Cutaneous Amebiasis in Pediatrics

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Background: Cutaneous amebiasis (CA), which is still a health problem in developing countries, is important to diagnose based on its clinical and histopathologic features.

Observations: Retrospective medical record review of 26 patients with CA (22 adults and 4 children) treated from 1955 to 2005 was performed. In addition to the age and sex of the patients, the case presentation, associated illness or factors, and method of establishing the diagnosis, clinical pictures and microscopic slides were also analyzed.

Conclusions: Cutaneous amebiasis always presents with painful ulcers. The ulcers are laden with amebae, which are relatively easy to see microscopically with routine stains. Erythrophagocytosis is an unequivocal sign of CA. Amebae reach the skin via 2 mechanisms: direct and indirect. Amebae are able to reach the skin if there is a laceration (port of entry) and if conditions in the patient are favorable. Amebae are able to destroy tissues by means of their physical activity, phagocytosis, enzymes, secretagogues, and other molecules.

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Cutaneous amebiasis (CA) can be defined as damage to the skin and underlying soft tissues by trophozoites of Entamoeba histolytica, the only pathogenic form for humans. Cutaneous amebiasis may be the only expression of the disease or may involve other organs, usually the gastrointestinal tract. The liver, lungs, and especially the central nervous system may also be involved.

Other species of Entamoeba, such as Entamoeba hartmanni, Entamoeba coli, and Entamoeba gingivalis, are nonpathogenic. Interestingly, another species, Entamoeba dispar, identified by Brumpt in 1925, has been recognized as being responsible for many cases of CA in patients previously interpreted as “healthy carriers.” Entamoeba dispar is morphologically indistinguishable from E histolytica but genetically and serologically different.

Entamoeba moshkovskii, which is morphologically indistinguishable from E histolytica and E dispar but biochemically and genetically different, has been considered until recently to be primarily a free-living (nonpathogenic) ameba. The early isolates of E moshkovskii were free-living forms found in sewage, but human isolates have now been detected in North America, Africa, Australia, and some parts of Europe. The group of amebae known as free-living amebae, Acanthamoeba, Balamuthia, and Naegleri, are opportunistic organisms that act as pathogens, usually in the immunocompromised host, who can develop disease in any organ, such as the skin and central nervous system. This kind of amebiasis has become more common during the last few years. To determine the forms of presentation of CA in pediatric patients and the mechanisms by which amebae reach the skin, we performed a retrospective study of patients cared for during the last 50 years at 2 major hospitals in Mexico City, Mexico.

METHODS

All patients with an unequivocal diagnosis of CA based on the clinical and histopathologic identification of trophozoites were retrieved from our files at the Clinic for Pediatric Dermatology of the Hospital General de México and from the Department of Pathology of the Hospital de Especialidades of the Centro Médico Nacional IMSS, from 1955 to 2005. The clinical information was collected from the clinical records and/or by histopathologic request. Paraffin-embedded blocks that housed skin specimens were recut and stained with hematoxylin-eosin. Slides were prepared to be read under the microscope.

Bacteriologic studies from ulcers and necrotic edges and parasitoscopic analysis from stool samples were performed at the time of presentation for care. Results of these tests were retrieved from patient records. Clinical pictures of all patients were taken before and after treatment.
RESULTS

There were 22 adults and 4 children (all <2 years old) identified with CA. The constant and common clinical denominator of the 4 children was a putrid, painful ulcer, which ranged from 1 to several perineal ulcers. Ulcers showed a gray-white necrotic base, with red edges, that extended rapidly in diameter and depth, during a period of weeks, at the rate of approximately 1 cm/wk. The ulcer measured from a few millimeters to several centimeters (Figure 1 and Figure 2).

The 4 pediatric patients were all toddlers using diapers. All these patients had amebic colitis and developed amebic diarrhea. The diaper maintained contact of the trophozoites with the skin. Therefore, the anatomical sites of the ulcers were in the diaper area: anus and perianal area, buttocks, perineal, inguinal folds, and pubis. Patient 1 has been previously described by 1 of us (M.M.) as an example of this disease in children.

