

ATYPICAL CLINICAL VARIANTS IN NEW WORLD CUTANEOUS LEISHMANIASIS: DISSEMINATED, ERYSIPELOID, AND RECIDIVA CUTIS DUE TO *LEISHMANIA (V.) PANAMENSIS*

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Abstract. In recent times, there has been an increase in the number of reports for new and rare variants of cutaneous leishmaniasis (CL). Here, we describe three unusual clinical forms of CL identified in Ecuadorian children. A total of 131 patients with CL were diagnosed over a 2-year period of active search. In 3 (2.29%), the lesions were very unusual; these included erysipeloid, recidiva cutis (LRC), and disseminated leishmaniasis (DL). The erysipeloid case is characterized by erythematous and indurated plaque seen on the face of a 5-year-old boy; the LRC one is differentiated by slowly progressing red-brown papules around large scars of healed sores in a 6-year-old girl, and the DL case is characterized by dozens of cutaneous ulcers distributed in the whole body of a 1-year-old girl. *Leishmania* parasites were isolated by lesion aspirate and analyzed by the technique multilocus enzyme electrophoresis (MLEE). All three isolates were identified as *Leishmania (Viannia) panamensis*. These distinct clinical variants rarely have been reported previously in the American cutaneous leishmaniasis, and for the first time *L. (V.) panamensis* was identified as the etiologic agent. Our cases extend the spectrum of clinical presentations in New World leishmaniasis.

INTRODUCTION

New World tegumentary leishmaniasis is best known for the destructive, mutilating lesions of mucocutaneous leishmaniasis (MCL) or “espundia.” However, cutaneous leishmaniasis (CL) includes a variety of clinical forms. The most common clinical form is the “classical” ulcer, which starts as a nodule, becomes an ulcer with an indurated raised outer border and sharply incised central crater, and then usually heals over a period of months. But, some lesions do not ulcerate and heal but persist as spreading nodules as in diffuse cutaneous leishmaniasis (DCL) and in the atypical CL of Central American countries.¹ Another clinical variant, “Uta,” is seen in the highlands of Peru and Ecuador and is characterized by small, usually single crusted papules.^{2,3} Verrucous, Chiclero ulcer, and sporotrichoid lesions (pian-bois) are also described.

Disseminated cutaneous leishmaniasis (DL) and leishmaniasis recidiva cutis (LRC) are rare variants. DL is characterized by the appearance of multiple pleomorphic lesions in > 2 noncontiguous areas of the body and has been reported exclusively from Brazil⁴ and a solitary case from French Guiana and Ecuador.^{5,6} LRC is characterized by red-brown papules that appear in or around the scar of a healed sore.⁷ The erysipeloid form, which is characterized by erythematous, indurated swollen plaques without ulceration, has not been yet reported in the New World. Other unusual variants are reported, but in the Old World, such as paronychia, chancriform, annular, palmo-plantar, erysipeloid, zosteriform, Whitlow, and sporotrichoid.^{8–10}

Determinants of the clinical presentations of disease are poorly understood but include factors related to the *Leishmania* species, the host's immune response, and, possibly, the saliva of the sandfly vector.¹¹ At least 16 different *Leishmania* spp. have been identified as causative agents in the human New World leishmaniasis falling into both subgenera *Leish-*

mania and *Viannia*.¹² It is generally accepted that certain species predominantly cause major clinical forms; for example, *L. (L.) chagasi* for the visceral form and *L. (V.) braziliensis* for MCL. However, many of the parasites are capable of producing in the human host a spectrum of disease rather than a single clinical form, thus *L. (L.) amazonensis* is associated with CL, MCL, post Kala-azar dermal leishmaniasis, and the visceral form.¹³

The usual clinical presentations of leishmaniasis are easily diagnosed by clinicians in endemic regions, but the unusual forms may give rise to difficulties in diagnosis and appropriate treatment. Here, we report three children with atypical variants of CL acquired in Ecuador, in whom the parasites were identified as *L. (V.) panamensis* by multilocus enzyme electrophoresis (MLEE).

MATERIALS AND METHODS

An active search for leishmaniasis was undertaken in the three natural regions of Ecuador (Pacific coastal, Andean, and Amazonian) in the period 2001–2003. Diagnosis of leishmaniasis was confirmed by the demonstration of amastigotes in slit smears and/or the presence of flagellated promastigotes in the USMARU medium.¹⁴ Parasite strain characterization was done for 11 different enzyme systems using cellulose acetate electrophoresis enzyme technique. Enzymes include 4 oxido-reductases, 2 isomerases, 4 transferases, and 1 hydrolyase. Technical conditions for preparation of samples, electrophoresis, and staining procedures were followed as described by Evans.¹⁴ For profile comparisons, WHO reference strains included in this study were as follows: *L. amazonensis* (MHOM/BR/73/M2269), *L. mexicana* (MNYC/BZ/62/M379), *L. braziliensis* (MHOM/BR/75/M2904), *L. panamensis* (MHOM/PA/71/LS94), and *L. guyanensis* (MHOM/BR/75/M4147). We also included *L. chagasi* (MHOM/BR/74/M2682) because is reported to be the causative agent of nodular atypical CL in Central American countries. The genetic relationship among the stocks were established according Sneath and Sokal.¹⁵

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FIGURE 1. Clinical image of patient 1, erythematous and indurated plaque in both cheeks joined by a large infiltrate through upper lip and nose. A punch biopsy had been performed 2 weeks ago at the center of the plaques.

