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Centrofacial Balamuthiasis: Case Report of a Rare Cutaneous Amebic Infection

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Keywords

Balamuthia mandrillaris; ameba; free living amebae; cutaneous balamuthiasis; skin infections

Introduction

Free-living ameba uncommonly infect the skin but can do so in both immunocompromised and immunocompetent patients (1, 2). Only a few genera of free-living ameba are recognized as human pathogens: *Acanthamoeba, Naegleria, Balamuthia*, and *Sappinia.* Exposure to these organisms is likely common due to their ubiquitous nature in the natural environment; however, clinically significant skin infection is quite rare. *B. mandrillaris* has a predilection for infection of the central facial skin and can also involve the central nervous system (CNS), leading to granulomatous amebic encephalitis (GAE), which is almost invariably fatal (1, 3–5). This report describes a patient with a large centrofacial cutaneous lesion due to *B. mandrillaris* infection, the diagnosis of which eluded dermatologists and dermatopathologists for over one year. (6–8)

Report of a Patient

A 91-year-old woman with a history of chronic obstructive pulmonary disease, hypertension, congestive heart failure, and monoclonal gammopathy of uncertain significance (MGUS) was referred to dermatology clinic for a non-healing, red plaque over her right cheek. She

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denied trauma to the area and had not traveled out of the state of Washington in decades; there was no history of fresh-water swimming. The lesion began approximately one year prior as a skin-colored bump and progressively enlarged, gradually developing into an erythematous and markedly indurated ("rock-hard") plaque (Figure 1). The patient underwent several biopsies, each with nonspecific pathologic findings of granulomatous dermatitis. Repeated cultures and histochemical stains were negative for atypical mycobacterial and fungal organisms. The slides from these biopsies were also reviewed at our institution and another referral center with a similar interpretation. Initially, granulomatous rosacea was the favored diagnosis, but the lesion continued to enlarge despite multiple treatment modalities including intra-lesional steroid injection, oral antibiotics, and electron beam therapy.

After failing to improve, the patient was referred to our institution a second time, and underwent a larger, incisional biopsy near the site of her previous biopsies. Additionally, previous histopathologic slides from prior punch biopsy specimens were reviewed a second time along with clinical photographs and clinical notes from the electronic medical record.

Hematoxylin-eosin-stained sections of the incisional biopsy specimen contained skin and subcutaneous fat. There was diffuse, non-caseating granulomatous inflammation involving the dermis and subcutaneous fat (Figure 2a). The overlying epidermis was thin, without other significant pathologic alteration. Some areas lacked granulomas, but instead showed a mixed inflammatory infiltrate comprising lymphocytes, mature plasma cells, as well as occasional eosinophils. Histochemical stains and PCR studies were negative for fungal and mycobacterial organisms. The key finding in routinely-stained histopathologic sections was the presence of rare cells with bubbly pale grey cytoplasm, small, perfectly round nuclei, and extremely large nucleoli occupying greater than one-half of the nuclear area imparting a targetoid appearance consistent with amebae (Figure 2b–d). In some organisms, the extremely large nucleolus could be readily mistaken for the entire nucleus, due to faintly staining-to-clear peripheral chromatin and inconspicuous nuclear membrane. These structures resembled histiocytes, but could be distinguished by careful morphologic examination (Table 1). The number of organisms exhibiting diagnostic morphologic features was sparse—approximately one diagnostic form per slide. Subsequent immunohistochemical staining highlighted many more organisms than could be appreciated in conventional sections. Retrospective analysis of the previous punch biopsies revealed the presence of scattered amebae in each of the specimens.

