) staining and by immunofluorescence test (Fig. 2). *Acanthamoeba* was also grown from the biopsied tissue and typed by polymerase chain reaction

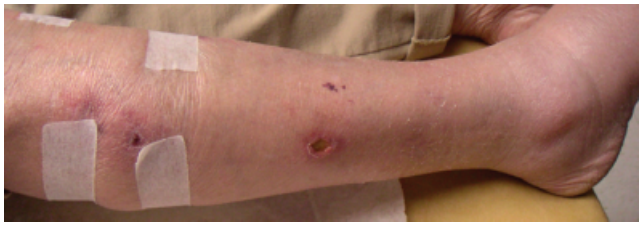

Fig. 1. Lower extremity lesions at the time of presentation.

(PCR) as *Acanthamoeba*, genotype T4, the most common genotype.

After consultation with the infectious disease service and CDC, she was started on intravenous amphotericin B lipid complex (ABLC) 7 mg/kg/day and intravenous voriconazole 6 mg/kg b.i.d. for the first 2 doses, followed by 4 mg/kg b.i.d. Within 1 week of this therapy, her symptoms began to improve. There was significant reduction in the tenderness and erythema around the lesions and no new lesions erupted on this regimen. She was then discharged to continue this regimen of ABLC and voriconazole in the ambulatory infusion unit.

A month later, she was noted to have a bacterial superinfection on one of her amebic skin lesions. She was given a course of dicloxacillin and ciprofloxacin for 2 weeks with resolution. Two months later, she was noted to have new lesions around some of the old *Acanthamoeba* lesions. These lesions were biopsied and the pathology showed a granulomatous dermatitis but no *Acanthamoeba* was recovered. Three months from her admission to our institution there was marked improvement of all of her skin lesions except one small ulcer at the posterior aspect of her right calf.

She was maintained on the regimen of daily intravenous ABLC and twice daily intravenous voriconazole for a total of 10 weeks. It was then decided to decrease her intravenous ABLC and voriconazole from every day infusions to 3 times a week and supplement the voriconazole by oral form 200 mg b.i.d. on other days. By this time, most of her amebic skin lesions had resolved; however, the small ulcer of the right calf started to have some purulent drainage. A repeat skin biopsy was obtained and pathology showed no evidence of *Acanthamoeba*. The culture from the skin biopsy grew group B β *Streptococcus*, coagulase-negative *Staphylococcus*, and diphtheroids. Although these organisms most likely represented skin colonization, it was decided to treat the patient with a 2-week course of dicloxacillin. Following this treatment, there was marked improvement in the appearance of the skin lesion. Her regimen of intravenous ABLC and voriconazole 3 times a week was maintained for a total of 4 weeks and then she was discharged home on oral voriconazole 200 mg b.i.d.

On follow-up 5 months from her presentation, she did not have any new skin lesions and the old lesions had healed well, with no further drainage (Fig. 3). She has been treated with oral voriconazole for 5 months after her discharge with complete recovery and the drug has been stopped with no recurrence.

In our patient, the most likely source of infection was water from a local creek. The patient was using the creek as the source of water for her domestic use.

Discussion

Acanthamoeba species have been isolated from almost every environmental niche in both cyst and trophozoite form. They are ubiquitous, free-living amoebae known to thrive in a variety of aquatic sources. In humans, the cysts are potentially infectious because of their ability to convert to trophozoites. However, only the trophozoites can invade tissue. Trophozoites convert to cyst under unfavorable conditions. Some of the organisms *Acanthamoeba* can be easily

