Disseminated Acanthamoeba Infection Presenting With Cutaneous Lesions in an Immunocompromised Patient

A Case Report, Review of Histomorphologic Findings, and Potential Diagnostic Pitfalls

Annie O. Morrison, MD,1 Robert Morris, MD,1,2 Amie Shannon, MD,3 Scott R. Lauer, MD,4 Jeannette Guarner, MD,1 and Colleen S. Kraft, MD1

From the Departments of1Pathology and Laboratory Medicine and 2Dermatology, Emory University, Atlanta, GA; 3Department of Dermatology, Louisiana State University, Baton Rouge; and 4Department of Pathology, Alegent Creighton Health, Omaha, NE.

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ABSTRACT

Objectives: Free-living amoebas are exceedingly rare causes of cutaneous infections and present unique diagnostic and therapeutic challenges. We describe a case of disseminated acanthamoebiasis with cutaneous manifestations and summarize additional diagnostic, prognostic, and therapeutic highlights.

Methods: A 58-year-old man with relapsed chronic lymphocytic leukemia had several weeks of progressive, painful ulcerations on the forehead, arms, abdomen, and thighs. A biopsy was performed for histopathologic evaluation.

Results: The biopsy specimen showed inflammatory infiltrate with abscess formation involving the epidermis, dermis, and subcutis. Scattered cells showed nuclei with a prominent central karyosome, dispersed chromatin, and either abundant foamy basophilic cytoplasm or two well-demarcated cytoplasmic walls. Acanthamoeba species was confirmed by polymerase chain reaction from the formalin-fixed, paraffin-embedded tissue.

Conclusions: Cutaneous lesions from acanthamoebiasis are exceptionally rare but should be included in the differential diagnosis of necrotic cutaneous lesions in immunocompromised patients. Although infrequently encountered, pathologists need to be aware of the morphologic features of free-living amoebas. Immunohistochemical and molecular studies can confirm the diagnosis. Multiagent treatment regimens, when initiated empirically, have been more successful than single-agent regimens, but infections involving the central nervous system are almost universally fatal.

Free-living amoebas are found ubiquitously throughout nature and are known to thrive in fresh water. Several species that cause severe human disease include Acanthamoeba species, Naegleria fowleri, and Balamuthia mandrillaris. Primary cutaneous amoebic infections as well as cutaneous lesions from disseminated amebiasis are much more common in immunocompromised patients. Although amoebic infections are exceedingly rare, they are likely underrecognized and thus underdiagnosed or misdiagnosed. With this in mind, it is important for pathologists to be aware of their histomorphologic appearance and diagnostic pitfalls when evaluating immunocompromised patients with new skin lesions. In these settings, a unique infectious differential diagnosis should include rare entities such as fungal, mycobacterial, and amoebic infections.

Case Presentation

A 58-year-old man with diabetes and chronic lymphocytic leukemia (CLL) had a 3-week history of progressive,
nonhealing, painful crusted cutaneous ulcerations with black eschars on his forehead Image 1A, arms Image 1B, thighs, and abdomen. Approximately a dozen lesions, ranging from 1 to 5 cm, were present, surrounded by significant edema and erythema. Complaints of headache and chronic sinusitis symptoms were noted on admission history. No evidence of focal neurologic deficits was found on examination. The patient’s CLL had previously been treated with chemotherapy and a related donor hematopoietic stem cell transplant. However, his CLL had recently recurred, and he was pancytopenic at the time of presentation with a WBC count of 1,000 to 2000 cells/μL. The patient had been hospitalized for pneumonia 1 month prior to seeking evaluation for his cutaneous lesions. Since his last admission, the patient had been feeling well but had recently developed fevers. He reported possible contact with raw sewage during a home remodeling project but denied any recent travel or freshwater lake exposure. The clinical differential diagnosis included leukemia cutis, disseminated varicella zoster, fungal infection, ecthyma gangrenosum, or ecthyma due to Staphylococcus species or Streptococcus species. The patient was admitted for fevers and further evaluation of his cutaneous lesions. Skin biopsy specimens were taken and sent for routine culture and histopathologic evaluation.