Diagnosis was clinically suspected and confirmed by skin biopsy. Trophozoites of *E histolytica* were identified as round or oval unicellular basophilic structures, measuring 20 to 50 µm, often surrounded by a clear halo, which is assumed to be tissue retraction due to dehydration, and with a nucleus measuring 4 to 7 µm (Figure 3). By performing a smear from the edge of the ulcers, we were to show the amebae in 2 of our patients (patients 1 and 3).

At least 1 ulcer that involved the epidermis and dermis to a variable depth was seen. Often there were wide areas of necrosis, with fine granular and eosinophilic bland material with nuclear debris. Surrounding the ulcers was a mixed inflammatory infiltrate of neutrophils, lymphocytes, and eosinophils, generally in association with extravasated erythrocytes. Erythrophagocytosis by amebae was a constant feature in CA and represents a microscopic sign of its pathogenicity. No granulomas are seen in amebiasis.

In all 4 pediatric patients, microscopic examination of the stool sample showed a cyst of *E histolytica*; cultures of the ulcers yielded *Staphylococcus epidermidis* and *Escherichia coli*. Cultures from blood and cerebrospinal fluid yielded no growth of bacteria. In 2 patients (patients 1 and 4), we were able to perform serologic tests in which an enzyme-linked immunosorbent assay reaction was positive for *E histolytica*.

Chest radiographs from the 4 pediatric patients showed right hemidiaphragm elevation in 2 of them and abdominal radiography confirmed hepatomegaly in those 2, but no other alterations were seen in the 4 pediatric patients.

All these children were treated with dehydroemetine, 1 mg/kg daily for 10 days, and metronidazole, 30 mg/kg daily for 21 days. Escharotomy, cleaning, and dressing changes were performed daily for all patients. This regimen produced rapid improvement in days to weeks, with all ulcers healing by the second week of care. Patient 1, who had the most severe case of CA, was referred to the plastic surgery service for reconstruction of the vulva and perineum. The other 3 children healed without the need for reconstruction.
Table. Cutaneous Amebiasis in Pediatric Patients

<table>
<thead>
<tr>
<th>Patient No./Sex/Age</th>
<th>Reference(s)</th>
<th>Location</th>
<th>Associated Factors</th>
<th>Method of Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/8 mo</td>
<td>22</td>
<td>Vulvar</td>
<td>Dysentery, pneumonia, meningitis</td>
<td>Cytologic testing</td>
<td>Medical</td>
<td>Died</td>
</tr>
<tr>
<td>2/M/10 mo</td>
<td>22</td>
<td>Inguinal</td>
<td>Dysentery, pneumonia</td>
<td>Cytologic testing</td>
<td>Medical</td>
<td>Healed</td>
</tr>
<tr>
<td>3/F/13 mo</td>
<td>22</td>
<td>Vulvar</td>
<td>Dysentery</td>
<td>Cytologic testing</td>
<td>Medical</td>
<td>Healed</td>
</tr>
<tr>
<td>4/M/9 mo</td>
<td>23</td>
<td>Abdomen</td>
<td>Dysentery</td>
<td>Postmortem histopathologic analysis</td>
<td>Medical</td>
<td>Healed</td>
</tr>
<tr>
<td>5/F/4 mo</td>
<td>24</td>
<td>Vulvar</td>
<td>Liver abscess, dysentery</td>
<td>Histopathologic analysis</td>
<td>Medical, surgical</td>
<td>Healed</td>
</tr>
<tr>
<td>6/F/14 mo</td>
<td>25</td>
<td>Anal, rectal, perineal, vaginal</td>
<td>Dysentery</td>
<td>Histopathologic analysis</td>
<td>Medical, surgical</td>
<td>Healed</td>
</tr>
<tr>
<td>7/F/12 mo</td>
<td>26</td>
<td>Vulvar</td>
<td>Liver abscess, dysentery</td>
<td>Serologic testing</td>
<td>Medical</td>
<td>Healed</td>
</tr>
<tr>
<td>8/F/17 mo</td>
<td>27</td>
<td>Right orbita</td>
<td>Dysentery</td>
<td>Cytologic testing, histopathologic analysis</td>
<td>Medical, surgical</td>
<td>Healed</td>
</tr>
<tr>
<td>9/M/9 y</td>
<td>28</td>
<td>Perianal</td>
<td>Dysentery</td>
<td>Cytologic testing</td>
<td>Medical</td>
<td>Healed</td>
</tr>
<tr>
<td>10/F/7 mo</td>
<td>Present and 19</td>
<td>Vulvar, perineal</td>
<td>Dysentery</td>
<td>Cytologic testing, histopathologic analysis</td>
<td>Medical, surgical</td>
<td>Healed</td>
</tr>
<tr>
<td>11/F/5 mo</td>
<td>Present</td>
<td>Vulvar</td>
<td>Dysentery</td>
<td>Histopathologic analysis</td>
<td>Medical</td>
<td>Healed</td>
</tr>
<tr>
<td>12/F/9 mo</td>
<td>Present</td>
<td>Anal, perianal</td>
<td>Dysentery</td>
<td>Cytologic testing, histopathologic analysis</td>
<td>Medical</td>
<td>Healed</td>
</tr>
<tr>
<td>13/M/8 mo</td>
<td>Present</td>
<td>Entire diaper area</td>
<td>Dysentery</td>
<td>Histopathologic analysis, serologic testing</td>
<td>Medical</td>
<td>Healed</td>
</tr>
</tbody>
</table>

