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# A rare case of cutaneous acanthamoebiasis in a renal transplant patient

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## Abstract

A 35-year-old woman receiving immunosuppression for renal transplantation presented with a one-month history of tender skin nodules on her bilateral upper extremities. A skin biopsy revealed granulomatous inflammation in the deep dermis and the subcutaneous fat with foci of necrosis. Within the foci of necrosis were large histiocytoid structures with prominent nuclei. Periodic acid-Schiff stain revealed a round organism with a thick capsule, consistent with amoebal trophozoites. Testing with the Center for Disease Control revealed the organism to be *Acanthamoeba*. Despite antimicrobial therapy, the patient continued to develop subcutaneous nodules that extended to the lower extremities and trunk and ultimately extended to the bone, causing acanthamoebal osteomyelitis. Throughout the hospital course, the patient remained neurologically intact without evidence of central nervous involvement. A diagnosis of isolated disseminated cutaneous acanthamoebiasis secondary to iatrogenic immunosuppression was made. Historically, most cases of granulomatous amoebic encephalitis and cutaneous acanthamoebiasis have occurred in patients with HIV/AIDS. However, with the use of newer and more effective immunosuppressive regimens, both are occurring more frequently in the setting of iatrogenic immunosuppression. The rare and isolated cutaneous nature of this patient's presentation makes this case unique.

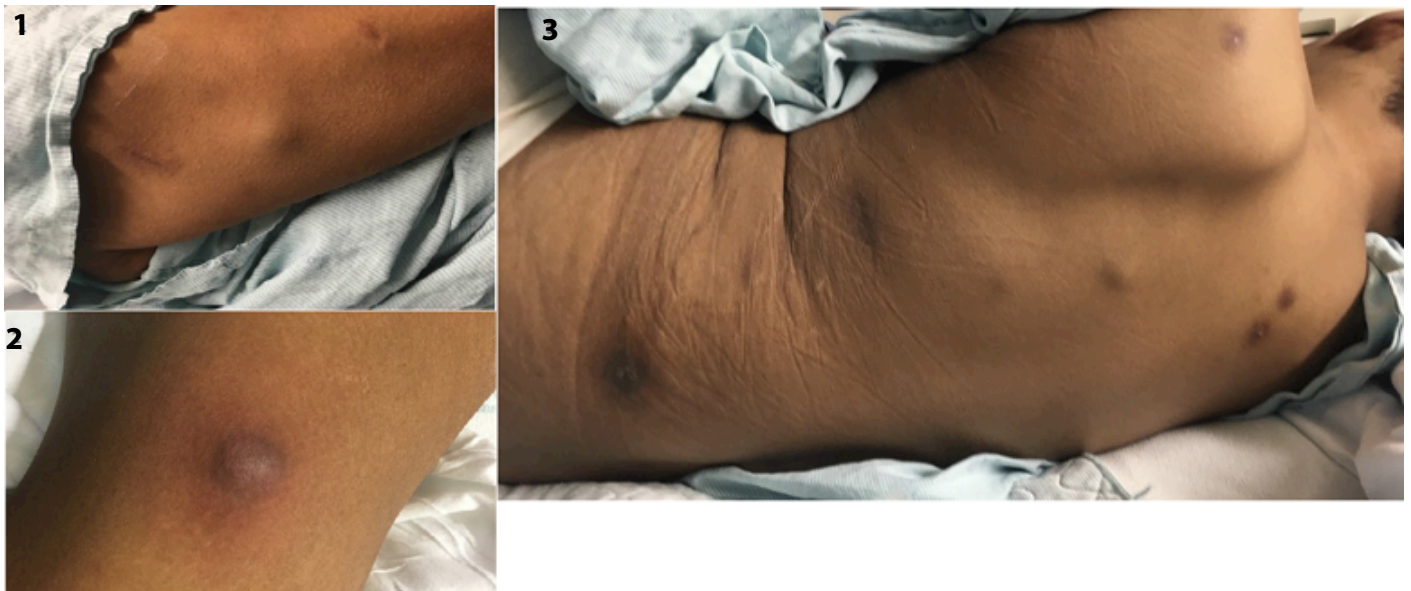
*Keywords: cutaneous acanthamoebiasis; free-living amoeba infection; acanthamoebic osteomyelitis; acanthamoeba*

