A 6-year-old child living in Nebraska presented with a 6-month history of a sore on the left arm. Treatment with a 10-day course of oral cephalexin was unsuccessful, and the lesion gradually increased to the size of a quarter with mild itching and tenderness. The child was afebrile throughout the course and was able to pursue normal activities. On examination, the lesion was a shallow 2 × 2 cm moist ulcer with no bleeding, minimal tenderness, and a few tiny satellite lesions surrounding the ulcer (Figure 1A). There was no associated palpable lymphadenopathy. No other skin lesions or other abnormal findings were noted in physical examination.

Skin (punch) biopsies were sent to the Centers for Disease Control and Prevention (CDC) for bacterial, mycobacterial, and fungal cultures. Histological sections stained with hematoxylin-eosin showed a hyperkeratotic epidermis in 1 biopsy and an ulcerated epidermis in another. A diffuse dense mixed granulomatous dermal inflammatory infiltrate of lymphocytes, histiocytes, plasma cells, neutrophils, and multinucleated giant cells was present throughout the biopsies (Figure 1B). Inflammation extended into the epidermis. Multiple intracellular oval 2–4 µm in size organisms were identified inside macrophages (Figure 2A) on high-power light microscopy. Giemsa-stained touch preparations demonstrated round to oval organisms measuring 2–4 µm with a 1 µm round nucleus and a smaller bar-shaped paranuclear kinetoplast (Figure 2B). A microbe was isolated in culture.

Questions:
• What is the most likely organism causing the cutaneous lesion in this child?
• What additional history would “connect the dots” between the causative microbe and this child?
• What differential diagnosis should be considered in evaluation of ulcerating skin lesions?

Figure 2. (A) High power (1000x) microphotograph of H&E stained section shows multiple intracellular oval 2–4 mm in size organisms inside macrophages. (B) High power (1000x) microphotograph of touch preparation stained with Giemsa stain shows numerous intracellular microorganisms that have a round nucleus and smaller bar-shaped paranuclear kinetoplast.
Leishmaniasis describes a group of infectious diseases caused by species of the protozoan genus *Leishmania* [1]. Leishmaniasis is the 9th most common infectious disease worldwide but is considered a “neglected tropical disease” [2]. The genus has >20 pathogenic species with 1 or more endemic to >90 countries [3, 4]. There are approximately 1.1 to 1.6 million new cases and 70 000 deaths worldwide each year [1, 5]. Approximately 50 to 100 cases per year are reported in the United States [6]. Cutaneous leishmaniasis (CL) is approximately 3 times more common than visceral leishmaniasis (VL). Some infections are asymptomatic. Disease course and prognosis vary greatly among the different species, posing challenges in the advancement of research, disease control, and prevention [3].

**Vector, Reservoir, Transmission and Pathogenesis**

*Leishmania* spp are divided into Old World (Africa, Europe, Middle East and Asia) and New World (Americas) groups. All forms of leishmaniasis are transmitted by the bite of female phlebotomine sandflies [1, 7]. Animal reservoirs for some species include rodent and canine species [2]. Humans are needed to maintain the life cycle of some *Leishmania* spp (anthroponotic transmission), including *Leishmania tropica* [1]. *Leishmania* promastigotes are regurgitated from the gut of the sandfly into the skin while feeding. Sandfly saliva may induce vasodilatation in the skin that helps establish the infection. The incubation period ranges from a few weeks to several years [1, 4]. Our patient developed the lesion 2 months after the exposure.

After inoculation, promastigotes are phagocytized by macrophages and enveloped by a vacuole that fuses with a lysosome. In the lysosome, promastigotes lose their flagella and transform into amastigotes, which multiply, rupture the phagolysosome, and infect other mononuclear phagocytes. Sandflies ingest amastigotes, which then transform into promastigotes [1, 2, 5].