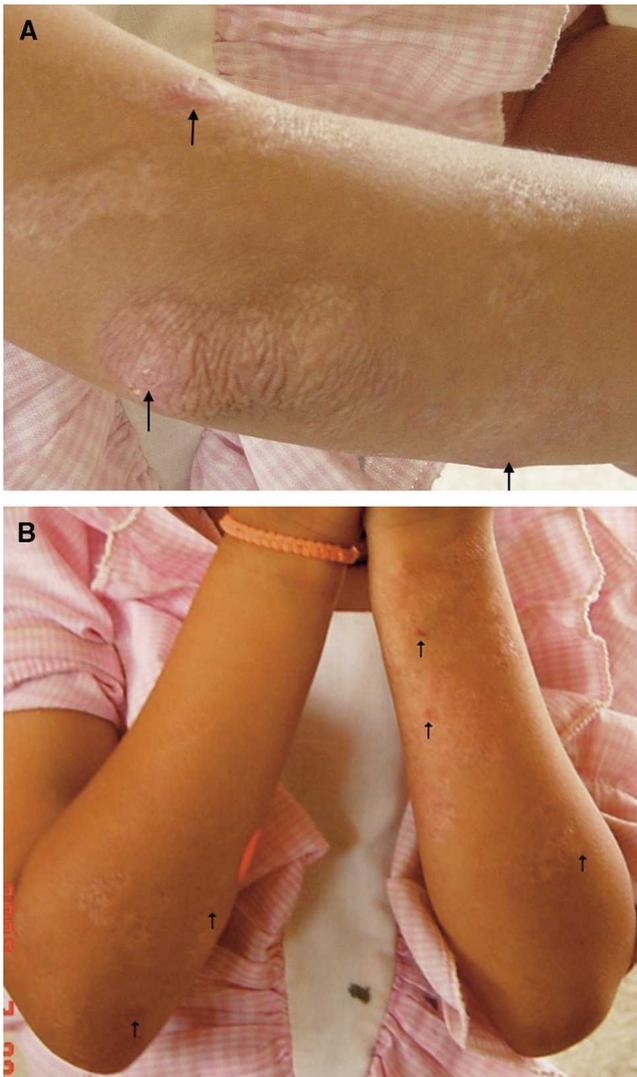


FIGURE 2. **A** and **B**. Photographs of patient 2 showing typical recidivans cutaneous lesion, with several small red-brown papules (arrows) at the edges of extensive scars where *Leishmania* parasites were isolated.

All patients received treatment consisting of parenteral injections of meglumine antimoniate (Glucantime; 20 mg Sb kg⁻¹ day⁻¹ for 15 days) as is recommended by the Ecuadorian Ministry of Public Health. The study adhered to the ethical rules of the Central University of Ecuador in accordance with Ecuadorian government law.

RESULTS

A total of 131 patients were diagnosed to have CL. Three of them had atypical disease and are described in this report. All three came from leishmaniasis-endemic areas of subtropical Ecuador (humid subtropical forest) at 800–1000 m elevation. Results of epidemiologic, clinical features, and treatment of the rest of the patients and characterization of their parasites are reported elsewhere.

Patient 1. A 4-year-old boy presented with a large painless erythematous lesion on the face (Figure 1). It had evolved from an initial papule in the left cheek first noticed 5 months earlier and which gradually spread. The lesion was treated



FIGURE 3. Ulcerative lesions disseminated during 3 months on the head, trunk, legs, and arms in our 1-year-old patient of disseminated cutaneous leishmaniasis. Note cutaneous lesions in the sole.

with topical steroids, followed by topical antibiotics and systemic penicillin, but without improvement. On examination, we found a well-nourished boy, without fever, with a painless, erythematous and indurated plaque on cheeks, nose, and upper lip, but without lesions on the mucous membranes.

Patient 2. A 6-year-old girl presented with a 3-year history of seven red-brown papules slowly expanding at the periphery of healed sores on her right and left upper limbs involving arms, elbows, and forearms. Physical examination of her right arm showed three extensive atrophic scars of healed sores, with four small, red-brown papules at their periphery, and on her left forearm three small red papules in the periphery of extensive scars. The scars were atrophic, ill-defined, depressed, whitish and pink in color and cosmetically disfiguring (Figure 2). These cutaneous changes were suspected to be cutaneous tuberculosis by the local physician. Detailed questioning revealed that scars represented previous ulcers that had healed after a year of evolution, without any treatment, and that after a further year the disease reactivated in the border of healed lesions and continued spreading at the borders.

