American Cutaneous Leishmaniasis in Infancy and Childhood

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Review

American cutaneous leishmaniasis in infancy and childhood

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Abstract

Infant and young child skin diseases are among the most common features of morbidity throughout the tropics. Because the skin is directly exposed to the environment, it is considerably affected by climatic and local conditions such as vectors and microorganisms, as in the case of leishmaniasis. In America the observed magnitude of cutaneous leishmaniasis in children has led to the study of increased risk of exposure of this group due to the possibility of peri- and intradomiciliary transmission. The present review pretends to make a concrete approach all through the broad and main figures of this parasitic disease, including the clinical, physiopathological, epidemiological, diagnostic, and therapeutic aspects, in order to be used as a practical source of reference for pediatricians leading with tropical cutaneous pathology in the region.

Introduction

The leishmaniases are a diverse group of clinical syndromes caused by protozoan parasite species of the genus *Leishmania* (Ross, 1903).[1] Every year, an estimated 1.5–2 million children and adults develop symptomatic disease in which cutaneous forms embrace 1–1.5 million of the total cases with a higher incidence when subclinical infections are included.[2] The World Health Organization (WHO) ranked cutaneous leishmaniasis as a category 1 (severely neglected) emerging and uncontrolled disease[3] and has created the slogan "Small bite, big threat" to highlight the increasing burden of vector-borne diseases.[4]

The first precise descriptions of parasites from lesions of cutaneous leishmaniasis were made over 100 years ago, in 1885, by Colonel C.C. Cunningham of the Indian Medical Service, who described macrophages packed with what we know now to be amastigotes; subsequently, Borovsky, a Russian military surgeon, achieved a more detailed description of the parasites including the characterization of the nucleus and kinetoplast.[5] It was not until 1903, however, that Sir William Leishman, examining the spleen of a British soldier with kala-azar who had been stationed at Dum Dum near Calcutta, India, first recognized the parasite of the visceral disease.[1,5]

In the New World, evidence found in "huacos" (clay figures made by the Incas in Peru) revealed typical mutilations of the

nose and other deformities which suggest that leishmaniasis probably existed in America prior to the discovery of the continent by Columbus.[5] Towards 1885 localized and mucocutaneous leishmaniasis were already known in Brazil, mainly in the localities of Bahia and São Paulo, with the name of "Bauru Ulcer," as well as in Mexico's Yucatan peninsula by 1906 with the name of "Chiclero Ulcer", being described by Lindenberg and Seidelin, respectively.[1,5] In Ecuador the disease is known as angry sore ("sarna brava"), Colombian ulcer, or mountain leprosy (mucocutaneous leishmaniasis).[6–10] Interestingly, in some countries of Central America where the disease appears to be modulated by the presence of inorganic particles contained in volcanic emanations, the disease is also known under the term of "mountain leprosy."[11,12]

Cutaneous leishmaniasis is usually classified under two headings: Old World, which comprises geographically southern Europe, the Middle East, Asia, and Africa, and New World cutaneous leishmaniasis, embracing Latin America. However, while most of the Old World species cause benign cutaneous disease, New World species cause a spectrum of disease ranging from mild cutaneous forms to also include severe mucosal lesions.[13]

Children constitute one of the most vulnerable groups for transmission of leishmaniasis because of their outdoor habits and their increased probability of exposure to vectors. For this reason, the present study attempts to include the most prominent epidemiological, clinical, diagnostic, and therapeutic aspects of this disease in a concrete manner, in order to be used as a practical source of reference for pediatricians leading with tropical cutaneous pathology.