**COMMENT**

Historically, the first patient with amebiasis seems to have been treated in Mexico by Mateo Aleman, the physician of the then archbishop and viceroy of New Spain, who in 1611 presented with “diarrhea followed a few days later by hepatic suppuration.” Nevertheless, Hippocrates recognized that “dysenteries in association with inflammation of the liver are bad,” and in 1875 Losch described amebic trophozoites in the stool and colonic ulcerations of a man with fatal dysentery. However, other authors state that the first identification of the parasite associated with diarrhea was made in children by Lamb and that Losch reproduced the intestinal disease in a dog by means of the feces from an individual with dysentery.

In children CA is rare; when it occurs, it usually, if not always, develops in the anal and perianal area and the genitalia, usually in association with amebic dysentery, as can be deduced from our 4 patients and 9 others mentioned in the literature (Table). Biagi and Martuscelli described 3 patients: a male with inguinal involvement and 2 females with vulvar ulcers, 1 of whom died of CA and the other who healed in a 10-day period after treatment with emetine hydrochloride. A 9-month-old boy with lesions on the abdomen died without treatment—the diagnosis was obtained post mortem. Alvarez Chacon, Wynne, and Rimsza and Berg each published articles describing a girl with ulcers on the vulva, which healed with medical treatment after approximately 10 days. Two other children with CA were exceptional because of where it developed on one child (on the right periorbital skin) and in the other because of the child’s age (a 9-year-old) and where it developed (perianal ulcers and diarrhea in the diaper area on child who did not wear diapers). Both responded well to medical treatment.

In general, all these children presented with dysentery, fever (body temperatures, 39°C-40°C), irritability, weight loss, anemia, and leukocytosis. When medical treatment (emetine, dehydroemetine, metronidazole, or diiodohydroxyquinoline) is initiated, CA responds soon and well; however, because of the destructive character of the disease, surgical repair is often needed.