A formalin-fixed tissue block from one of the punch biopsy specimens was then sent to the Centers for Disease Control and Prevention (CDC) for further characterization by polymerase chain reaction (PCR) and immunohistochemical analysis. DNA extracted from the skin specimen was positive for *B. mandrillaris*, and the cells of interest were immunoreactive using a free-living ameba immunohistochemistry assay (known to detect both *B. mandrillaris* and *Acanthamoeba* spp.), but appropriately non-reactive with antibodies against *Acanthamoeba* spp. (Figure 3). The patient was immediately referred to the infectious disease service, and began a CDC-recommended course of multi-agent antibiotic therapy comprised of azithromycin 500 mg daily, fluconazole 400 mg daily, and sulfadiazine

1500 mg four times a day. A magnetic resonance imaging (MRI) study did not show evidence of central nervous system (CNS) involvement.

The patient remained on this three-drug regimen for 5 months without any notable side effects. Her plaques softened and the total area of involvement was significantly reduced; however, there were some areas of slow progression near the midline of her face. At this point a course of miltefosine 50 mg three times a day, supplied by the CDC, was added in an effort to better control her disease.

Unfortunately, less than two weeks later, the patient developed nausea, anorexia, decreased appetite, and lower extremity swelling, which are known side effects of miltefosine, thus prompting its discontinuation. She also developed acute renal failure requiring hospitalization and discontinuation of her sulfadiazine. Her kidney function ultimately returned to normal and she returned to her previous state of general health. Neither the miltefosine nor the sulfadiazine were re-initiated.

Currently she remains on a 2-drug regimen of azithromycin and fluconazole and is followed clinically by dermatology and infectious diseases every 3 months. Due to the patient's age, overall medical condition, and the above-described severe adverse drug reactions, the goal of her current treatment regimen is now disease containment but not necessarily complete clinical clearance. She remains free of symptoms of CNS involvement.

Discussion

B. mandrillaris is one of just a few free-living ameba which cause human disease, along with *Acanthamoeba* spp., *Naegleria fowleri*, and *Sappinia pedata* (8). *B. mandrillaris* was first identified in 1986 within the brain of a mandrill that died of meningoencephalitis at the San Diego Zoo. Mandrills are primates of the Old World monkey family. Since 1986, approximately 150–200 cases of cutaneous and/or CNS infections in humans have been reported. *B. mandrillaris* is found worldwide, but the majority of reported cases appear to arise from Lima, Peru and the United States, mostly in California and Texas (6). Like other free-living amebae, *B. mandrillaris* organisms can complete their entire life cycle independent of a host organism (9). The major reservoir for the organism is soil; organisms have been isolated from garden soil, mud baths, and potted plants (10–13). The organism has also been identified in domestic water-based environments, including faucets, showerheads, and bathtubs (10, 14). Our patient has been an avid gardener, and garden soil is the suspected source of her exposure to this organism. Transmission of free-living ameba from the environment to hosts usually occurs via skin breakage or via the respiratory system (15). Alternate modes of infection reported in literature include organ transplantation (16). *B. mandrillaris* infection occurs in both immunocompromised and immunocompetent hosts, particularly children (1, 2, 17).

Cutaneous involvement alone is an unusual presentation of balamuthiasis in the United States where most cases do not have skin lesions at all (only GAE), and if skin lesions are present, they exist in combination with CNS manifestations (CDC unpublished data). This is in contrast to Peruvian cases, in which skin lesions precede CNS involvement (8). Cutaneous