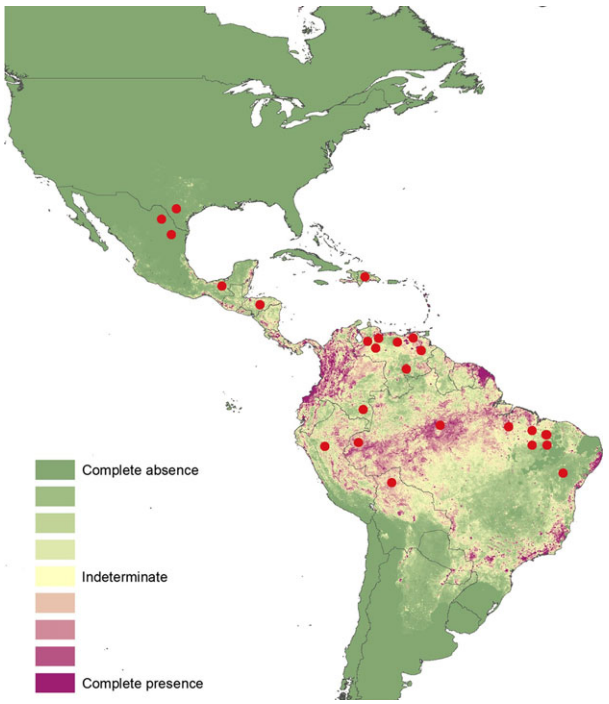

Figure 1 Geographic distribution of cutaneous leishmaniasis in the Americas highlighting areas of predicted risk (low probability of occurrence: green; high probability of occurrence: purple. Red dots depict those areas where diffuse cutaneous leishmaniasis has been reported. Modified from Pigott *et al.* eLife 2014; 3: e02851. doi: 10.7554/eLife.02851.003 – 10.7554/eLife.02851.007 and Magill AJ. The epidemiology of the Leishmaniases. Dermatol Clin 13: 505, 1995)

Epidemiological aspects

Whether a child lives in a rural village or an overcrowded peri-urban area, among the principal dangers posed by the immediate physical environment for contracting leishmaniasis is exposure to the disease vector (sandflies) secondary to invasion of the parasite's ecological habitat, generally, because of traveling to endemic areas or because of uncontrolled trends towards urbanization and consequent degradation of the local environment as occurs in deforestation.

Traditionally leishmaniasis has been known to affect mainly male patients carrying out outdoor activities such as fishing, hunting, and mining, as well as those dedicated to agricultural activities, being considered in the past as an occupational disease.[14–17] Nevertheless, in Latin America since the beginning of the past decade, there has been an increase in the total number of cases (Fig. 1) with broadest distribution among age ranges undertaking similarly both males and females and even cases of whole families suggesting an intra- and peridomiciliary pattern of transmission,[14] thus exposing infants to a greater risk of infection[18] (Fig. 1). Recently, a high frequency of American cuta-neous leishmaniasis was shown in young age groups and cases clustered in urban neighborhoods of Manaus, the largest human settlement in the Amazon.[18] A similar phenomena is observed in Argentina with over 50% of the cases reported from the Departments of Orán and San Martín (Salta Province), where the disease has reached hyperendemic proportions.[19] In these regions, the overall number of cases of ACL affecting children annually in the last 6 years has reached 6–12% among all reported cases, with most of the cases being localized forms (96%) and 4% presenting as mucocutaneous as per information of the regional sanitary office of the Province of Salta. Stereotypically, hyperendemic foci of ACL are also a common feature in certain areas of Venezuela such as in the states of Lara, Portuguesa, Yaracuy, Tachira, and Miranda, with 16% of the cases occurring in children ages 0 through 10 (Instituto de Biomedicina, unpublished data). In a study in Colombia, from 2004 to 2010, 380 children with ACL were assessed, 90% presented lesions of <3 months duration, 54% presented single lesions <30 mm in diameter, and 45% were ≤5 years old. Lesions on the head and neck were more frequent among children 0–5 years, and lesions below the head/neck were more frequent among 11- to 14-year-old children ($P = 0.004$). Using PAHO and WHO criteria, 26% and 53% of children, respectively, were eligible for local treatment.[20]

Epidemiologically, leishmaniasis in children has been difficult to study because of the lack of standardization among child age ranges[18]; very few works offer a detailed scale of ages comprising minor intervals,[21–24] but most of the reports usually embrace wide intervals of age leading to a deficiency of detailed knowledge among inherent features of minor groups.

