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Acanthamoeba Endophthalmitis During Treatment for Cutaneous Disease in a Renal Transplant Patient

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Abstract

Acanthamoeba infections are difficult to diagnose and treat. We present a renal transplant patient who developed *Acanthamoeba* endophthalmitis on therapy with posaconazole and miltefosine for cutaneous acanthamobiasis. The patient was maintained on intracameral voriconazole injections, and oral azithromycin, fluconazole, and flucytosine. This case highlights novel presentations and treatments for *Acanthamoebic infection.*

Keywords

Acanthamoeba; endophthalmitis; amoebiasis; miltefosine; posaconazole

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DISCLAIMER

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1. INTRODUCTION

Acanthamoeba spp. are free-living protozoa that are ubiquitously present in the environment and can be pathogenic in humans. The life cycle consists of the active trophozoite stage and the quiescent cyst stage. Infections due to *Acanthamoeba* are rare, but it is an increasingly recognized pathogen, largely because of the AIDS epidemic [1] and recurring keratitis outbreaks[2]. Transmission is thought to be via inhalation of cysts or primary cutaneous inoculation. Infection can be classified in two main categories: local corneal infection in immunocompetent contact lens wearers and and disseminated infection in immunocompromised hosts. These patients manifest with cutaneous lesions, rhinosinusitis, urethritis, and fatal granulomatous encephalitis [3]. In addition to its association with AIDS, disseminated *Acanthamoeba* infection has been reported in patients with heart [4,5], renal [6,7] and lung transplantation, as well as chronic lymphocytic leukemia [8]. Interestingly, there are few reports of intra-ocular involvement of *Acanthamoeba* in immunocompromised patients. We present a case of *Acanthamoeba* endophthalmitis in a patient with recent renal transplantation.

2. CASE REPORT

A 59 year old Jamaican woman presented to dermatology clinic with diffuse painful dermal and subcutaneous nodules four months after undergoing living related donor renal transplantation. There was indolent progression of the lesions with associated night sweats for two months before evaluation. At the time of presentation, her immunosuppression regimen consisted of prednisone, tacrolimus and mycophenolate mofetil. Physical exam revealed an acral distribution of numerous tender, erythematous, ulcerative papulonodules at various stages of evolution. Her last travel outside of the United States was to Jamaica two years before presentation; potential exposures included contact with manure while gardening on a regular basis. Her donor was asymptomatic.

She was empirically treated with doxycycline for presumed bacterial infection. Two biopsies taken from representative lesions revealed dense, diffuse neutrophil-rich dermatitis. Gram, Periodic acid-Schiff (PAS), Gomori methenamine silver (GMS) and Fite stains were negative for bacteria, fungi and mycobacteria, respectively. Bacterial tissue culture grew methicillin-resistant *Staphylococcus aureus* (MRSA) and *Stenotrophomonas maltophilia*; fungal and mycobacterial tissue cultures were negative. Serum beta-D-glucan and galactomannan were also negative.

Lesions became progressively more painful over the course of a week (Figure 1a). She was referred for hospitalization and consultation with Infectious Diseases. Clindamycin replaced doxycycline, with little improvement. Repeat biopsy revealed suppurative granulomatous dermatitis with tissue degeneration; Gram, PAS, GMS and Fite stains were again negative. While repeat biopsies suggested a non-infectious neutrophilic dermatosis, her clinical findings were not congruent with this pathology. Furthermore, her lack of bacteremia, as well as her failure to clinically improve on anti-MRSA therapy, suggested a persistent infectious etiology with an atypical pathogen. Clindamycin was discontinued and posaconazole was initiated for empiric antifungal coverage. Given the indolent and

unremitting nature of the lesions, the patient's immune suppressed status, and our lack of definitive diagnosis, the biopsy specimen was sent to the Centers for Disease Control and Prevention (CDC) for more extensive microbial testing. *Acanthamoeba* was identified in the skin biopsy section by hematoxylin & eosin (H&E) and GMS staining (Figure 2a–d). Further directed testing revealed positive immunohistochemical staining with amoeba pooled antibody, *Acanthamoeba* species antibody (Figure 2e–f), and *Acanthamoeba* DNA on real-time PCR (polymerase chain reaction). In the interim, there was arrest of lesion formation with some resolution of existing lesions on posaconazole monotherapy. Once pathology results were confirmed by CDC, miltefosine was added to this regimen in consultation with CDC.