To better understand the pathogenesis of CA, it is convenient to briefly review the life cycle of *E histolytica*. It consists of 2 stages: the cyst or infective stage and the trophozoites or tissue-invasive stage. The disease is usually acquired by ingesting food or water contaminated with cysts, which are 10 to 25 µm and have 4 nuclei; they are capable of surviving for days outside the body and are also able to survive the acidic environment of the stomach and excyst in the ileum. Each cyst gives origin to 8 trophozoites, which live in the lumen of the colon, where they multiply by binary fission and from where they may invade the intestinal wall and eventually penetrate a blood vessel and spread though the bloodstream, most often to the liver, or they may encyst and produce quadrinucleated cysts after 2 successive nuclear divisions. Therefore, amebae reach the skin and develop any of the patterns described herein through 2 mechanisms: direct and indirect transmission of the trophozoites.

Direct infestation results with the spread from the colon and rectum to anal, perianal, perineal, pubic, or genital skin, which is the mechanism of CA in infants (and is the most common form in adults) and thus deserves special mention not only for its rareness but also because all 4 of our pediatric patients share the same clinical picture with those previously described: they are all younger than 2 years.

Cutaneous amebiasis is preceded or accompanied by diarrhea. Because of these patients wear diapers, trophozoites are able to remain in contact for a longer time with the skin surface and, surely the association of diapers with humidity and ammonia due to urine and bacteria due to feces may play an adjuvant role.

Indirect transmission results when the trophozoites invade the intestinal wall, penetrate a vessel, and reach the liver; rarely, trophozoites invade other organs, such as
as the lung and/or chest wall, and migrate to the skin. However, any other area of the body may be infected via a contaminated hand by scratching.

Although CA is not a common disease, it certainly is still a public health problem in many areas. In Mexico, it was more frequent from 1960 to 1980, when its incidence was estimated to be 1 of every 300 dermatologic patients (children and adults) at the Hospital General de México. Most cases observed in Mexico have been treated in this institution, which assists mostly indigent people. Now, it may be less common because metronidazole, emetine, and dehydroemetine are readily and widely available.

Amebiasis is an even more important public health problem than CA. There are 500 million individuals infected with Entamoeba. Although most people are colonized with E dispar, which is not pathogenic, many of those individuals have E histolytica, with or without symptoms. An estimated 40,000 to 100,000 people worldwide die yearly of amebiasis. Cutaneous amebiasis should be considered in the differential diagnosis of any ulcer in the diaper area of a child and in other areas such as the abdominal wall (because of a colostomy site, draining of a hepatic abscess, or laparotomy incision). Malnutrition, poor hygiene, and preexisting disease contribute to the development of CA in infants and toddlers. Lysis and necrosis of the skin (and other tissues) are consequences of the interaction between the host and ameba. The necrosis, probably because of the presence of the parasite itself, is specific to this disease and is similar in any tissue: liver, intestinal wall, or lung. Amebae release proteases, collagenase, hyaluronidase, N-acetylglucosaminidase, phospholipase-A2, and secretagogues. Amebic motility and phagocytosis of erythrocytes are unquestionable histopathologic signs of pathogenicity, seen in all our cases. Experimentally, phagocytosis has not always been found to be related to virulence of E histolytica. In addition, ameba are capable of capping, ingesting, or shedding ameba-specific antibodies, which may explain the apparent ineffectiveness of antibodies to limit established infections. We hypothesize that CA is a rare, aggressive, and destructive form of the disease because of a more virulent strain or a specific susceptibility of the host.

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Author Contributions: Drs M. L. Magaña, Fernández-Diez, and M. Magaña had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: M. L. Magaña, Fernández-Diez, and M. Magaña. Acquisition of data: M. L. Magaña, Fernández-Diez, and M. Magaña. Analysis and interpretation of data: M. L. Magaña, Fernández-Diez, and M. Magaña. Drafting of the manuscript: M. L. Magaña, Fernández-Diez, and M. Magaña. Critical revision of the manuscript for important intellectual content: M. L. Magaña, Fernández-Diez, and M. Magaña. Statistical analysis: M. L. Magaña, Fernández-Diez, and M. Magaña. Obtained funding: M. L. Magaña, Fernández-Diez, and M. Magaña. Administrative, technical, or material support: M. L. Magaña, Fernández-Diez, and M. Magaña.

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