## Introduction

*Acanthamoeba* is a free-living amoeba that is ubiquitous in nature and thrives in aquatic environments. It has been cultured from many freshwater sources, soils, swimming pools, and domestic water supplies, including tap water and air-conditioning units [1]. The organism has a life cycle with two stages: trophozoite, which predominates in favorable conditions, and cyst, which is dormant and resistant to environmental stress. There are two well-defined infections in humans known to be caused by *Acanthamoeba* species: amoebic keratitis and granulomatous amoebic encephalitis (GAE) [2]. Amoebic keratitis commonly occurs in immunocompetent patients who rinse their contact lenses in contaminated water. Granulomatous amoebic encephalitis is a slowly progressive, usually fatal meningoencephalitis that occurs in severely immunocompromised patients. A third more uncommon condition caused by *Acanthamoeba* is disseminated acanthamoebiasis, typically occurring in immunocompromised patients. Disseminated acanthamoebiasis can involve the skin, lung, and other visceral organs [2]. Cutaneous acanthamoebiasis has been best documented in HIV/AIDS patients, but is occurring less frequently in this setting owing to the increase in use of antiretroviral regimens [3]. Herein we describe a case of cutaneous acanthamoebiasis and amoebic osteomyelitis in a patient receiving iatrogenic immunosuppression following renal transplant.

## Case Synopsis

In August, 2015 a 35-year-old woman presented to our dermatology clinic complaining of a four-week history of painful nodules on her bilateral upper extremities, face, and back (**Figure 1**, **Figure 2**, and