Biopsy specimens from lesions on the right forearm and right upper arm showed similar findings. Punch biopsy specimens to the level of the subcutis showed abscess formation within the dermis and subcutis consisting of a dense mixed inflammatory infiltrate, including lymphocytes, histiocytes and neutrophils Image 2A. Within the abscess, numerous individual cells demonstrated abundant vacuolated cytoplasm, a single round nucleus with a prominent karyosome, and dispersed chromatin Image 2B. The cytoplasm of these cells was either vacuolated or well demarcated by two cytoplasmic walls, with the outer wall (exocyst) being wrinkled and the inner wall (endocyst) being smooth Image 2E. The double-walled cysts were highlighted with Gomori methenamine silver (GMS) special stains Image 2F. These cells were also present in and around blood vessels and associated with damage to small- and medium-sized vessel walls with mixed inflammatory cell infiltrate Image 2C and Image 2D. The morphologic findings were highly suspicious for an Acanthamoeba species or Balamuthia species infection. Special stains were used to rule out other infectious entities. An acid-fast bacilli stain was negative for microorganisms. A mucicarmine stain ruled out a cryptococcal etiology of infection. CD68 was negative in the amoeba but positive in histiocytes in the background inflammatory infiltrate. Leukocyte common antigen (LCA or CD45) was also negative in the protozoans but positive in the background inflammatory cells. The amoebae were also negative for cytokeratin AE1/3, an epithelial marker. Taken together, these findings are most consistent with a cutaneous Acanthamoeba species infection. Formalin-fixed, paraffin-embedded tissue blocks were sent to the Centers for Disease Control and Prevention, where a multiplex real-time polymerase chain reaction confirmed the diagnosis of Acanthamoeba species.1

Throughout the hospital course, blood and wound cultures remained negative for mycobacterial and fungal growth. Magnetic resonance imaging did not demonstrate central nervous system (CNS) involvement at the time of admission. The patient was empirically placed on intravenous amphotericin B, as well as meropenem and metronidazole, for suspected amoebic sepsis. Ketoconazole 2% topical cream and silver sulfadiazine were applied to the
Image 21  
A. Skin biopsy specimen with dermal abscess (H&E, ×20).  
B. Amoebic trophozoites (arrows) with associated inflammatory cells (H&E, ×400).  
C, D. Amoebic trophozoites (arrows) with associated vasculitis (H&E, ×400).  
E. Amoebic cyst with double-contoured walls (arrow) (H&E, ×1,000 oil emersion).  
F. Amoebic cyst with double-contoured walls (Gomori methenamine silver, ×1,000 oil emersion).
wounds twice a day, and affected areas were scrubbed with topical 0.12% chlorhexidine. Other medications considered, such as 5-flucytosine, pentamidine, and fluconazole, were deemed inappropriate due to the patient’s pancytopenia. New lesions developed daily, and it was decided they were too numerous and widespread for surgical debridement. Given the patient’s refractory CLL, lack of improvement on chemotherapy, and the degree of immunosuppression with continued pancytopenia, a more aggressive treatment approach was not recommended. He was referred to hospice, and a palliative treatment plan was initiated, including discontinuation of all antimicrobials. The patient died 3 weeks after his hospital admission.

Discussion

Cutaneous and disseminated amoebic infections are extraordinarily rare and usually caused by Acanthamoeba species or Entamoeba species, although, less commonly, B mandrillaris has been implicated. Cutaneous entamoebic infections usually occur secondary to gastrointestinal involvement and often show an anogenital distribution, although secondary inoculation of other skin sites can also occur. Acanthamoeba species are responsible for four clinicopathologic entities in humans: nasopharyngeal and cutaneous infections, which can both disseminate; granulomatous amebic encephalitis with an insidious onset of weeks to years; and amebic keratitis that is generally associated with corneal trauma and contact lenses. CNS involvement usually develops following an untreated primary cutaneous infection. Alternatively, the amoebae enter through the respiratory tract, disseminate systemically, and invade the brain.

Primary cutaneous acanthamoebiasis has a drastically different outcome and prognosis, depending on whether there is CNS involvement. In patients without CNS involvement, the onset of cutaneous acanthamoebic lesions is acute to subacute, with multiple lesions continually developing. These patients generally have a favorable prognosis and show good response to treatment with initiation of appropriate therapy. Conversely, patients with CNS involvement by Acanthamoeba species (amoebic encephalitis) generally develop cutaneous lesions as a late manifestation of systemic disease, which carries a very poor prognosis and is almost universally fatal.