balamuthiasis characteristically presents with painless swelling and skin redness; however, physical exam findings vary widely, including ulcers, indurated plaques, and polypoid/warty configurations, sometimes mimicking cutaneous neoplasms such as squamous cell carcinoma (8, 9, 18). *B. mandrillaris* has a predilection for skin of the central face and extremities, and lesions are usually solitary. Cutaneous disease typically has a subacute to chronic clinical course – month to years may pass before a definitive diagnosis is made. GAE has a prodromal phase with nonspecific neurologic signs (e.g., headache, fever, nausea, photophobia) lasting weeks to months followed by a rapidly progressive phase which may be heralded by seizures, focal sensory-motor deficits, or lethargy soon followed by coma and death in over 90% of the reported cases (2, 8). Given the rarity of amebic infections and nonspecific symptoms, clinical diagnosis of *B. mandrillaris* infection is frequently incorrect. Most likely, a significant proportion of cases go undiagnosed and unreported. Even when *B. mandrillaris* is clinically suspected, histopathologic and laboratory diagnosis can still be challenging. Serologic tests can detect circulating antibodies against ameba by ELISA, indirect immunofluorescence, and Western blot. In addition, direct immunofluorescence staining with rabbit anti-*Balamuthia* sera exists as well. Immunohistochemical assays targeting free-living amebae have also been developed. Recently, PCR assays using primers against mitochondrial rRNA gene regions specific for *Balamuthia* have been developed. Real time PCR assays can have exquisitely high sensitivity, with the capability of detecting as few as a single ameba per sample (9). Given the rarity of suspected *B. mandrillaris* infection, these tests are not widely available outside of a few reference laboratories such as CDC. Because the diagnosis is usually not suspected clinically, pathologists can have a pivotal role in facilitating timely diagnosis. The histopathologic inflammatory pattern is usually non-caseating granulomatous inflammation or mixed inflammation. Usually, both trophozoites and cysts are present in tissue specimens. Nevertheless, recognition of the organisms is hindered by their sparse number relative to the extensive inflammation, as well as their resemblance to histiocytes. Cysts are round, 15–30 μm in diameter, have a thick outer wall, a bubbly cytoplasm with refractile granules, and an inconspicuous nucleus. They are easily mistaken for degenerating histiocytes. Trophozoites are round, oval, or irregular in shape and 12–60 μm in diameter. Most are uninucleate and contain bubbly amphophilic cytoplasm. The most helpful findings are the small nuclei with distinctive morphology imparted by a perfectly round shape, an extremely large nucleolus—(the “karyosome”)—more than one half the diameter of the nucleus, and a thin or unapparent nuclear membrane. However, not all trophozoites have the characteristic nuclear features and if the nuclei of the trophozoites are not represented in the plane of section, the organisms will likely go unnoticed. Also, *Balamuthia* and *Acanthamoeba* trophozoites have similar morphology in histopathologic sections and distinction may be difficult. The presence of multiple nucleoli may favor *Balamuthia* trophozoites over *Acanthamoeba* (8) (Figure 2c). If the pathologist suspects amebic infection in biopsy specimens, immunohistochemical stains and molecular PCR assays can provide diagnostic confirmation and species identification.

For patients presenting with cutaneous lesions, the most feared complication is CNS involvement and development of GAE, which is fatal if untreated or if treatment is delayed to the advanced stages of the disease. Unfortunately, the majority of the reported GAE cases have been diagnosed at autopsy. Nevertheless, there are reports in which GAE has been

diagnosed early and successfully treated (19, 20). Therefore, early biopsy of skin lesions and correct histopathologic diagnosis before patients develop advanced CNS injury may be lifesaving in some cases.

Conclusion

This report serves to raise awareness of cutaneous lesions due to *Balamuthia mandrillaris*, a rare and potentially deadly infection when complicated by CNS involvement. Delayed diagnosis is typical due to the rarity of this disorder, its nonspecific clinical findings, and nonspecific histopathologic findings—with the exception of scattered organisms exhibiting subtle but characteristic morphologic features. When the diagnosis is clinically unsuspected, biopsy of skin lesions may provide the first and only avenue for timely diagnosis and early intervention. Thus, infection by *B. mandrillaris* and other pathogenic amebae should be included in the histopathologic differential diagnosis of granulomatous dermatitis, and dermatopathologists should be familiar with the appearance of these organisms in routinely stained histopathologic sections.