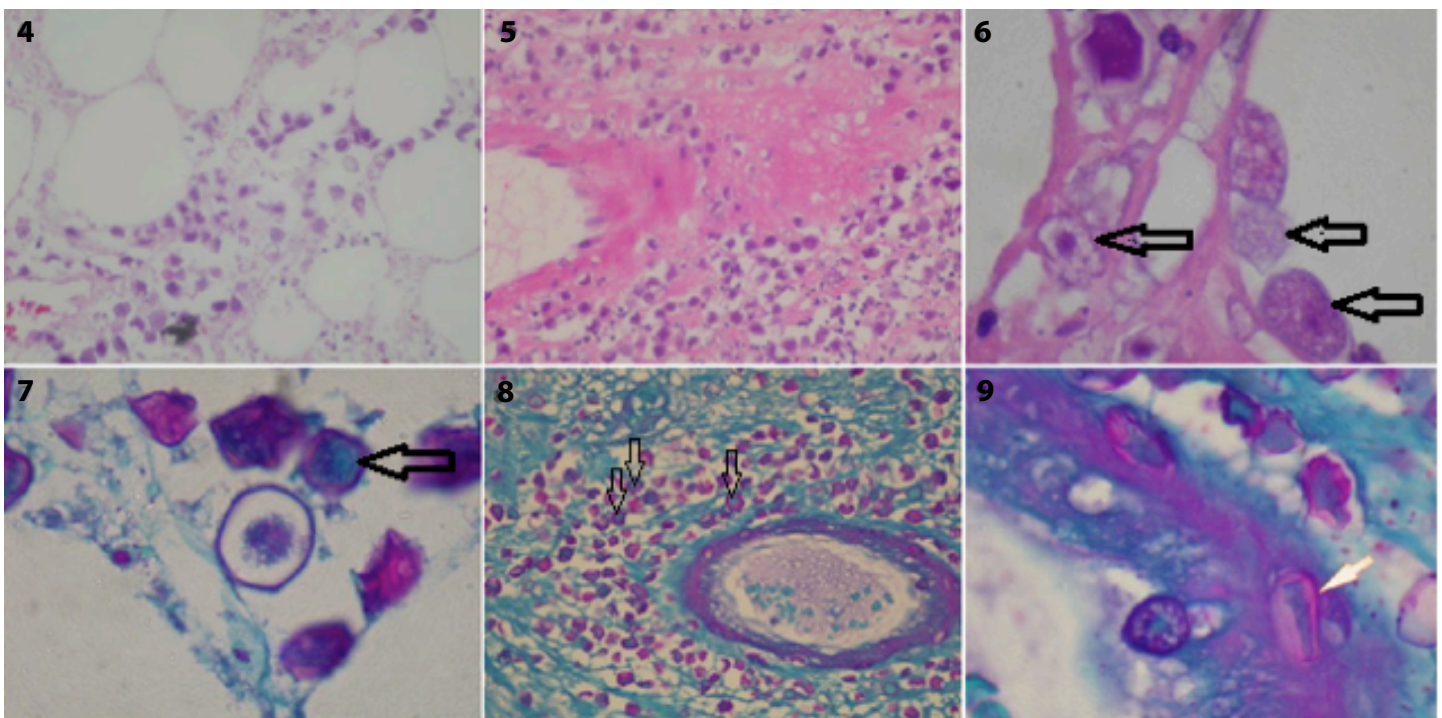


**Figures 1 - 3.** Subcutaneous nodules on upper extremities (1, 2) and back (3).

**Figure 3).** Her past medical history was significant for end-stage renal disease secondary to uncontrolled diabetes mellitus. The patient underwent a living-related renal transplant in 1997 that was complicated by antibody mediated rejection in 2014. At the time of presentation, the patient was status post therapeutic plasma exchange and treatment with rituximab and on chronic immunosuppression with oral tacrolimus, mycophenolate mofetil, and prednisone.

A skin biopsy from a representative lesion on the left arm showed granulomatous inflammation and large histiocytoid structures with prominent nuclei within foci of necrosis (Figures 4-6). Periodic acid-Schiff (PAS) stain revealed round organisms with a thick capsule, consistent with amoebae (Figures 7-9).

The patient was subsequently admitted to a nearby hospital for further evaluation of the amoebic infection. MRI of the brain and spinal



**Figures 4-6.** Skin biopsy with H&E staining demonstrating granulomatous dermal and subcutaneous inflammation surrounding large histiocytoid structures with prominent nuclei consistent with amoebic trophozoites (arrows in **Figure 6**); **Figures 7-9:** Period acid-Schiff stain of round amoebic trophozoites (demonstrated by arrows) with prominent nucleoli and a thick capsule within foci of necrosis.

cord was performed and did not reveal any focal lesions, masses, or gross abnormalities. Similarly, a cerebrospinal fluid analysis was found to be normal with no evidence of amoebae on stain or culture. Further analysis via polymerase chain reaction (PCR) of the skin biopsy by the CDC revealed amoebic infection with *Acanthamoeba*. This was confirmed by histological stains and culture of *Acanthamoeba* from the biopsy sample. The patient did not improve despite antimicrobial therapy with flucytosine, fluconazole, pentamidine, and sulfadiazine. She was then placed on miltefosine after receiving approval from the CDC. However, she was not able to tolerate any of these regimens owing to various toxicities, including intractable nausea and vomiting, liver dysfunction, kidney dysfunction, and electrolyte disturbances. Over the next three months, the nodules spread to involve bilateral upper and lower extremities, face, and trunk; many lesions ulcerated. She later developed acanthamoebal osteomyelitis of the left proximal fibula requiring surgical debridement. Tissue samples confirmed the presence of acanthamoebal cysts. This was, again, confirmed by the CDC by examination of the samples, culture, and PCR.

At present, the patient's cutaneous lesions have failed to improve despite multiple trials of different antimicrobials and she is being weaned off iatrogenic immunosuppression. She has restarted a trial of miltefosine and her treatment is ongoing.

## Case Discussion

Transmission of *Acanthamoeba* is believed to occur by exposure of skin or the upper respiratory tract to contaminated water or soil. In one case report, a patient presented with cutaneous acanthamoebiasis after swimming in a stream that she frequently visited [4]. Similarly, Sells et al. reported a case of cutaneous acanthamoebiasis in a patient with chemotherapy-induced neutropenia who was exposed to *Acanthamoeba* through use of a portable continuous positive airway pressure machine with a contaminated humidifier [3]. Upon further questioning, it was discovered that our patient had been using a neti pot with unsterile water to rinse her nasal passages for two weeks prior to the appearance of skin lesions. This exposure of potentially contaminated water to the patient's

upper respiratory tract serves as a possible source of infection.