Etiology and pathogenesis

Despite great variations in disease form, all *Leishmania* are spread from animal reservoirs by *Phlebotomus* or *Lutzomya* sandflies, but in some cases, even humans can be the main reservoir which constitutes one of the main risk factors for transmission in children.[18,25] *Leishmania* organisms have a relatively simple life cycle[1] in which flagellated promastigotes pass into the vertebrate host (human) during the bite of a female sandfly during a blood meal. These promastigotes develop into amastigotes within tissue macrophages and invade other reticuloendothelial cells; the cycle is completed when sandflies ingest circulating amastigotes with their bloodmeal on an infected individual.[1,25]

There are currently three organisms in the *L. mexicana* complex and four in the *L. braziliensis* complex that are known to infect humans,[1] although at present fourteen recognized species of *Leishmania* within the subgenera *Leishmania* and *Viannia,* which may produce a variety of cutaneous and mucocutaneous lesions in man, have been described.[26] Although *L. infantum* (*L. chagasi*) usually causes visceral diseases in children,[27] cutaneous lesions are not uncommon.[28] In addition *L. infantum* is known to affect a significant proportion of the infant population in certain areas of Brazil[29] highlighting the importance of asymptomatic carriers as in other parts of the world.[30]

Localized cutaneous leishmaniasis has, as an etiologic agent, any member of the neotropical subgenera *Viannia* and *Leishmania,* with *L (V) braziliensis*, as described by some authors, one of the most important parasites associated with this form.[22,31–33] In the Brazilian Amazon region, *L. guyanensis* has been implicated as the main etiological agent of localized cutaneous leishmaniasis.[34,35] In Ecuador *L. panamensis* and *L. guyanensis* have been linked to zoonotic cutaneous leishmaniasis, predominantly in the subtropical and tropical lowlands of the Pacific region, while *L. amazonensis, L. equatorensis*, and *L. mexicana* are known to be the main players involved in both the Andean and coastal regions.[6–10] Mucocutaneous leishmaniasis has been mainly associated with infection by *L. (V) braziliensis,*[31,36,37] as well as in borderline disseminated cutaneous form, which also exhibit parasites belonging to the *L. braziliensis complex*[38] as well as other species from the *Viannia* subgenus.[26] Lastly, anergic diffuse cutaneous leishmaniasis can be produced by apparently all members of the *L. mexicana* complex, most cases reported around the world (Fig. 1) being caused by infection with *L. amazonensis* and *L. pifanoi.*[37,38]

Immunological basis of the clinical spectrum

The clinical spectrum of American cutaneous leishmaniasis is characterized by the two polar forms of the disease, one of which, localized cutaneous leishmaniasis, shows a relatively competent immune response which results in spontaneous healing of lesions in a significant proportion of patients; and the other polar form, anergic diffuse cutaneous leishmaniaisis, is characterized by a specific T cell immunodeficiency, which determines progressive extension of lesions.[39] On the other hand, intermediate forms of the disease like mucocutaneous leishmaniasis reflect a partial immunodeficiency characterized by the inability to eliminate *Leishmania* and, in a proportion of patients, the development of exaggerated delayed type hypersensitivity.[40]

T cells mediate acquired resistance to leishmaniasis, being the CD4+ subset crucial for this resistance, whereas CD8+ T cells seem to participate more in the memory events of the immune response than as effector cells involved in parasite elimination.[41–43] It has been demonstrated that resistance and susceptibility to leishmaniasis is clearly associated with one of the two phenotypically distinct subsets of CD4+, namely a Th1 or Th2 cell response.[42,43]

Th1 cells, which are responsible for delayed type hypersensitivity, produce a characteristic profile of lymphokines, including IFN-γ and IL-2, which are associated with protective cell-mediated reactions[39] as seen in localized cutaneous leishmaniasis. On the other side, Th2 cells also produce a characteristic profile of lymphokines, including IL-4, IL-5, and IL-10 which are important in the synthesis of antibodies, as well as suppression of cell mediated immunity, which can explain the absence of lymphocyte proliferation, a remarkable characteristic of antigen specific immunodeficiency in cases of anergic diffuse cutaneous leishmaniasis.[39,43,44]

Arising out of this and bearing in mind the objective of the present work, it is important to consider that the immaturity of the infant's immune system and the absence of prior immunity and exposure to the parasite are potential contributors to finding high rates of infection among infants and young children living and traveling to endemic areas. Additionally, we should consider that malnutrition is a common problem affecting children in developing countries and that this condition is associated with a significant impairment of cell-mediated immunity, phagocyte function, complement system, antibody concentrations, and cytokine production, making the child more vulnerable to infection.[45,46]