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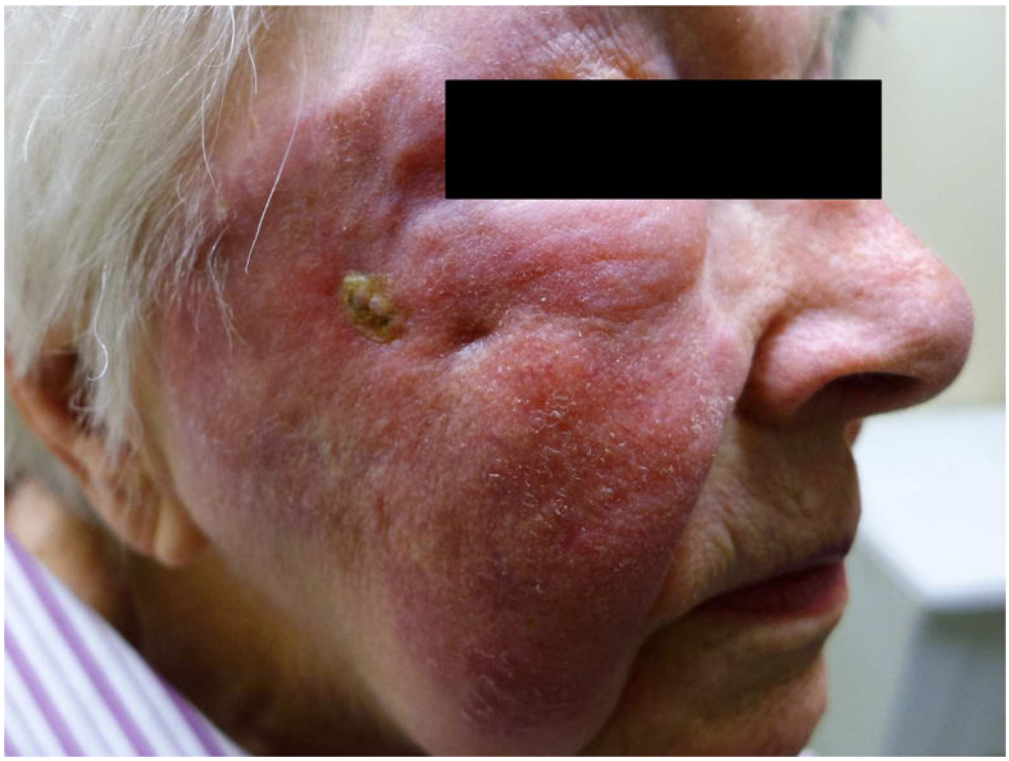
