The genus Acanthamoeba includes species of free-living soil and water ameba that have been implicated in a small number of human diseases.

Disseminated Cutaneous Acanthamebiasis: A Case Report and Review of the Literature

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GOAL
To recognize and treat cutaneous acanthamebiasis

OBJECTIVES
Upon completion of this activity, dermatologists and general practitioners should be able to:
1. Explain the clinical presentation of cutaneous acanthamebiasis.
2. Recognize the histologic appearance of cutaneous acanthamebiasis.
3. Discuss the treatment options for cutaneous acanthamebiasis.

CME Test on page 263.

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Mr. Paltiel and Drs. Powell, Lynch, Baranowski, and Martins report no conflict of interest. The use of all drugs discussed in this article for the treatment of Acanthamoeba infection are mentioned off-label because there are currently no drugs indicated by the US Food and Drug Administration for the treatment of this infection. Dr. Fisher reports no conflict of interest.

Acanthamoeba species have been identified as the etiologic agents in 2 well-defined clinical entities, amebic keratitis and granulomatous amebic encephalitis (GAE). Less commonly, Acanthamoeba species have been identified as the cause of disseminated disease in debilitated and immunocompromised patients. Cutaneous acanthamebiasis, often a reflection of disseminated disease, is an increasingly recognized infection since the emergence of acquired immunodeficiency syndrome (AIDS) and the use of immunosuppressive drugs. The disease portends...
a poor prognosis and is uniformly fatal if the infection involves the central nervous system (CNS). We describe a patient with advanced AIDS who presented with disseminated cutaneous lesions, headache, and photophobia, and in whom a diagnosis of cutaneous acanthamebiasis was made based on the results of a skin biopsy. A multidrug therapeutic regimen was begun that included sulfadiazine; the patient responded favorably to treatment. This paper also reviews 36 previously reported cases of cutaneous acanthamebiasis with delineation of clinical, diagnostic, histologic, and prognostic features, as well as discusses treatment options.

Cutaneous Acanthamebiasis

Acanthamoeba are free-living protozoa that are present ubiquitously in the environment. They are found in water, soil, and air samples throughout the world and have been cultured from the throats of both healthy and immunocompromised asymptomatic individuals. The life cycle of Acanthamoeba consists of a feeding and replicating trophozoite stage and a resilient, dormant cystic stage. At least 16 species of Acanthamoeba have been identified, of which several have been associated with human disease.

The pathogenic potential of Acanthamoeba was established in animal models by Culbertson et al in 1959. The earliest report of human infection by Acanthamoeba may have been reported by Kernohan et al in 1960 when they attributed a brain granuloma to an Iodamoeba butschlii infection. The organism was later identified as Acanthamoeba. Since then, more than 100 cases of granulomatous amebic encephalitis (GAE) and hundreds of cases of amebic keratitis have been reported. GAE is a slowly progressive, fatal central nervous system (CNS) infection primarily affecting immunocompromised patients.

Amebic keratitis is a sight-threatening infection that affects the general population of developing countries, as well as healthy individuals worldwide who wear contact lenses. Cutaneous acanthamebiasis, often a manifestation of disseminated extracerebral disease, is extremely rare, with only 37 cases, including the present report, described to date. Dissemination of the ameba is postulated to occur by hematogenous spread from a primary focus within the skin or the upper or lower respiratory tract. The prognosis of cutaneous acanthamebiasis is dismal, with a mortality rate of at least 74% in patients without CNS involvement and 100% in patients with CNS involvement.

We present a patient with acquired immunodeficiency syndrome (AIDS) and disseminated cutaneous acanthamebiasis with possible involvement of the CNS whose general condition and cutaneous lesions improved with a prompt antiparasitic therapeutic regimen that included sulfadiazine and antiretroviral therapy.

Case Report

A 51-year-old woman with AIDS, a history of cytomegalovirus retinitis, and multiple episodes of Pneumocystis carinii pneumonia was admitted to the hospital with numerous pruritic, painful cutaneous nodules that had developed over a 2-week period. The initial skin lesion appeared as a small papule on her right forearm that slowly enlarged as other nodules appeared in a generalized distribution over the next 5 to 7 days. Some of the nodules ulcerated, draining purulent fluid and forming necrotic eschars. On admission, the patient reported no chills or fever but complained of photophobia and a 1-week history of severe headache localized to the right frontal region.

On physical examination, the patient was cachectic, photophobic, oriented yet drowsy, and in mild respiratory distress. Multiple intradermal and subcutaneous nodules (0.5–2 cm in diameter), some with overlying erythema, were present on her face, arms, chest, back, legs, and thighs. A deep ulcer covered by a 3×4-cm eschar was noted on the dorsum of her right forearm and an additional ulcer was noted on her leg (Figure 1). Ophthalmologic examination revealed no evidence of active disease and neurologic examination was nonfocal.