Clinical and diagnostic aspects

Depending on the species of the infecting *Leishmania* and the infected person's cell-mediated immune response, a wide spectrum of clinical forms of the disease can develop.[47–50] In many ways, the variation in disease is analogous to that found in leprosy.[25,51] As mentioned above, the spectrum is defined by

the two polar forms of the disease, represented by localized cutaneous leishmaniasis (LCL) and anergic diffuse cutaneous leishmaniasis (DCL). The intermediate forms of the spectrum are represented by mucocutaneous[34] and borderline disseminated cutaneous leishmaniasis.[26]

Regarding diagnosis, it basically rests on the direct visualization of the parasite in the microscope in Giemsa stained smears or histological sections; the direct visualization of amastigotes using slit skin smears (Fig. 2a–b) is very useful and simple, giving rapid results[24] and avoiding the traumatic event of a biopsy to the infant. In general, sampling from the edge of a recently appeared lesion is the site of choice to obtain tissue samples by scraping, biopsy, or needle aspiration.[51] Fine needle aspiration has also proven to be a promising diagnostic method for culturing and identification (being also easier and less painful to perform than a biopsy for children) but requires experienced hands and exhibits a variable grade of sensitivity.[13,52]

Tissue samples should be taken from the edge of the lesions where the parasite activity is greater,[53,54] and noble anatomic areas such as the face should be respected; routine stains as well as immunoperoxidase stains usually help to reveal the amastigotes well.[25] Culture is performed in special media (Novy-Nicolle-McNeal) and may take up to 4 weeks;[1,25] however, Schneider's *Drosophila* medium supplemented with fetal bovine serum is often more effective in primary isolation from New World cutaneous leishmaniasis and takes between 2 and 7 days.[1]

Several standardized and sensitive serological assays are available.[55] Among the serologic methods, the agglutination tests (direct agglutination test [DAT] and fast agglutination screening tests [FAST]) are usually specific and sensitive methods.[56,57] ELISA-based techniques are also useful because they allow high throughput screening of a large number of samples, with sensitivities ranging from 80 to 85% and sensitivities of 95 to 100%.[58,59] However, such tests are frequently positive in endemic areas[25] because of previous infection or cross-reactivity with other parasitic infections such as *Trypanosoma cruzi*.[27] Detection of parasite DNA in tissue specimens is usually most sensitive in diagnosis and can even allow molecular characterization to a species level, but due to scarce economical resources, it is difficult to practice in developing countries.[60–64] Nevertheless, PCR-based diagnosis remains the gold standard to identify the causative parasite at a species level and therefore decide the most accurate therapeutic approach for the patient.[65,66]

The Montenegro test, which is an intradermal injection of killed promastigotes and is read 48 hours after its application, provides a reliable test except in cases of anergic diffuse cutaneous leishmaniasis, where it is generally negative as a result of a defective cell-mediated response presented by patients showing this clinical form. It is also negative during the first 3 months, and results can be variable because of the lack in uniform standardization in its manufacturing between different laboratories. Besides, Montenegro test does not differentiate past exposure from active disease and may remain positive after cure.[67]

The best diagnostic approach seems to be the combination of different laboratory tests to increase detection sensitivity.[68] In an endemic area of American Cutaneous Leishmaniasis due to *L. guyanensis* and *L. braziliensis*, the combination of skin smear, detection of parasite DNA in tissue specimens by polymerase chain reaction (PCR), and histopathology increased diagnostic sensitivity to 94%.[68]

Having reviewed these basic concepts, we now describe in detail the main characteristics for each clinical feature of the disease.

Localized cutaneous leishmaniasis

Based on our clinical experience, the initial lesion is usually described as a firm erythematous papule often attributed to an "insect bite" occurring mainly in exposed areas (face and upper and lower limbs). After some time, the lesion gradually enlarges peripherally, presenting usually on its center a serosanguineous crust that ends up developing into an ulcer (Fig. 3a–c). In addition, initial lesions can be present as a vesicle with intense infiltration in its borders or even as erythematous plaques. Spontaneous healing has been described.[69]

The polymorphic nature of leishmaniasis leads to innumerable descriptive forms such as chromomycoid, piodermoid, leproid,[41] nodular, verrucous, and psoriasiform forms[1] among others. Nevertheless, ulcerated lesions are the most common and characteristic feature of this benign polar form of the disease, which can appear as single, few, or occasionally