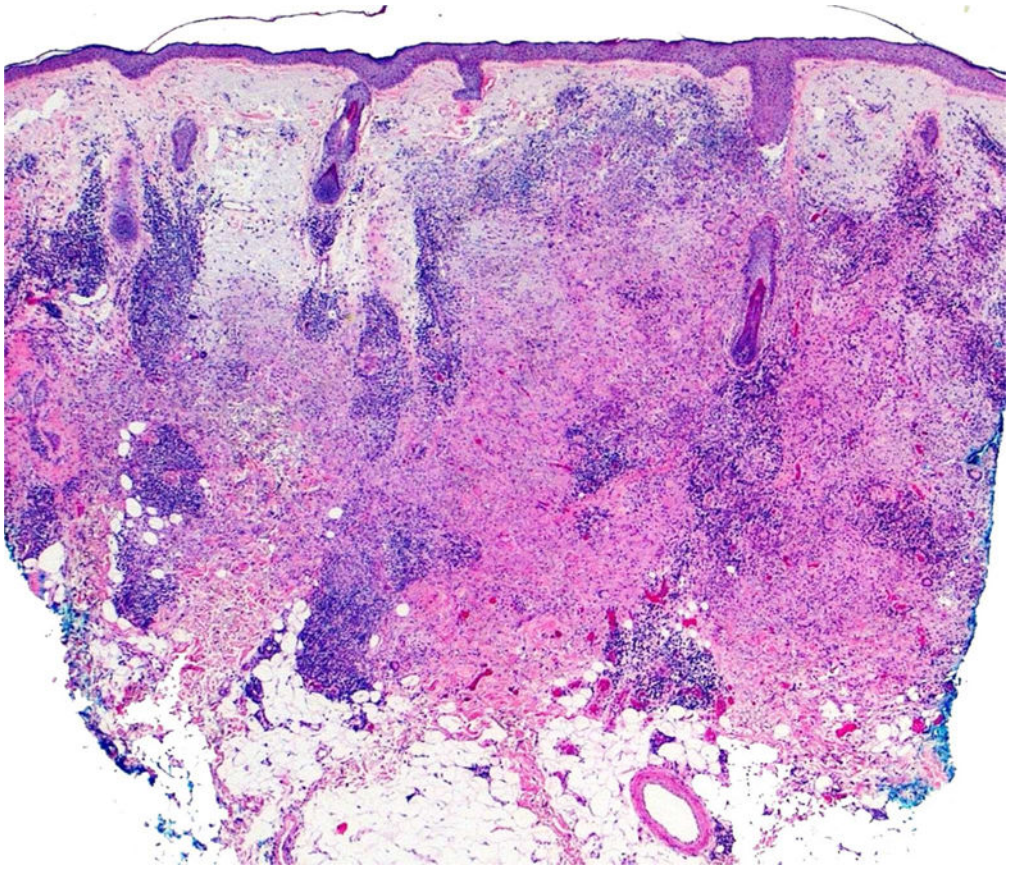
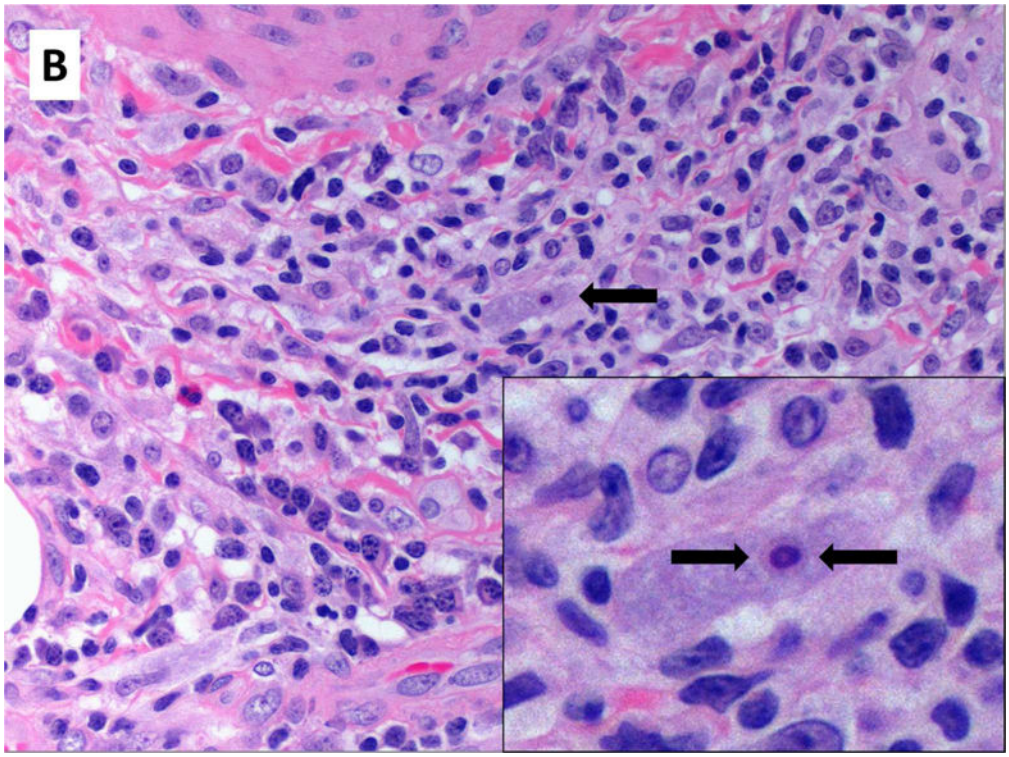