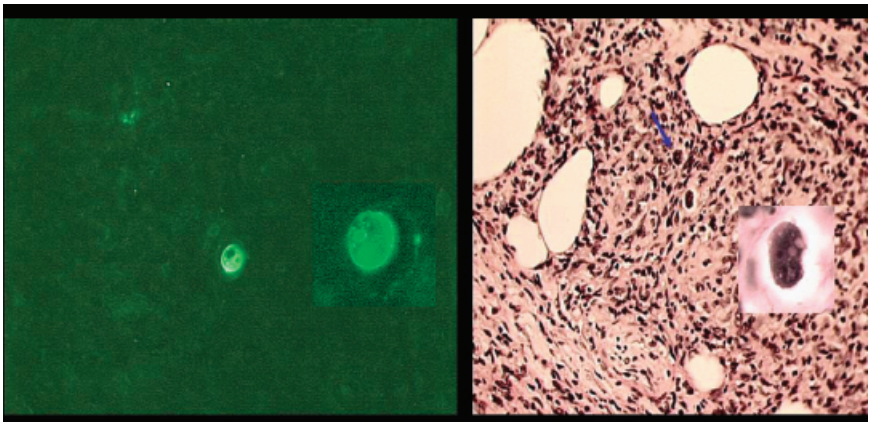

Fig. 2. *Acanthamoeba* trophozoites by immunofluorescence and staining. Left, immunofluorescence pattern of *Acanthamoeba* trophozoite in the patient's tissue section, × 100. Inset, a higher magnification of the amoeba, × 1000. Right, a tissue section with a single *Acanthamoeba* trophozoite (arrow). Hematoxylin and eosin (H&E), × 100. Inset, a higher magnification that shows the characteristic nuclear morphology of the trophozoite. H&E, × 1000.

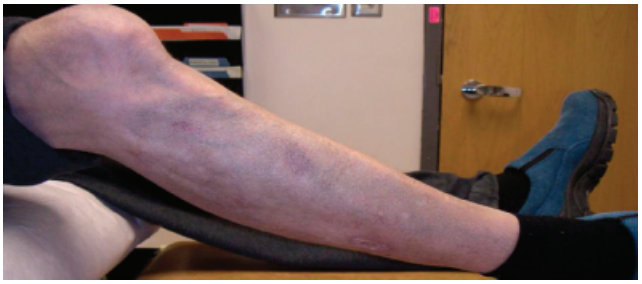

Fig. 3. Remarkable improvement in the lower extremity lesions 5 months after treatment.

confused with include *Rhinosporidium*, *Prototheca*, *Cryptoccoccus*, and *Blastomyces*.

Granulomatous amoebic encephalitis (GAE) is the most well described of the infections affecting humans (1, 2). It has mostly been described in immunocompromised patients. The sinuses and lungs are the primary sites from which *Acanthamoeba* can disseminate. The skin is also believed to be a portal of entry for *Acanthamoeba*. Skin involvement can precede GAE for several weeks to months. The infection usually starts as a single nodule or multiple nodules that enlarge, ulcerate, and spread over weeks to months and later involve the CNS. The skin lesions usually involve the face, trunk, and extremities. These lesions are typically 0.1–3.0 cm in diameter, nodular, papular, or pustular. They can be tender or nontender. Rare descriptions include foot ulcers, tumor-like mass, and paraumbilical patch. The skin infection may or may not disseminate. Disseminated acanthamoebiasis is almost universally fatal and successful outcome is most commonly described in patients with predominant mucocutaneous involvement. Early diagnosis and treatment of skin lesions is essential because of the fatal nature of disseminated disease. Our patient did not have evidence of dissemination outside the skin. An extensive discussion of the skin involvement in *Acanthamoeba* infection is provided in the article by Sison et al. (3).

Risk factors for *Acanthamoeba* skin infection include traumatized areas like surgical scars, concurrent varicella zoster lesions, bites (including human bites), and mechanical trauma. Differential diagnoses of *Acanthamoeba* skin infection include vasculitis, zygomycosis, dermatophytes, phaeohyphomycosis, and atypical mycobacterial infection. Entities that may be considered in other cases are cat-scratch disease, cryptococcal skin infection, and disseminated sporotrichosis.

The various modalities to diagnose *Acanthamoeba* skin infection include tissue histology, smears of tissue with Giemsa or trichrome staining, immunofluorescence with rabbit antisera, culture on non-nutrient agar plates seeded with *Escherichia coli*, or tissue culture. Monoclonal antibodies have been used to identify trophozoites in brain tissue. More recently, PCR has been used to identify the type of *Acanthamoeba*.