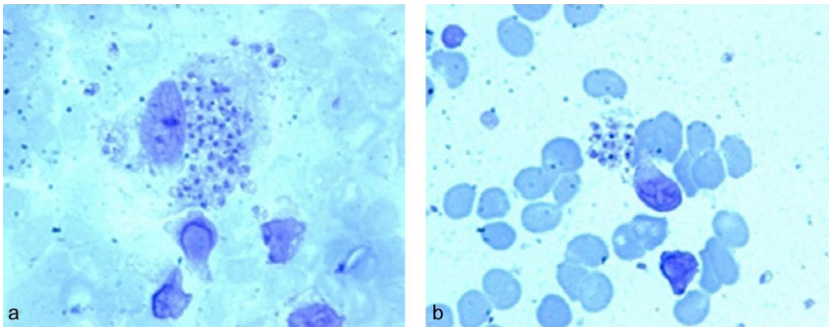

Figure 2 Skin smear (a) Numerous intracellular amastigotes replicating within a macrophage from a patient with severe anergic diffuse cutaneous leishmaniasis. (b) Parasites disposed in groups, note the typical round nucleus and rod-shaped kinetoplast in the body of the amastigotes. (Giemsa stain ×500)

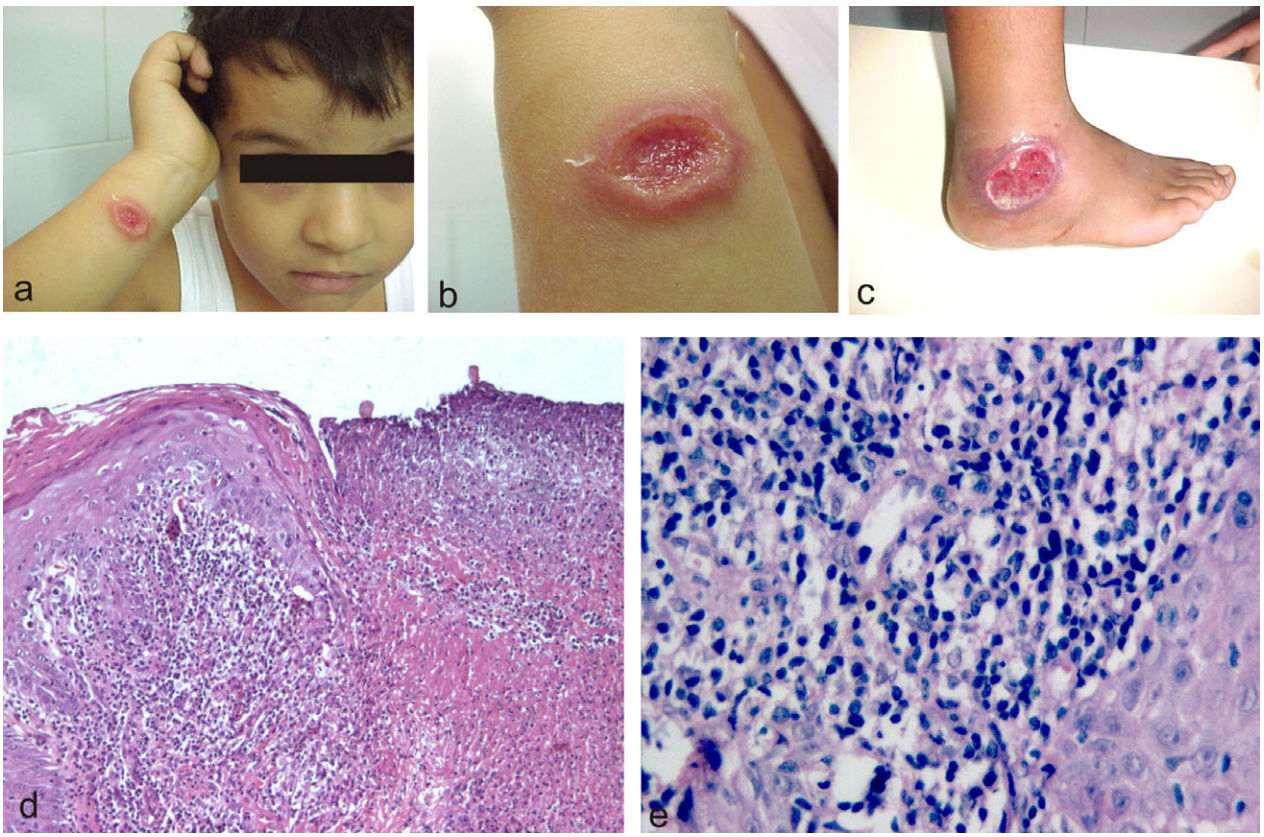

Figure 3 (a) A 3-year-old child exhibiting an American cutaneous leishmaniasis localized lesion in the forearm. (b) Detail of the lesion: typical ulcer showing significant infiltration of the edge of the lesion. (c) Ulcerated lesion in the ankle of a 6-year-old female patient with pronounced infiltration and erythematous-elevated borders with extensive perilesional surrounding erythema; also, some fibrinoid and purulent secretion can be noted at the base of the ulcer due to secondary infection. (d) Histological section of a localized lesion showing irregularly acanthotic epidermis flanking an ulcer with purulent and necrobiotic found (hematoxylin-eosin ×100). (e) Detail of the histological section standing out the diffuse macrophagic granuloma invaded by numerous lymphoid cells with very scarce amastigotes contained in the vacuolated macrophages, typical feature of LCL (hematoxylin-eosin ×400)

numerous lesions.[1,5,42,44] Associated symptoms like pruritic sensation at the site of the lesion[1] or stabbing pain may be referred by the patients, although ulcerative lesions are usually painless unless secondarily infected.[1,5] Initially there can be slight lymphangitis with modest adenopathies, but in advanced stages or when there is an associated secondary infection, lymph nodes can be intensely swollen and lymphatics can be easily palpated as thick cords in the vicinity of the lesions.