Before further evaluation, brain MRI was performed and was found to be normal. MRI of the sinuses were done on initial presentation as she had reported several months of right nasal congestion and nasal drip. Biopsy showed ulcerated squamous mucosa with acute on chronic inflammation, granulation tissue formation and prominent plasma cells, suggestive of reactive etiology.

After two months of posaconazole and a month of miltefosine, the patient continued to have slow clinical improvement in her cutaneous disease. However, during a routine dermatology visit she reported that she felt like she had "gravel" in her right eye. Of note, she was not a contact lens wearer. She was referred for evaluation by ophthalmology to rule out ocular *Acanthamoeba* involvement. Physical examination of the right eye was significant for 3+ inferonasal injection with nodularity and scleral thinning (Fgure 1b). The cornea was clear without infiltrate and with white endothelial plaque and dusting of white blood cells inferiorly. Anterior chamber on the right showed 2 to 3+ cells, very stagnant with 4+ flare, representing inflammation in the anterior chamber. Vitreous fluid was noted to be normal. Cultures were taken but were not diagnostic, and specialized cultures for *Acanthamoeba* were not performed.. The patient did have visual deficits and was started on voriconazole subconjunctival and intracameral injections. She was referred to a corneal specialist for further diagnostic and therapeutic recommendations given the real possibility of loss of vision in the right eye. After this evaluation, a three week trial of sulfadiazine 1.5 g every 8 hours was initiated in hope of improved penetration to the vitreous. Anterior chamber tap performed by a uveitis specialist was performed four months after initial diagnosis, and real-time PCR of the sample was positive for *Acanthamoeba*.

The patient continued with once to twice weekly intracameral and subconjunctival injections of voriconazole and dexamethasone. Due to anemia on sulfadiazine, she was switched to an oral regimen of fluconazole 600 mg daily, flucytosine 1500 mg every 8 hours, and azithromycin 500 mg daily, based on a weight of 60 kg and serum creatinine of 0.9–1.0 mg/dL, There was a flare of the uveitis and scleritis which appeared to worsen with lowering of the mycophenylate mofetil and prednisone doses, that improved slightly when doses were increased Trimethoprim/sulfamethoxazole was not used because of concern for nephrotoxicity. Ocular inflammation was worse on flucytosine every 8 hours and improved when increased to every 6 hours. She has now undergone almost a year of intracameral and subconjunctival therapy with some preservation of vision. She remains on systemic therapy with improvement of skin lesions (Fgure 1c) although the eye remains inflamed (Figure 1d).

3. DISCUSSION

Cutaneous lesions are the most frequent sign of disseminated acanthamobiasis and are seen in up to 90% of patients with disseminated disease [1]. Skin involvement may be the only disease manifestation or it may precede visceral involvement by weeks to months [1,9]. A predominantly acral distribution of lesions has been previously reported; the predilection for acral sites remains unexplained [6,9]. Skin infection most commonly manifests as ulceronecrotic papulonodules, though lesions are polymorphous and have presented as indurated papules and plaques [9,10], deep dermal and subcutaneous nodules [1,9], panniculitis, non-healing ulcers and intramuscular abscesses [1]. No cutaneous finding is pathognomonic, and the differential diagnosis for immuncompromised hosts often includes other inflammatory an infectious dermatoses including furunculosis, neutrophilic dermatoses, deep fungal and atypical mycobacterial infection.

Cutaneous acanthamobiasis histologic findings are variable: predominantly neutrophilic infiltrates (as seen in our patient), mixed inflammatory infiltrate, leukocytoclastic necrotizing vasculitis, panniculitis and abscess formation have all been documented [1,9]. In many reported cases of cutaneous acanthamobiasis, initial skin biopsies failed to identify the inconspicuous *Acanthamoeba* and only revealed variable degrees of inflammation. While both the cyst and trophozoite stage of *Acanthamoeba* can be seen on H&E without special stains, there is a tendency to overlook their presence in tissue given their resemblance to histiocytes [1,6]. Importantly, the fact that the cyst cell wall often stain positively with PAS and GMS may lead to a misdiagnosis of fungal infection, if acanthamobiasis is not on the clinical differential diagnosis [1,6]. Additionally, many reported cases revealed negative tissue culture on initial workup, as seen in our patient [1,4,7,9].