**Epidemiology**

Temperature, rainfall, and relative humidity, influence sandfly distribution, and thus occurrence of human disease. Epidemics may occur when large groups of nonnative or immunocompromised people enter an endemic area [1, 2]. Such events may be driven by natural disasters or armed conflicts. Tourism, urbanization of rural areas, and deforestation may influence exposure of individuals or populations. Cutaneous leishmaniasis prevalence increases with age up to approximately 15 years and then...
levels off, possibly due to immunity acquired from childhood infection in endemic areas. Other risk factors for disease include malnutrition, human immunodeficiency virus/acquired immune deficiency syndrome, household design, and exposure to domestic animals [1].

Endemic cases in the United States have been acquired in Texas and Oklahoma [5]. Cutaneous leishmaniasis has been recognized in a number of US military personnel returning from Afghanistan, Kuwait, and Iraq, with 522 cases reported from 2000 to 2004 [8]. Leishmania major has been most common overall. In Afghanistan, CL is predominantly caused by *L. tropica*, which is the predominant species in Afghanistan, with a disease prevalence of 1.9% overall with variation between different regions [9].

### Clinical Presentation of Leishmaniasis

Localized CL is the most common manifestation and typically begins as a small area of erythema that develops into a nodule which then ulcerates. Ulcers usually are surrounded by raised borders and often are covered by a central dry crust or scab [2]. Regional lymphadenopathy may occur, mimicking sporotrichosis [2, 4]. Lesions of CL are usually painless when not secondarily infected [4]. Spontaneous healing is common but may take 6–15 months with *L. tropica* [1]. Dissemination of amastigotes from the initial site of infection can lead to diffuse skin lesions across the entire body [1]. Diffuse CL is more common with *Leishmania aethiopica*, *Leishmania amazonensis*, and *Leishmania Mexicana* [2].

Up to 25% of localized CL cases, especially those caused by New World species, may progress to mucosal leishmaniasis (ML). Mucosal infection is most commonly caused by New World species, and especially *Leishmania braziliensis* [1]. The nose is most often involved, but lesions can occur in the mouth or throat. Nasal lesions are associated with congestion and inflammation. Ulceration and disfiguring perforation of the nasal septum can occur, with significant psychosocial impact. ML never heals spontaneously, can result in secondary bacterial infections, and is difficult to treat [1]. *Leishmania tropica* infections that result in chronic and persistent skin lesions are termed leishmaniasis recidivans and can progress to mucosal involvement [2].

Visceral leishmaniasis is most commonly caused by *Leishmania donovani* (Old World) and *Leishmania infantum* (New World) and presents with fever, malaise, weight loss, splenomegaly, hepatomegaly, hypergammaglobulinemia, and pancytopenia. The term kala-azar (“black fever” in Hindi) is applied to severe cases of VL. Untreated VL usually is fatal and has a case fatality rate of 10% in treated patients [4, 5]. In a group of American military personnel serving in Operation Desert Storm, *L. tropica* infection developed into viscerotrophic leishmaniasis, presenting with a chronic low-grade fever, malaise, fatigue, and occasionally diarrhea. Infection in the troops did not progress to hepatosplenomegaly, cachexia, and deterioration associated with VL [2].

### Diagnosis of Cutaneous Leishmaniasis

Diagnosis of CL requires parasitological identification by microscopic examination of biopsy smears or aspirates, histopathological examination of lesion biopsies, or culture of biopsies or aspirates [1]. Microscopic examination of skin biopsies is the most common and inexpensive diagnostic test but cannot distinguish the various *Leishmania* spp. Culture is recommended for species identification where more sophisticated techniques are available [1]. Leishmania promastigotes from biopsy specimens can be grown on Novy-MacNeal-Nicolle culture medium, Schneider’s insect medium, or other media containing fetal calf serum. Cultures are incubated at 24–26°C for a few days to several weeks [1, 2]. Species identification by PCR or isoenzyme identification is also recommended to guide appropriate treatment [4]. These tests are available at World Health Organization or CDC laboratories [2].

Splenic aspirates have the highest diagnostic sensitivity (>95%) for VL, but the procedure can be associated with life-threatening hemorrhage. Serologic testing can provide supportive etiologic evidence [5].