Histopathology reveals a typical immune granuloma with epithelioid differentiation, particularly in early nonulcerated lesions; intense destructive ulcerative reaction and chronic secondary infection often observed at the time of diagnosis may produce significant necrosis (Fig. 3d); also few parasites can be seen except in very early lesions (Fig. 3e).[40,70,71] The evaluation of cell-mediated immunity through DTH skin test is positive in 90% of the patients, and 5% show exaggerated reactivity. Serological tests are positive in more than 90% of the patients at the time of diagnosis.[40]

Mucocutaneous leishmaniasis

Mucocutaneous leishmaniasis represents one of the most important manifestations of the leishmaniasis spectrum;[38] it is the most destructive form of cutaneous leishmaniasis and usually follows a primary infection that appeared to heal some time earlier.[25] Usually these patients have a history of having suffered from localized cutaneous leishmaniasis that appear to respond adequately to therapy, but months or even years after the initial disease, they develop lesions on the upper respiratory tract (Fig. 4a–b).[38] Mucosal lesions may also result from the extension of an active contiguous skin lesion. Even though this form of leishmaniasis has traditionally been attributed to infection with *Leishmania braziliensis*, it is now known that other species of the *Viannia* subgenus such as *L. panamensis, L. guyanensis,* and *L. peruviana*, may also cause mucosal involvement.[72] As a result of its insidious nature, it is usually seen more commonly in adults than in children, although pediatric cases have been well documented.[18,19]

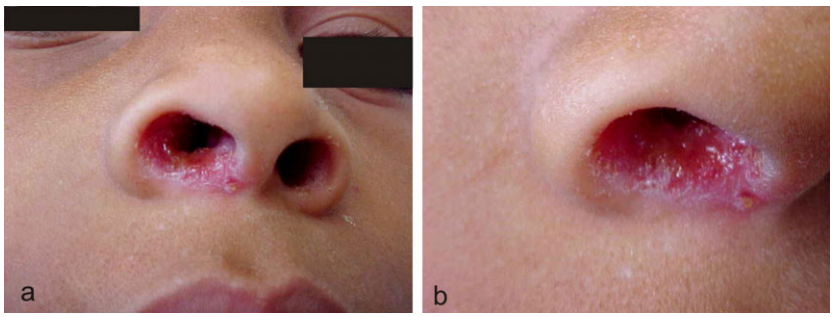

Figure 4 (a–b) Mucosal lesion of the nose in a case of mucocutaneous leishmaniasis

Recently, experimental data has suggested that the strong hyperinflammatory response observed in MCL is due to a high burden of a non-segmented dsRNA virus *Leishmania* RNA Virus (LRV) in metastasizing strains, which in turn exacerbate the inflammatory response of the host.[73]