The patient’s most recent CD4 count and viral load were 3 cells/mm³ and 34,875 copies/mL, respectively. A deep incision biopsy of a skin nodule on the patient’s right thigh was performed. Bacterial tissue cultures of the thigh nodule grew Enterococcus faecalis. Mycobacterial, fungal, and viral culture results of the tissue were negative. Blood culture results were negative for bacterial, mycobacterial, and fungal growth. Serum cryptococcosis and histoplasma antigens were negative, as was the urine histoplasma antigen.

Histologic sections of the skin biopsy showed an intense inflammatory infiltrate of lymphocytes within the deep dermis, subcutis, and fascia, admixed with neutrophils, plasma cells, and eosinophils. Diffuse areas of collagen and fat necrosis were noted throughout the areas of inflammation. Numerous Acanthamoeba trophozoites measuring 10 to 15 μm were scattered throughout the inflammatory infiltrate. These structures, best visualized on hematoxylin-eosin (H&E) staining, contained a centrally located nucleus and clear nucleolus surrounded by copious vacuolated cytoplasm. Fewer
encysted forms were present, and they contained a scalloped inner endocystic wall surrounded by a less ruffled outer ectocyst wall (Figure 2). Culture of the tissue sample was performed in a medium inoculated with *Escherichia coli* as a nutrient source; results of the culture demonstrated trophozoite forms with acanthopodia formation, confirming the organism to be *Acanthamoeba*.

Computed tomography (CT) of the brain was unremarkable; however, magnetic resonance imaging of the brain showed cerebral volume loss and nonspecific foci of increased signal intensity in the periventricular and subcortical white matter, basal ganglia, and posterior fossa with no abnormal enhancement. These findings were interpreted to be secondary to human immunodeficiency virus (HIV) infection. Cerebrospinal fluid (CSF) analysis showed one mononuclear leukocyte and 2 erythrocytes. The CSF glucose and protein levels were 50 mg/dL and 17 mg/dL, respectively (reference ranges, 50–75 mg/dL and 15–45 mg/dL, respectively). CSF culture results were sterile and were negative for cryptococcus antigen. Results of microscopic examination showed no evidence of amebic organisms in the CSF.

Three days after admission, the patient was prescribed a therapeutic regimen of pentamidine 160 mg intravenously once a day and oral 5-flucytosine 1 g every 6 hours. Unfortunately, new nodules continued to appear, and some of the existing nodules enlarged and ulcerated forming necrotic eschars. Because of the patient's poor response, sulfadiazine and highly active antiretroviral therapy (HAART) were added to the therapeutic regimen.

The appearance of new nodules subsequently ceased, and the patient experienced slow regression of existing nodules. The patient's general well being also improved as her photophobia resolved and her severe headaches, which initially required intravenous narcotic analgesia, diminished.

After completing a 14-day course of intravenous pentamidine, the patient was discharged in stable condition on a therapeutic regimen of 5-flucytosine 1 g every 6 hours, sulfadiazine 1 g every 6 hours, and HAART therapy consisting of tenofovir 300 mg/d, lamivudine 300 mg/d, and abacavir 600 mg/d. Three months after discharge, no evidence of CNS decline was noted. Improvement in the patient's general condition and in her cutaneous lesions continues despite less than optimal compliance with the treatment regimen.

**Comment**

Cutaneous lesions are present in 90% of patients with disseminated acanthamebiasis, making it the most common sign of disseminated disease. The primary cutaneous lesions in patients with acanthamebiasis are polymorphic and are commonly described as intradermal or subcutaneous nodules that are erythematous or violaceous, ranging from a few millimeters to several centimeters in diameter. In addition, papules, pustules, plaques, cellulitis, and intramuscular abscesses all have been described. Lesions can be pruritic, tender, or nottender and they typically evolve through a course of enlargement, suppuration, and ulceration. A necrotic eschar may develop and then slough, thereby deepening the