Figure 1.
Clinical appearance of an erythematous and indurated plaque on the right cheek. The lesion shown is approximately 1-year old.





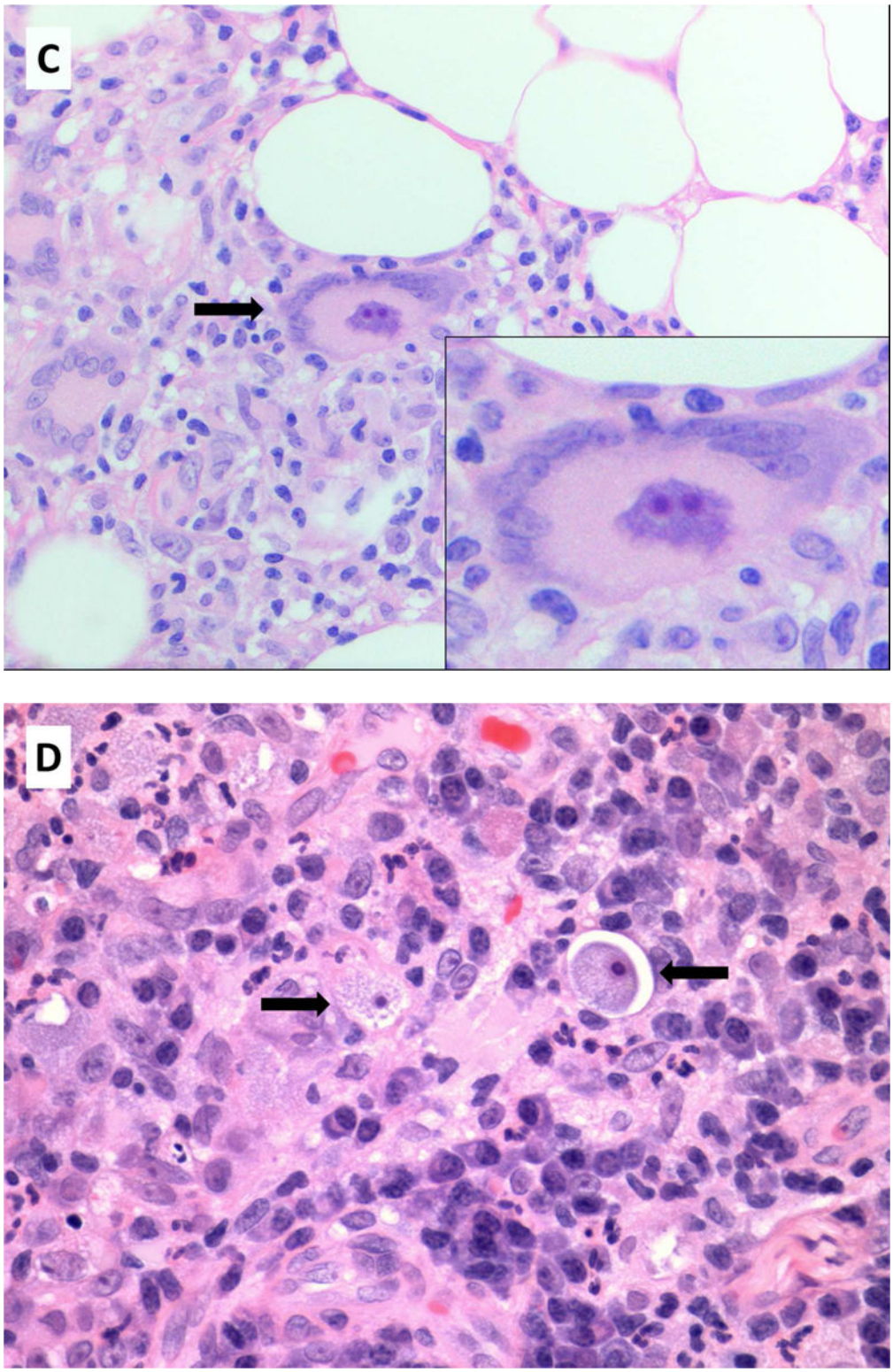


Figure 2.

a. Non-caseating granulomatous inflammation and lymphoid aggregates involving the dermis and subcutaneous fat without epidermal abnormalities (hematoxylin-eosin, ×20).

b. An amebic organism (arrow and inset) with pale-gray, bubbly cytoplasm, round nucleus, and prominent nucleolus, imparting a targetoid appearance in an area of chronic inflammation (hematoxylin-eosin, ×400).

c. An area of granulomatous inflammation with a binucleate ameba inside of a multinucleated histiocyte giant cell (arrow and inset)(hematoxylin-eosin, ×400).

d. Two amebae (arrows) with retraction artifact imparting a lacunar appearance on the right (hematoxylin-eosin, ×400).