Lesions can occur in any area of the respiratory system: nasal, buccal, pharyngeal, and laryngeal.[49–52] The initial symptoms are those of a chronic respiratory tract infection often associated with exudates or epistaxis associated to erythema of the mucosa which can rapidly progress and ulcerate, invading the cartilage and destroying the septum.[74–77] Finally, as described by some authors, the inflamed and infiltrated tissue slackens, leaving exposed the extensive destruction of the mucosa and cartilage of the different anatomical structures such as nasal fossae and spreading into contiguous areas such as pharynx, soft palate, tonsils, and other soft tissues including tongue and gums.[78,79]

The histopathological features are very alike to those found in localized cutaneous leishmaniasis; the mucosal tissue may exhibit a tuberculoid granulomatous reaction or also abundant infiltrate of lymphocytes and plasma cells with few histiocytes and scanty parasites; necrosis of the cartilaginous structures, being the main sequel.[80]

Exacerbated response to DTH in skin test has been described.[26,81] In Venezuelan patients, this exaggerated reaction occurs in less than 50% of the patients[40] with an inverse relationship between the size of the mucocutaneous lesions and the intensity of the hypersensitivity reaction, though more extensive lesions are associated with higher antibody levels.[40]

Borderline disseminated cutaneous leishmaniasis

This is an intermediate form of cutaneous leishmaniasis in which patients present disseminated forms of the disease and in which it has been possible to determine the location of the primary skin lesion (s) and the secondary ones.[26] Lesions are characterized by extensive vegetating and verrucous plaques or ulcers with a typical cobblestone center and multiple satellite lesions (Fig. 5b). It can also appear as a rapid dissemination of more than 100 erythematous papules (acneiform lesions) and/or multiple ulcerated lesions (Fig. 5a).[26,82,83]

In our experience, it is not common to see this form of the disease in children, and in most of the cases, adult patients present with concomitant systemic illnesses like metabolic disease (diabetes), autoimmune diseases (multiple sclerosis, myasthenia gravis), or even concurrent infectious illness like Chagas disease.[84,85]

The histology of this feature can show a nodular infiltration of lymphocytes and plasma cells in the dermis, with rare macrophages and parasites.[26] In our personal experience, we have observed that the majority of patients present an intensely vacuolated granuloma with numerous parasites within the vacuoles in the upper dermis, and that, in the profoundness of the dermis, it is frequent to find macrophagic granulomas with epithelioid differentiation including scarce giant cells with very few parasites; therefore, we have chosen to name this histological type as 100 erythematous papules bipolar leishmaniasis (Fig. 5c–d).

During dissemination of the parasite, which is a critical stage of the disease the DTH skin tests are generally negative, reflecting an *incomplete failure* of the cellular immune response what has prompted the adoption of the term "borderline."[26,82]

Anergic diffuse cutaneous leishmaniasis

Anergic diffuse cutaneous leishmaniasis, the opposite polar form of localized cutaneous leishmaniasis[40] is a relatively rare form of New World cutaneous leishmaniasis[26] described for the first time in Venezuela[86,87] and since then subsequently described in other countries of the Americas (Fig. 1), including the United States of America,[36] and outside the continent in countries like Ethiopia and Japan.[5,87,88] It is mainly characterized by multiple nonulcerated nodules or plaques that cover extensive areas of the body[38] resembling lepromatous leprosy. In general, there is diffuse infiltration of the skin, on which appear a large number of papules, tubercules, nodules, and plaques that rarely ulcerate[40,89,90] but can be aesthetically devastating (Fig. 6a–b). Rarely involvement of the nasopharyngeal mucous membranes can occur[40,89,90] but never become destructive as do those of typical mucocutaneous leishmaniasis. Most cases initiate in childhood and evolve until adulthood in an insidious fashion, but fortunately the disease is rare both in children and adults.[91]