Figure 1. Disseminated acanthamebiasis presenting with ulcerated lesions on the forearm (A) and leg (B).
The differential diagnosis of nodular and ulcerative cutaneous lesions is broad and includes deep fungal or mycobacterial infections, pyoderma gangrenosum, and vasculitis. The histologic findings of the cutaneous lesions in acanthamobiasis may show granulomatous inflammation, which is notably absent in immunocompromised patients with severe disease and CNS involvement. Other reported histopathologic features include leukocytoclastic or necrotizing vasculitis, panniculitis, and acute and/or chronic inflammation. The diagnosis of *Acanthamoeba* infection requires visualization of amebic trophozoites and/or cysts, which may be found perivascularly. Ideally, a culture should be performed on the organisms with subsequent morphologic examination. Trophozoites and cysts both contain a single nucleus and a nucleolus. *Acanthamoeba* cysts vary in size depending on the species, but commonly range from 13 to 30 mm in diameter. Trophozoites contain slender projections termed acanthopodia, which aid in motility.
finding of Acanthamoeba requires a high index of suspicion because the ameba have been mis-
taken for macrophages, Rhinosporidium seeberi, Cryptococcus neoformans, Prototheca wickerhamii, and Blastomyces dermatitides.11,24 An incorrect diagnosis of a deep fungal infection is sometimes made when histologic evaluation is done with Gomori methenamine silver or periodic acid–
Schiff stains. The amebic cyst wall picks up those stains in a pattern reminiscent of a fungal cell wall, leading to the missed diagnosis.24

Among the 37 reported cases of cutaneous acan-
thamebiasis, 27 patients were HIV positive (aged 8 months–60 years; mean, 34 years).5-13 A history of AIDS-defining illnesses was reported in 74% of patients, and CD4 counts ranged from 0 to
566 cells/mm³ (median, 28 cells/mm³). In addition to cutaneous involvement, patients with HIV/AIDS also presented with concomitant amebic sinusitis (13/27), osteomyelitis (3/27), uveitis (2/27), pneumonia (2/27), and infection of the CNS (con-
firmed in 2/27; suspected but unconfirmed in 4/27). Involvement of the nasal septum (5/27) and palate (4/27) was not uncommon. Symptoms on presenta-
tion often included fever,5,7,11,20 nasal congestion/discharge,8,9,13,21 epistaxis,13,14 and cough.14 Patients with presumed or confirmed CNS involvement developed headaches,17,21 fever,10 altered mental status,17,20 hemiparesis,19 lethargy,17 spasticity,21 and seizures.14

The mortality rate for cutaneous acanthamebiasis in the setting of HIV/AIDS without evidence of CNS involvement is at least 75%. Of the patients who died, the duration of illness until death ranged from 9 weeks to 2 years (average, 7.5 months). The development of CNS symptoms in HIV-positive patients with cutaneous acanthamebiasis resulted in death in all patients within days to weeks of the appearance of symptoms.17,19,25,27,30

In addition to patients with HIV/AIDS, cuta-
nceous acanthamebiasis has been described in 7 non-
HIV, immunosuppressed patients aged 7 to 61 years (mean, 35 years). Six of the patients were trans-
plant recipients,24-29 and one patient was receiving long-term steroid therapy.30 Five patients died from their infections, and 2 patients were treated suc-
cessfully (resolution of all lesions). In one success-
fully treated case, immunosuppression was lowered, and the patient was given pentamidine with
5-flourocytosine.29 In another successfully treated case, immunosuppression was maintained, and the patient responded to pentamidine and topical chlorhexidine and ketoconazole cream.26

In exogenously immunocompromised patients with cutaneous acanthamebiasis, additional sites of involvement included CNS (3/7), lungs (2/7), adrenal glands (2/7), kidney (1/7), pancreas (1/7), and bone (1/7). In the 3 patients with CNS involvement, cutaneous lesions preceded neurological symptoms in 2 patients,27,30 and the lesions occurred after the expression of focal neurological symptoms in one patient.25 This suggests that cuta-
nceous lesions can be either an initial or late mani-
festation of disseminated acanthamebiasis.

Although cutaneous acanthamebiasis is largely a disease of immunocompromised patients, 3 patients with this disease (aged 5 years, 24 years, and unknown) were apparently healthy.31-33 In one patient, the history of illness could not be elicited;33 in the other 2 patients, lesions developed at a site of prior trauma.32,33 In these other-
wise healthy patients, the course of the illness was more protracted than in the immunocompromised patients. Lesions remained localized from 6 months to more than a year prior to involvement of other sites. In 2 cases, the symptoms were exacerbated after the patients received systemic steroids.32,33
All 3 patients died after infection spread to the CNS.31-33

In any patient with disseminated cutaneous acanthamebiasis presenting with neurological symp-
toms, a diagnosis of GAE, meningitis, or meningoen-
cephalitis is often made postmortem.19,20,27,30 Premortem diagnosis may be facilitated by a brain biopsy because radiographic or CSF analyses are often nonspecific or nondiagnostic. There are case reports of patients with disseminated disease and CNS involvement whose CSF never yielded amebic organisms. However, there also are reports of 3 patients with strictly localized CNS involvement who had amebic organisms on CSF wet mounts.35,36
In patients with disseminated acanthamebiasis and extensive CNS involvement documented at autopsy, premortem CSF findings were within reference range20 or showed intermediate elevation in white blood cell count and protein.19,27,30 Radiographic findings in patients with GAE may show hypodense lesions on CT scans, which may enhance on T2-weighted magnetic resonance imaging.37,38 Isodense or hyperdense lesions also are
seen on brain CT scans of patients with GAE; however, CT findings are normal in up to 12% of patients with GAE.38 Normal magnetic resonance imaging findings in patients with CNS involve-
ment also have been reported.36 In the present case, no definitive evidence of CNS infection was noted on CSF or radiographic analysis.