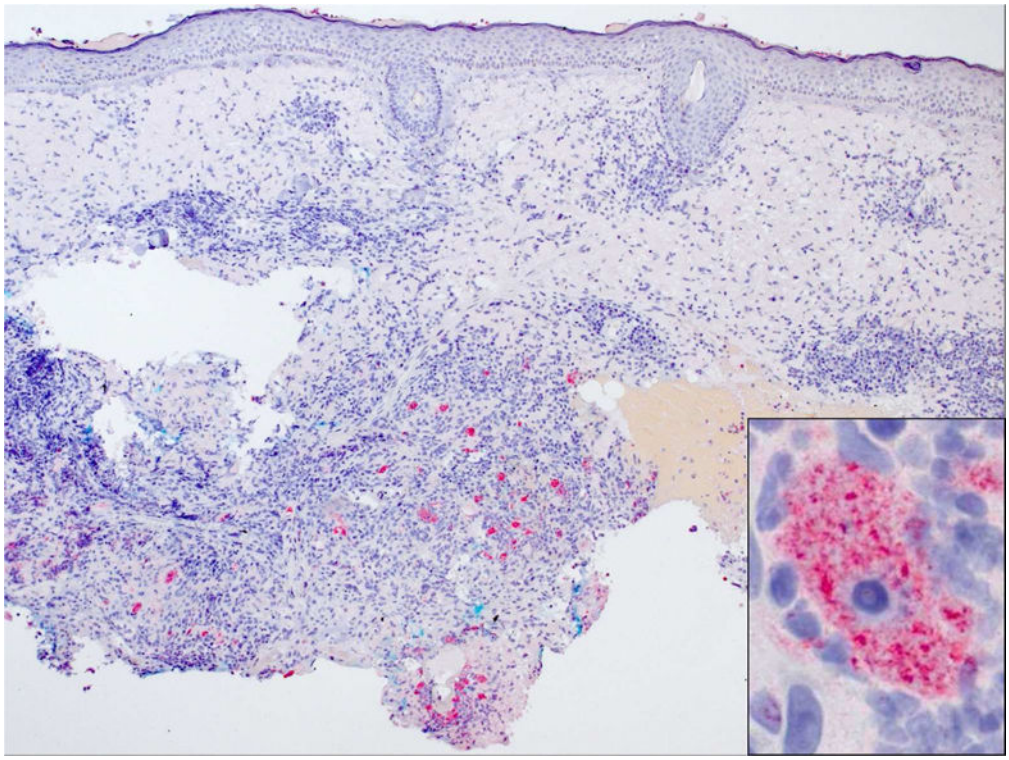


Figure 3.
Immunohistochemical staining with a red chromogen highlights multiple amebae in the deep dermis with granular cytoplasmic immunoreactivity (inset)(anti-free living amebae pooled antibody,×40).

Table 1

Morphologic comparison of *B. mandrillaris* trophozoites and histiocytes in H&E-stained sections

	Trophozoites	**Foamy histiocytes**	**Epithelioid histiocytes**
Cytoplasm	Bubbly, faint amphophilic	Bubbly, colorless	Solid, eosinophilic
Nucleus	Small and perfectly round	Oval-to-reniform	Oval-to-reniform
Nuclear membrane	Delicate-to-absent	Thin	Thin
Nucleolus	Large, sometimes occupying nearly the entire nucleus	Inconspicuous	Inconspicuous