Acanthamoeba endophthalmitis is a rarely reported entity, usually seen as a complication of keratitis [11]. To our knowledge, this is the first reported case of disseminated cutaneous acanthamebiasis complicated by endophthalmitis. There is no consensus regarding the first line antimicrobial therapy to treat acanthamoebiasis; treatment is largely tailored based on the outcome of empirical treatment related in published case-reports. However, there is agreement that multidrug therapy is more efficacious compared to monotherapy, given that most available therapeutics are amebastatic and not amebicidal [3]. Cutaneous lesions and disseminated infection have been treated with various combinations of amphotericin B, rifampin, 5-fluorocytosine, itraconazole, ketoconazole, fluconazole, voriconazole, metronidazole, azithromycin, pentamidine and miltefosine, with mixed results[5,12–14]. The current regimen includes drugs with known penetration into the aqueous humor, including azoles [15] and azithromycin[16]. Since CNS disease usually results from hematogenous spread from a primary pulmonary or cutaneous site, and is almost universally fatal, prevention of such spread is crucial to patient survival, and early and aggressive therapy is warranted.

This case highlights the importance of considering acanthamobiasis in immunocompromised patients with generalized ulceronodular cutaneous lesions. This case is also only the third case of the use of miltefosine in a solid organ transplant recipient; given overall efficacy a good tolerability, it may merit consideration as part of first-line therapy[5]. Prompt diagnosis requires a high index of suspicion; alerting the pathologist to the possibility of

acanthamobiasis will likely expedite diagnosis, obviate further workup, hasten administration of appropriate therapy, and possibly prevent CNS dissemination.

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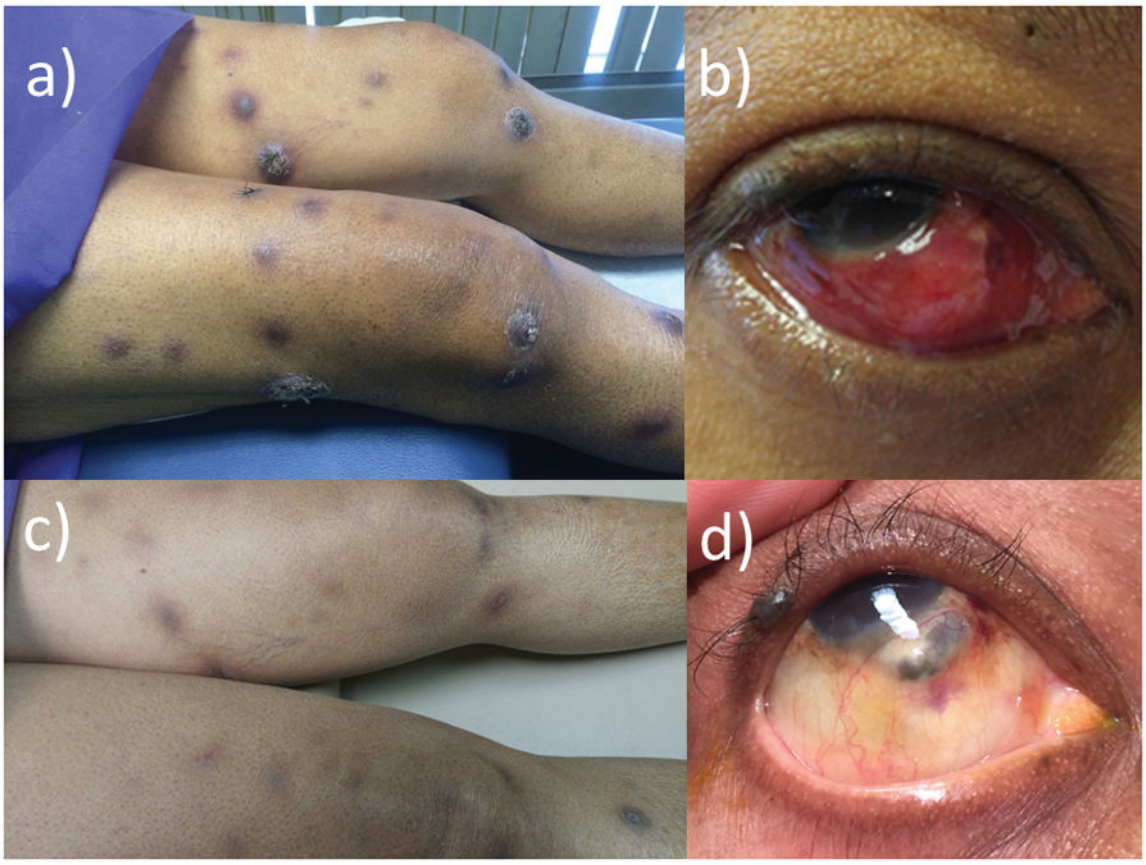