The optimal management of disseminated *Acanthamoeba* infections has not been determined. Even though amphotericin is ineffective *in vitro* (4), there are a few case reports describing its use with other agents to treat *Acanthamoeba* (5, 6). Ketoconazole, neomycin, and paromomycin have been found to be cysticidal *in vitro* (4). In a mouse model, rifampin has been found to be effective (7). Sulfadiazine has been found to be protective in experimentally infected mice (8). The susceptibility to 5-fluorocystosine has conflicting reports (9–11). Successful treatment with intravenous pentamidine and oral itraconazole in a patient with renal transplant has been described (12). A combination of fluconazole, sulfadiazine, and surgical excision was used successfully in a case of granulomatous encephalitis with a solitary brain lesion (1). A combination of flucytosine, pentamidine, fluconazole, sulfadiazine, macrolide antibiotic, and phenothiazines has been described to treat *Balamuthia* amoebic encephalitis (2). Sison et al. (3) have described treatment of disseminated cutaneous *Acanthamoeba* infection in an AIDS patient with ketoconazole and 5-fluorocytosine. Oliva et al. (13) described a successful treatment of disseminated cutaneous acanthamoebiasis in a lung transplant recipient with pentamidine, 5-fluorocytosine, itraconazole, and topical chlorhexidine gluconate/ketoconazole cream. A summary of the above information is provided in Table 1.

Several unique features distinguish our case from those in the current literature. First, the *Acanthamoeba* was diagnosed relatively easily on the first skin biopsy. Often, multiple biopsies and samples are necessary. A big contributing factor was review by an experienced pathologist and early contact with the CDC. Second, we were successfully able to use voriconazole in combination with ABLC to treat the skin infection with complete resolution of lesions and prevent progression to multisystem or CNS involvement. We used ABLC along with voriconazole as consolidation therapy. We used this combination based on the documentation in the literature showing successful use of amphotericin and azoles in the treatment of *Acanthamoeba* infections in immunocompromised hosts. Third, we did not significantly modify the immunosuppressive regimen of the patient and were able to achieve a successful outcome. Voriconazole has significant interactions with calcineurin inhibitors and sirolimus, commonly used in the immunosuppression of lung transplant recipients. The dose of calcineurin inhibitors needs to be reduced in patients on voriconazole and similar trough levels can be obtained as before starting the antifungal agent. The only other case report of disseminated skin *Acanthamoeba* infection in a lung transplant recipient by Oliva et al. (13) had a successful outcome but it involved lowering their immunosuppression for the graft.

Summary of drug(s) effective against *Acanthamoeba*

Drug(s) used	Report type	References
Amphotericin B	Ineffective *in vitro*, successful use in clinical case reports	(4–6)
Ketoconazole, neomycin, paromomycin	Cysticidal *in vitro*	(4)
Rifampin	Mouse model	(7)
Sulfadiazine	Mouse model	(8)
5-flurocytosine	Conflicting reports	(9–11)
Intravenous pentamidine and oral itraconazole	Case report in a renal transplant patient	(12)
Fluconazole and sulfadiazine (along with surgery)	Case report in granulomatous encephalitis	(1)
Ketoconazole and 5-fluorocytosine	Case report of disseminated cutaneous infection in AIDS	(3)
Pentamidine and 5-fluorocytosine and itraconazole and topical chlorhexidine/ketoconazole	Case report of disseminated cutaneous infection in lung transplant patient	(13)

Table 1

Based on the experience of one of the authors of this article (G.S.V.), voriconazole appears to be active at 2.5 μg/mL. It completely inhibited the trophozoites (10^5/mL), however, it was not cidal, as the trophozoites survived 3 days after the drug was removed from the culture medium. Longer incubation time with the drug may be helpful.

We treated our patient with a prolonged course of intravenous therapy because of insurance reasons. Oral voriconazole is effectively absorbed and a shorter course of intravenous therapy was possible. However, in this case, it was more beneficial for the patient to receive intravenous therapy, as the cost of oral voriconazole was prohibitive for her.

We believe that voriconazole is a new addition to the treatment of *Acanthamoeba* infections. Given the rare nature of disease, a randomized controlled trial of treatment with ABLC along with voriconazole in this condition may not be possible; however, these drugs should be considered in patients with cutaneous *Acanthamoeba* as an alternative therapy.

Our case also highlights that the care of the transplant patient does not finish when the patient is discharged after transplantation. Not only airborne exposures have to be considered, but other activities that place the patient at risk (e.g., gardening) and untreated water exposures may increase the risk of protozoal and fungal infections. Proper evaluation of patient exposures can help avoid complications such as those described in this case.

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