Interestingly, immunocompetent patients are more likely to have CNS involvement and secondary cutaneous lesions, whereas immunocompromised patients more frequently have the isolated primary cutaneous skin infection. Although it seems counterintuitive, it has been reported that immunocompromised patients frequently have better outcomes than immunocompetent patients. This is likely because isolated cutaneous infections without CNS involvement are nearly exclusively seen in the setting of immune suppression.

Immunocompromised patients without CNS involvement frequently die of their underlying condition or a different opportunistic infection, despite favorable responses to treatment of their cutaneous acanthamoebiasis. It was suspected that our patient’s cutaneous infection was the result of dissemination, leading to his sepsis syndrome at the time of initial presentation, failure to improve on a multiagent antimicrobial regimen, and, ultimately, his death. In the current English literature, approximately 40% of patients with acanthamoebic infections have a history of exposure to untreated fresh water, which was not present in our patient, although exposure to untreated sewage may have been the source of exposure in our patient.

Although Acanthamoeba species can be cultured on a nonnutrient agar with a bacterial food source such as Escherichia coli, growth can be slow and may be complicated by a low inoculation from the biopsy, previous antimicrobial agents inhibiting amoeba growth, or a particularly fastidious amoeba strain that does not adapt well to in vitro growth. In the setting of an acutely ill patient where time is of the essence, as was the case in our patient, the diagnosis of amoebic infections often falls to the pathologist signing out the biopsy slides.

Histopathologic diagnosis of free-living amoebic infections can be difficult if the inflammatory infiltrate is dense, there is abundant necrosis, and very few protozoans are present in the tissue. From a morphologic perspective, a nucleus featuring a prominent round karyosome and dispersed fine chromatin is key to the diagnosis; however, the karyosome can be confused with a nucleolus. Cysts may not always be present in these infections; however, the presence of the exo- and endocyst walls can be of great diagnostic help. Amoeba can sometimes be difficult to differentiate from macrophages, and although CD68 can be negative in the amoeba as in this case, some amoebas may show positive staining. Cysts can be confused with fungi since they are highlighted with the GMS stain, although the double wall should alert the pathologists to the possible diagnosis of amoebiasis. Immunohistochemical and fluorescent assays have been used to highlight the different amoebas, yet definitive speciation can only be performed using molecular techniques.

Treatment of amoebic infections is often initiated empirically and includes various multiagent therapeutic regimens that cover Acanthamoeba species and B mandrillaris, which can also cause amebic encephalitis. There are rare case reports of patients with acanthamoebic encephalitis who are successfully treated with antimicrobial combinations that included sterol-targeting azoles (clotrimazole,
miconazole, ketoconazole, fluconazole, or itraconazole), pentamidine, 5-flucytosine, and sulfadiazine, but CNS involvement is fatal in most cases. Acanthamoebic keratitis responds well to combination therapy with chlorhexidine gluconate and polyhexamethylene biguanide along with propamidine isothionate (Brolene), hexamidine (Desomodine), or neomycin. There are reports of cutaneous Acanthamoeba species infections having good responses to treatment with a combination of an intravenous lipid formulation of amphotericin B and voriconazole or itraconazole. As with most diseases, recovery and survival are ultimately dependent on the patient’s immune and functional status, how early the infection is diagnosed, and how quickly the appropriate treatment is initiated.

In summary, our case highlights the importance of including rare entities, such as cutaneous amoebic infections, in the differential diagnosis of new skin lesions in immunocompromised patients. In such patients, skin biopsies with careful histologic evaluation are an essential part of the workup, since free-living amoebae cannot be routinely cultured. Although amoebiasis rarely presents as cutaneous lesions, it generally carries a worse prognosis when diagnosed as a disseminated systemic infection with CNS involvement rather than an isolated primary cutaneous infection. Successful treatment of cutaneous acanthamoebiasis is dependent on multiple patient factors relating to the extent of disease progression and capacity to tolerate treatment. Last, not all patients with free-living amoebic infections report exposure to untreated fresh water.

Corresponding author: Annie O. Morrison, MD, Dept of Pathology and Laboratory Medicine, Emory University Hospital, 1364 Clifton Rd NE, Rm G159, Atlanta, GA 30322; anniemorrisonmd@gmail.com.

References