Patient 3. A 1-year-old girl presented with dozens of cutaneous ulcers distributed in her head, trunk, arms, and legs (Figure 3). Past medical history revealed that approximately 4 months earlier, her mother observed a solitary ulcer on the child's left thigh. At the same time, the mother and a brother had similar but localized ulcers. After a week, the patient developed multiple new skin lesions disseminated over different regions of the body, which persisted. The child suffered from chronic malnutrition. The local physician diagnosed chicken pox at first, but later a generalized impetigo, and prescribed topical and parenteral antibiotics, to which she showed no response. On physical examination, a total of 69 lesions, either between crusted papules and ulcers, were counted on all parts of the body even on the palms and soles, but mucous membranes were not affected.

Diagnosis and identification of *Leishmania* isolates. Microscopy showed intracellular *Leishmania*, and culture yielded promastigotes. The three isolated stocks were identified as *L. (V.) panamensis* by comparing their enzyme profiles for 11 enzyme systems with the profiles of those of selected WHO reference strains. The most useful system to differentiate between subgenera and among *Viannia* species was the phosphogluconate dehydrogenase (Figure 4), but differences were also found in the glucose-6-phosphate dehydrogenase and nucleoside hydrolase. The UPGMA dendrogram built from the Jaccard's distance matrix drew the same cluster (similar isoenzyme profile) between our three stocks and *L. (V.) panamensis* reference stock (data not shown). *L. chagasi* migrated far from our samples. Treatment resulted in clinical cure in all three patients.

DISCUSSION

Because of the rarity of the atypical clinical forms of cutaneous leishmaniasis reported here, even physicians working in such an endemic area misdiagnosed them as chicken pox, erysipelas, and cutaneous tuberculosis and therefore patients were treated inappropriately. The rarity of these variants in the current study (2.29%) is corroborated by other surveys carried out in the country and in other endemic regions in the New and Old Worlds.^{1,4,9,10,16} Lesions at unusual sites are

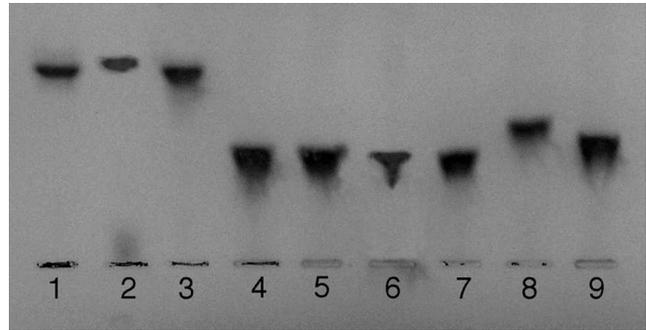


FIGURE 4. Comparison of the isoenzyme pattern for 6-phosphogluconate dehydrogenase enzyme system of reference strains (WHO recommended) with our three isolates. Lane 1, *L. mexicana*. Lane 2, *L. amazonensis*. Lane 3, *L. chagasi*. Lanes 4–6, patients 1–3, respectively. Lane 7, *L. panamensis*. Lane 8, *L. guyanensis*. Lane 9, *L. braziliensis*.

also rarely reported, but several lesions on palms and soles occurred in our 1-year-old patient.

The differential diagnosis of "classical" ulcers of CL includes infected insect bites, traumatic ulcers, fungal, mycobacterial, and spirochete infections, and squamous cell carcinoma.¹⁷ Disseminated leishmaniasis (DL) should be differentiated from small pox, paracoccidioidomycosis, and staphylococcal infection⁶ and as in our case with chicken pox and impetigo; in addition, lesions in Brazilian patients resembled leprosy and acne.⁴ The erysipeloid form on the face should be distinguished from systemic lupus erythematosus, cellulitis and erysipelas, rosacea with lymphoedema, and sarcoidosis. LRC is commonly misdiagnosed as lupus vulgaris, but blastomycosis, sarcoidosis, and tinea incognita must be also considered.¹⁸

Interestingly and for the first time in the clinical spectrum of American tegumentary leishmaniasis, *L. (V.) panamensis* was identified in all three distinct variants of CL reported here. Previously, *L. (V.) braziliensis* in Brazilian patients and *L. (V.) guyanensis* in a French Guiana patient were identified in DL^{4,5} and *L. (L.) amazonensis* and *L. (V.) braziliensis* in LRC forms.¹⁹

WHO²⁰ stated that *L. (V.) panamensis* cause lesions that are normally ulcers. However, the current findings and other reports incriminate this species as the etiological agent for other clinical forms such as Chiclero ulcers and even for mucosal and for MCL.²¹ As the clinical pattern of leishmaniasis is determined by the interaction between the host immune response and the strain of the parasite implicated,²² the fact showed in this report that the same parasite cause several clinical forms suggests that the host immune response is critical in determining the outcome of *L. (V.) panamensis* infection. Indeed, atypical clinical features and locations of *Leishmania* are common in patients co-infected with HIV.^{23,24}

Estimating the importance and complexity of clinical features of leishmaniasis and skin diseases in the Tropics, it is worth reporting unusual and rare clinical forms and localizations of such diseases. Physicians and researchers need to appreciate that the local identified species of *Leishmania* are capable of causing atypical diseases, and familiarity with the different clinical presentation of leishmaniasis may facilitate the diagnosis, and therefore all early treatment may improve outcome.

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