Cutaneous Amebiasis: 50 Years of Experience

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Although cutaneous amebiasis (CA) is a rare disease, it is a public health concern worldwide, particularly in developing nations. It gains importance because of its severe clinical course, which can be confused with other disorders. Therefore, knowledge of its clinical features, histopathology, and pathogenesis is essential. We present a retrospective analysis over 50 years of 26 patients with CA who were diagnosed and treated at 2 Mexican institutions. Our main focus was to draw clinical information to identify mechanisms by which amebae reach the skin, occurring in a relatively small percentage of infected individuals. The recorded data included age and sex of the patients, form of presentation, any associated illnesses and/or factors, and methods for diagnosis. Histologic slides were reviewed in all cases; cytologic preparations also were available for 6 cases. Most patients were male (overall male to female ratio, 1.9 to 1). The disease always presented as painful ulcers containing varying amounts of amebae microscopically; the amebae were fairly easy to identify with routine stains, particularly when examination of tissue or smears was prepared from the edges of the ulcer instead of the necrotic centers. Erythrophagocytosis by the trophozoites was found and represented an unequivocal sign of its pathogenicity. We review the 2 mechanisms by which the organisms reach the skin. Most cases resolve with the use of specific antiamebic drugs; however, if left untreated, progression is rapid and unrelenting, sometimes with massive destruction of skin and subcutaneous tissues. Therefore, CA is a particularly virulent form of amebiasis.

Cutaneous amebiasis (CA) can be characterized as injury to the skin and underlying soft tissues by trophozoites of Entamoeba histolytica.1,2 Other species of the genus such as Entamoeba hartmanni, Entamoeba coli, Entamoeba gingivalis,3 and Entamoeba dispar4 are considered nonpathogenic. Entamoeba dispar has now been recognized as responsible for many cases of amebiasis in patients who were previously considered “healthy carriers.” It is morphologically indistinguishable from E histolytica but genetically and serologically different.5,6 Entamoeba moshkovskii is morphologically indistinguishable from E histolytica and E dispar but also is biochemically and genetically different; until recently, it has been considered to be a primarily free-living ameba and is nonpathogenic for the immunocompetent host.7 Cutaneous amebiasis may be the only expression of disease, but more commonly it has been associated with amebic colitis and/or involvement of other organs such as the liver and lungs and exceptionally the central nervous system.8,12

Free-living amebae (ie, Acanthamoeba, Balamuthia, Naegleria) are opportunistic organisms that act as pathogens, usually in an immunocompromised host, and can develop disease in any organ including the skin and central nervous system. Reports of this form of amebiasis have become more common.8-14

We conducted a retrospective study of cases of CA that presented over 50 years to better understand the presentation of different forms of CA, the mechanisms by which amebae reach the skin, and the criteria for clinical diagnosis as well as histologic features.

Methods

All patients with an unequivocal diagnosis of CA (1955-2005) based on the clinical course and histopathologic identification of trophozoites were

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retrieved from our files at the Service of Dermatology at the Hospital General de México, Mexico City, and the Department of Pathology at the Hospital de Especialidades Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City. The clinical information was collected from the medical records and/or the histopathology requisition form. Paraffin blocks housing skin specimens were recut and stained with hematoxylin and eosin and periodic acid–Schiff. The slides were examined individually and then jointly. Papanicolaou-stained smears from the ulcers were performed in 6 cases prior to biopsy. These smears also were examined in the same way by the 3 investigators.

Bacteriologic cultures from the necrotic center and edges of the ulcers as well as stool analysis for ova and parasites were performed in all cases. Chest and abdominal radiographs also were performed. Clinical data were registered from all of the patients including age, sex, and clinical course before and after treatment.

Results
A total of 26 patients were reviewed including 15 new adult cases as well as 7 adult and 4 pediatric cases that had been included in a prior report. The age range of the 22 adult patients was 21 to 63 years (mean age, 42 years); there were 16 men and 6 women (male to female ratio, 2.7 to 1). The age range of the 4 infants...

Figure 1. An ulcer from an amebic abscess at the site of a catheter.
Figure 2. Ulcers of the penis, a common presentation of cutaneous amebiasis.
Figure 3. Several wide and destructive ulcers involving the perianal area and genitalia in a male.
was 5 to 9 months (mean age, 7.25 months); 1 infant was male and 3 were female.

The presence of 1 or several variably sized, painful, and malodorous cutaneous ulcers with a gray-white and deeply set necrotic base and slightly raised, red edges was common in all patients (Figures 1–4). The ulcers measured a few millimeters to several centimeters; CA ulcers tend to rapidly increase in width and depth, sometimes reaching the underlying skeletal muscle. Biopsies confirmed the presence of amebae in the ulcer site of all patients. In 6 patients, amebae were identified by cytologic smears of the lesions prior to biopsy (Figure 5).

Microscopically, the trophozoites of *E histolytica* were fairly easy to identify, even on hematoxylin and eosin–stained sections and cytology preparations. They generally were round or oval, unicellular, pale, basophilic organisms measuring 20 to 50 μm, and often were surrounded by a clear halo, which was presumed to be a retraction artifact due to dehydration of the tissue. A nucleus measuring 4 to 7 μm usually was present (Figure 6).