Cutaneous acanthamoebiasis poses a diagnostic challenge, in part because presentations can be variable. Lesions may include papules, pustules, nodules, ulcers, and eschars that are typically most concentrated on the extremities and face [5]. Definitive diagnosis is made by identification or isolation of the amoeba from tissue samples. *Acanthamoeba* cysts and trophozoites may be visualized using H&E, Giemsa, or PAS staining [2]. However, the diagnosis can be difficult to make on histology alone. Galarza et al. reported 5 cases of cutaneous acanthamoebiasis [6], all of which were initially misdiagnosed on routine histology. Steinberg et al. reported a similar case in which multiple biopsies were performed without identification of the causative organism [7]. The diagnosis was made postmortem when retrospective analysis of the histological samples revealed cysts and trophozoites that were previously missed. This is due in part to the fact that trophozoites of *Acanthamoeba* closely resemble inflammatory cells, particularly large histiocytes [1]. The presence of tissue necrosis and granulomatous inflammation on skin biopsy in the setting of immunosuppression should prompt consideration of amoebic infection. Typically, several biopsies are performed before the diagnosis is made. Therefore, early diagnosis requires a high index of suspicion and an experienced dermatopathologist.

Diagnosis can be made by culture using a non-nutrient agar on a plate containing *Escherichia coli* [8]. A polymerase chain reaction (PCR) has also been developed which detects a highly conserved, yet specific sequence, to the *Acanthamoeba* genus [2]. PCR is commonly used by the CDC, in combination with histology and culture, to confirm the diagnosis of *Acanthamoeba* infection. Tissue samples from the involved sites, in this case, active skin lesions, should be biopsied and samples sent to the CDC for confirmation of the diagnosis [2].

Treatment regimens for cutaneous acanthamoebiasis often include combinations of antibiotics, antifungals, and anti-parasitic medications. Walia et al. reported a case of successful treatment of cutaneous acanthamoebiasis in a lung transplant patient using combination of amphotericin B and voriconazole

[4]. Similarly, Migueles and Kumar reported a case of cutaneous acanthamoebiasis in an HIV/AIDS patient that showed dramatic improvement after one week of treatment with pentamidine, itraconazole, topical ketoconazole, and topical silver nitrate [1]. Kandukuri et al. also reported a case of cutaneous acanthamoebiasis in a lung transplant patient successfully treated with 5-flucytosine, azithromycin, trimethoprim/sulfamethoxazole, pentamidine, voriconazole, and miltefosine [9]. Miltefosine, a kinase B inhibitor that has historically been used to treat leishmaniasis, is now available directly from the CDC for treatment of free living amoeba infections [10]. The use of miltefosine has been limited by the rarity of Acanthamoeba infection, but in a small number of cases has shown a survival advantage. Unfortunately, all therapeutic modalities are only tentatively successful and many carry significant toxicity.

Cutaneous acanthamoebiasis is very rare and few cases have been reported in the literature. Of the cases that have been reported, only one was in a renal transplant patient [7]. The vast majority of reported cases occurred in patients with HIV/AIDS. This has declined owing to the increase in use of antiretroviral medications for HIV. However, with the use of more potent novel immunosuppressive medications, infections caused by extremely rare opportunistic organisms are expected to increase, especially in solid-organ transplant recipients [11]. As iatrogenic immunosuppression becomes more common and more efficacious, cases such as this in non-HIV patients will likely become more frequent. Therefore, one must maintain a high index of suspicion when patients with immunosuppression present with persistent cutaneous lesions that are not better explained by bacterial or fungal infection, especially when skin biopsies reveal necrosis and granulomatous inflammation.

## Conclusion

This case is unique because of the rare and isolated cutaneous nature of this patient's presentation. The presence of concurrent amoebic osteomyelitis in the absence of CNS involvement adds to the rarity of this case. The case further illustrates the difficulty of treating patients with Acanthamoebal infections.

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