The treatment for acanthamebiasis has not been well established and is based largely on in vitro sensitivity of the organism to a number of
chemotherapeutic agents, and on a small number of reports of successfully treated cases. The Table lists common antimicrobial agents used in the treatment of patients with disseminated cutaneous acanthamebiasis and their reported response. The Table includes only immunocompromised patients with disseminated cutaneous acanthamebiasis without evidence of CNS involvement. Patients with CNS involvement were excluded because the rapid course of illness in those patients makes evaluation of therapy difficult.

Although few patients experienced marked resolution of disseminated cutaneous acanthamebiasis, it appears that the inclusion of 5-flucytosine in the therapeutic regimen was associated with the greatest number of improved cases. In general, a multidrug regimen appears to be more effective than monotherapy. Surgical debridement of affected areas has been beneficial in some cases, and it should be considered in patients with localized disease, in particular. Topical chlorhexidine has been used adjunctively in some successfully treated cases of cutaneous acanthamebiasis. In exogenously immunocompromised patients, lowering the dose of the immunosuppressants led to disease-free survival in one patient but had no benefit in 2 other patients, presumably because of the advanced stage of the disease.

In the present case, our patient’s disease initially progressed despite the administration of pentamidine and 5-flucytosine. Stabilization and subsequent resolution of the lesions began after the addition of sulfadiazine and HAART to the therapeutic regimen. In patients with HIV disease and acanthamebiasis, there are no reports demonstrating whether the administration of antiretrovirals can alter the course of the disease. Although sulfonamides have not been used frequently in the treatment of disseminated acanthamebiasis, the utility of sulfonamides in the treatment of Acanthamoeba infection has been shown by Allen and Culbertson, who reported that experimental animal infection with Acanthamoeba species can be both prevented and cured with sulfadiazine. Additionally, Cleland et al reported improvement in a patient with Acanthamoeba meningocerebral infection who was treated with sulfamethazine, though long-term follow-up was not feasible. Furthermore, Singhal et al reported the successful treatment of 2 immunocompetent patients with Acanthamoeba CNS infection using a combination of trimethoprim/sulfamethoxazole, ketoconazole, and rifampin. These data, combined with the observations of our patient’s therapeutic course, suggest that sulfadiazine therapy was important to our patient’s clinical improvement and thus should be strongly considered in the treatment of disseminated Acanthamoeba infection. Sulfonamides, however, must be used with caution in patients with HIV/AIDS because of this patient population’s

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Marked Improvement</th>
<th>Minimal to Moderate Improvement</th>
<th>No Improvement</th>
</tr>
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<tbody>
<tr>
<td>5-Flucytosine</td>
<td>55,7,10,11</td>
<td>38,14,18</td>
<td>312,15,26</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>312,15,26</td>
<td>214,18</td>
<td>67,10,14,18,24</td>
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<tr>
<td>Itraconazole</td>
<td>210,26</td>
<td>118</td>
<td>41,12,15,26</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>217,26</td>
<td>35,8,11</td>
<td>314,18</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>112</td>
<td>215,16</td>
<td>412,15,26</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>16</td>
<td>0</td>
<td>411,14,20,24</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>112</td>
<td>118</td>
<td>212,24</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0</td>
<td>0</td>
<td>35,14,34</td>
</tr>
</tbody>
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*Some patients were treated with a combination of above regimens and are included in more than one regimen.*
high incidence of adverse reactions, especially fever, myalgia, and rash.\textsuperscript{31}

Amebic infections, though rare, have become increasingly recognized in recent years as a result of the emergence of AIDS and the availability of effective immunosuppressive regimens for the prevention of transplant rejection and the treatment of autoimmune diseases. Prompt diagnosis of acanthamebiasis is crucial to a patient's survival because delay in treatment has led to rapid deterioration and death in all reported cases. Although optimal therapy has not been established for this condition, previously reported cases and this case report suggest that efforts to restore the patient's immune system, as well as treatment with a multidrug regimen containing 5-flucytosine and sulfadiazine, may offer the best chance of long-term survival.

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REFERENCES

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