Nuclei are commonly seen in wide areas of necrotic tissue debris and appear as finely granular, eosinophilic, bland material with nuclear dust. The necrosis often reaches the entire thickness of the subcutis into the muscle. This kind of necrosis, possibly due to the presence of the parasite itself, is characteristic of CA. It also is similar to other affected anatomic sites such as the liver, intestinal wall, and lung. This finding was highly suggestive, if not diagnostic, of amebiasis.

There was a mixed inflammatory infiltrate consisting of neutrophils, lymphocytes, and eosinophils, generally in association with extravasated erythrocytes in all patients. Erythrophagocytosis by amebae was a constant feature in our patients with CA and represented an unequivocal microscopic sign of its pathogenicity. No granulomas were seen, which generally is true of amebiasis.
Comment
Amebiasis is public health concern worldwide, particularly in developing nations. The first encounters with amebiasis were most likely recorded by Hippocrates who discussed dysentery in association with inflammation of the liver. In 1875, amebic trophozoites in the stool and colonic ulcerations were described in a man with fatal dysentery. The parasite also was reported to be associated with diarrhea in children. 16

The first case of CA most likely was published by Jiménez18 in 1872. The patient was a young man with an amebic liver abscess; he was treated with drainage through the chest wall and subsequently developed destructive skin ulcers around the catheter. In 1949, another case of CA in a 34-year-old man with 3 ulcers was published. The diagnosis of CA was based on a smear from the perianal ulcer, which showed amebae; the patient was cured with emetine.19 Another case of a 45-year-old woman who developed a severe and fatal form of CA was published in 1956.20 It presented on the left ala nasi and grew to destroy the central structures of her face. The diagnosis was made following her death once trophozoites were identified on slides that were prepared from the borders of her large ulcer. The authors also presented a detailed review of the cases of CA that had already been published.21

Based on our evaluation and previously reported cases, we propose that there are at least 3 clinical patterns of presentation of CA: (1) CA affecting the anus, perianal region, and genitalia; (2) CA on the chest wall linked to the placement of a catheter and sites of a colostomy or laparotomy; and (3) other cases affecting the face, trunk, and/or extremities. Children generally develop the first pattern of CA, usually in association with amebic dysentery, as in our 4 cases15 and 7 more cases described in the literature.21-23 However, adults can develop any of these patterns, which frequently but not always are associated with colonic amebiasis.24-26

Understanding the life cycle of *E histolytica* helps to explain the propagation of the disease. There are 2 stages: the cyst stage or infective stage, and the trophozoite stage or tissue-invasive stage. In the cyst stage, food and water sources are contaminated. Amebae measure 10 to 25 μm and have 4 nuclei. They are able to survive for a brief time outside of the body and can survive the acidic environment of the stomach. They also inhabit the ileum where they activate 8 trophozoites as they move on to the lumen of the colon, particularly the cecum, which is the preferred site. They multiply by binary fission and invade the intestinal wall, eventually penetrating the blood vessels and spreading through the bloodstream, most often to the liver, gaining access to the portal circulation. They may return to the quadrinucleated cyst stage after 2 successive nuclear divisions.27

Amebae reach the skin and develop any of the 3 clinical patterns through 2 mechanisms: direct transmission and indirect transmission of the trophozoites.2 Direct transmission results in the spread from the colon and rectum to the anus, perianal/perineal regions, and pubic or genital skin. It is the most common form in adults but also is the mechanism of disease in infants. Indirect transmission results when blood-borne trophozoites reach the liver or rarely other organs such as the lung and/or the chest wall, migrating to the skin. However, any other area of the skin may be infected by scratching with a contaminated hand. Male genitalia may become infected from anal intercourse.

Cutaneous amebiasis is an uncommon disease but is still found in many areas of the world. In Mexico, occurrence was frequent from 1960 to 1980; its incidence was estimated to be 1 of 300 dermatology patients (children and adults) at the Hospital General de México.28 An impressive reduction in incidence was achieved when metronidazole, emetine, and dehydroemetine became readily and more widely available. Intestinal amebiasis is still a global public health issue because there are 500 million individuals infected with *Entamoeba*, both with and without symptoms. It is estimated that 40,000 to 100,000 individuals die each year of amebiasis worldwide.17

Amebae release several enzymes to break down tissue, including protease, collagenase, hyaluronidase, α-N-acetylglucosaminidase, phospholipase A1, and unspecified secretagogue. Amebae also are mobile. Phagocytosis, engulfing a number of cells such as erythrocytes, is an unquestionable histopathologic sign of the pathogenicity of CA.2 Phagocytosis was present in all our cases, even though experimentally it has not always been related to the virulence of *E histolytica*.29

Conclusion
Cutaneous amebiasis is a severe form of amebiasis. It possibly occurs in association with more virulent strains of amebae or because of specific and unidentified factors that lead to greater susceptibility of the host, which could explain why CA is so rare, aggressive, and destructive.2 Once immobilized by specific antibodies, amebae can localize the antigen-antibody complexes to a cap on the cell surface, subsequently ingesting or shedding and becoming mobile once again. In this manner, they evade the immune response, which explains the apparent ineffectiveness of antibodies to limit established infections.30
REFERENCES