Figure 1.

(a) Initial presentation of *Acanthameoba* infection of the skin. (b) New right eye infection with *Acanthamoeba* after 2 months of therapy. (c) Improvement in skin nodules after 2 months of oral therapy. (d) Improvement in the right eye after a year of oral and intracameral therapy.

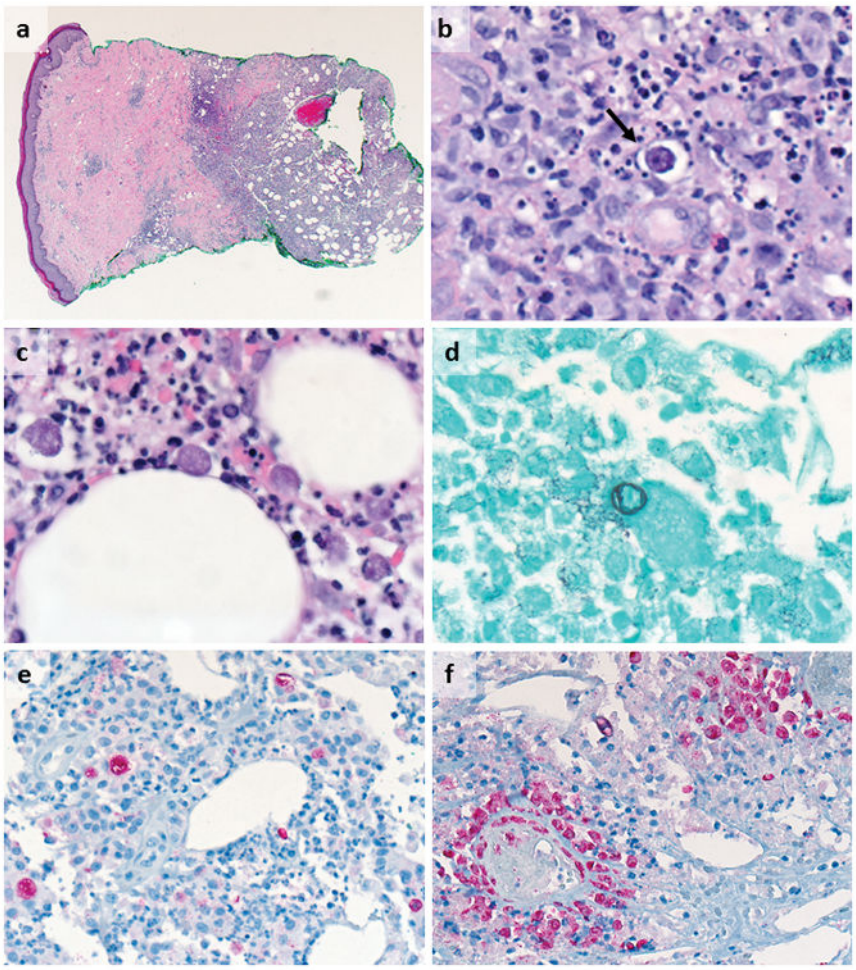

Figure 2.

(a) Photomicrograph of the skin lesion shows predominantly subcutaneous suppurative granulomatous dermatitis (H&E). (b) *Acanthamoeba* trophozoites (arrow) surrounded by neutrophilic and histiocytic infiltrate (H&E). (c) High magnification of trophozoites. (d) Cyst of *Acanthamoeba* species stained by GMS. (e) Immunohistochemistry staining shows *Acanthamoeba* species antigens in red stained trophozoites. (f) Abundant *Acanthamoeba* species antigens in trophozoites, blood vessels wall and macrophages.