### Treatment of Cutaneous Leishmaniasis

Therapy for CL is indicated to reduce dissemination, promote healing and reduce morbidity. For cutaneous lesions without the risk of dissemination or mucosal involvement, topical therapy such as cryotherapy, thermotherapy and compounded paramomycin for single dose are options. Treatment is not always necessary.

Sodium stibogluconate (SSG), a pentavalent antimonial drug, at 20 mg/kg per day parenterally (intravenous or intramuscular) for 20 days, has been the mainstay of therapy for CL [4]. Toxicities to SSG include arthralgias, myalgias, chemical pancreatitis, and elevated liver function tests (LFTs), which requires monitoring. Parasite resistance has been increasingly observed [3]. Sodium stibogluconate is only available in the United States through the CDC via an Investigational New Drug (IND) protocol (without charge) [5]. Indications to stop treatment include the development of arrhythmias, prolongation of the corrected QT interval to >0.50 seconds, T-wave inversion with concave ST segments, elevation of LFTs to 4–5 times the upper normal limit, or moderate to severe clinical pancreatitis. Intraleisonal injections of SSG have also been used [10].
Increasing clinical evidence suggests that liposomal amphotericin B is a favorable alternative to SSG [11, 12]. The regimen commonly used for CL and ML 3 mg/kg intravenously daily for 6 to 10 days. Toxicities appear minimal with such short courses [10]. For VL in immunocompetent patients, 3 mg/kg daily on days 1–5, 14 and 21 is approved. For VL in immunocompromised hosts the approved regimen is 4 mg/kg daily on days 1–5, 10, 17, 24, 31 and 38 for a total of 40 mg/kg. Amphotericin B deoxycholate also is effective against CL and ML but carries risk of nephrotoxicity. Oral azoles have mixed results for CL.

Miltefosine was approved by the US Food and Drug Administration in March 2014 for treatment of VL and CL due to New World L. braziliensis, Leishmania panamensis, and Leishmania guyanensis in adults and adolescents at least 12 years of age [5]. A regimen for persons weighing 30–44 kg (One 50 mg oral capsule twice a day for 28 days) has been approved. One 50 mg capsule 3 times a day for 28 days is approved for those weighing ≥45 kg. In a study of 116 children ages 2 to 12 years old with CL due to New World leishmaniasis spp, miltefosine was superior to the antimonial meglumine with a cure rate of 83% at 26 weeks [13]. Miltefosine was superior to antimonials against CL in Brazil in another study that included 30 children ages 2 to 12 years old [14]. Miltefosine was tolerated well in both studies.

Prevention

Prevention of CL has predominately focused around treatment of those infected rather than reservoir control or reduction of human-vector contact, due to the nonfatal nature of CL [1]. Use of insecticides and pyrethroid-treated bed nets while visiting endemic areas can provide up to 50%–65% protection against infection or disease [1, 6]. Most individuals who have had leishmaniasis are resistant to subsequent infection by the same species, suggesting that vaccination could be protective. Efforts to develop effective vaccines against leishmaniasis are longstanding and development is currently underway. Current promising vaccine candidates include live-attenuated strains of Leishmania parasites [15] and multiantigen approaches to induce T cell-based immunity [16].

### Outcomes of Case/Answers to Questions

At the time of this child’s diagnosis, our recommendations were to treat with SSG. This agent was obtained from the CDC with local institutional review board approval under IND procedures [4]. Sodium stibogluconate was administered at a dose of 21 mg/kg per day intravenously for 20 days. A baseline electrocardiography and baseline laboratories to include LFTs, complete blood count with differential, amylase, and lipase were obtained and repeated on a weekly basis. The child developed a slight elevation of serum aspartate aminotransferase concentration (74 U/L) and mild neutropenia that did not require cessation of therapy. Six days into treatment, the lesion became dry with a dark scab on the surface and had induration and erythema on the edges. Two days after treatment completion, the surface scab was dry and thick and the induration and erythema had resolved. One month posttreatment, the lesion was epithelialized with a thin flat scar.

Leishmania tropica infections can be prone to relapse, but this child’s prognosis appears good because there was only a single lesion that responded to treatment.

### Acknowledgments

Potential conflict of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

### References