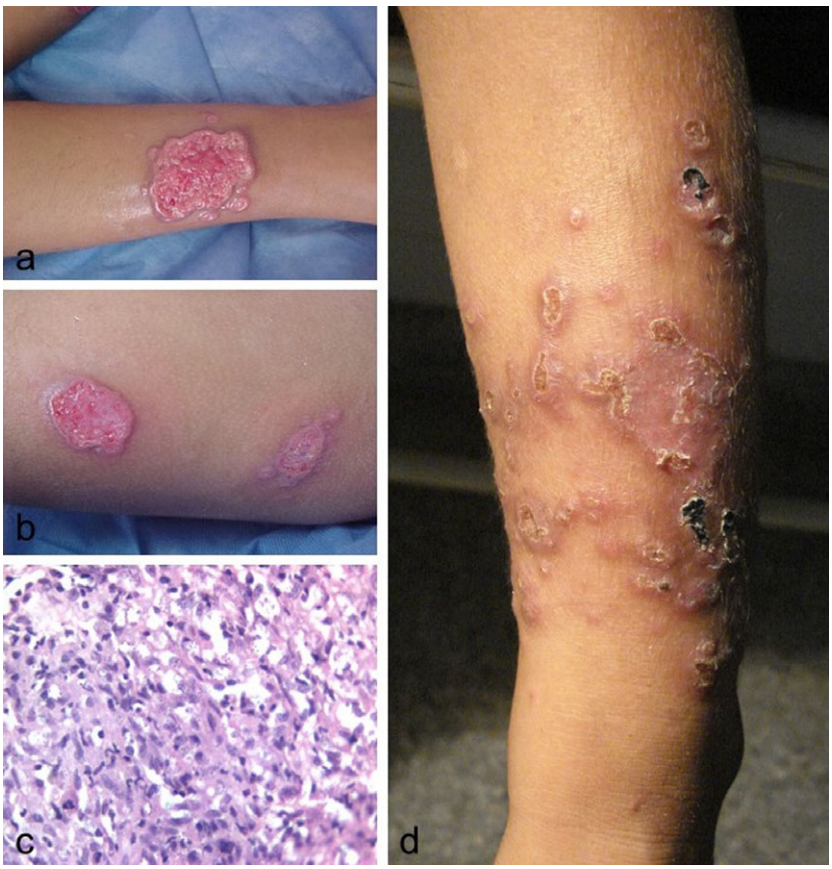

Figure 5 (a, b) Extensive irregular ulcers with a rough center and multiple satellite lesions in a 7-year-old child. (c) Tissue section exhibiting a superficial vacuolated granuloma with areas of solid epithelioid differentiation towards the depth of the lesion (hematoxylin-eosin ×400). (d) Extensive and disseminated papulonodular and ulcerated lesions scattered in the leg of a 5-year-old female patient

In the dermis the histopathological feature is a severe infiltration of vacuolated macrophages containing abundant amastigotes within the vacuoles; lymphocytes and plasma cells are rare, giving the infiltration the aspect of a macrophagic granuloma (Fig. 6c–d).[86,90,92–94]

The delayed-type hypersensitivity (DHT) skin tests are negative except in very rare early diagnosis or after aggressive treatments where positive reactions can occur.[40]

Differential diagnosis

This is probably one of the most important challenges in pediatric dermatology since a child presenting with a rash, an ulcer, or other dermatoses, can exhibit a very wide range of possible diagnosis given that skin problems are among the most common complaints in this stage of life.

In localized forms, initial papules or crusted lesions should be differentiated from arthropod bites or impetigo; ulcerous lesions may resemble acute cutaneous infections such as pyodermas (a common group of pathologies among the pediatric population) and in which impetigo, furunculosis, and ecthyma are important to consider. Other pathologies resembling acute cutaneous leishmaniasis are: anthrax, orf, syphilis, yaws, tropical ulcer, myiasis, dracunculosis, pyogenic granuloma, tularemia, and malignancies.[1,5,95]

Nodular lesions are also challenging and must bring into consideration possibilities like sporothrichosis, onchocerciasis, foreign body granuloma,[1] milkers nodule,[1] keratoacanthoma, blastomycosis, and other subcutaneous infections such as panniculitis. Verrucous vegetating plaques may resemble yaws or chromomycosis as do some other erythemato-squamous dermatosis.[1,5,74]

When evaluating cases of mucocutaneous compromise, the possibility of rhinosporidiosis, blastomycosis, histoplasmosis,[1] and Wegener's granulomatosis[74] must be ruled out.

Finally lesions of anergic diffuse cutaneous leishmaniasis are very alike to those of lepromatous leprosy, requiring in many occasions the assistance of laboratory diagnosis for its confirmation; keloids and lobomycosis[96] are also some of the diagnostic possibilities in this pole.

Treatment

The immense expense of treatments and the many side effects of available drugs like antimonials pose a great challenge at the time of treating children with leishmaniasis. Local versus

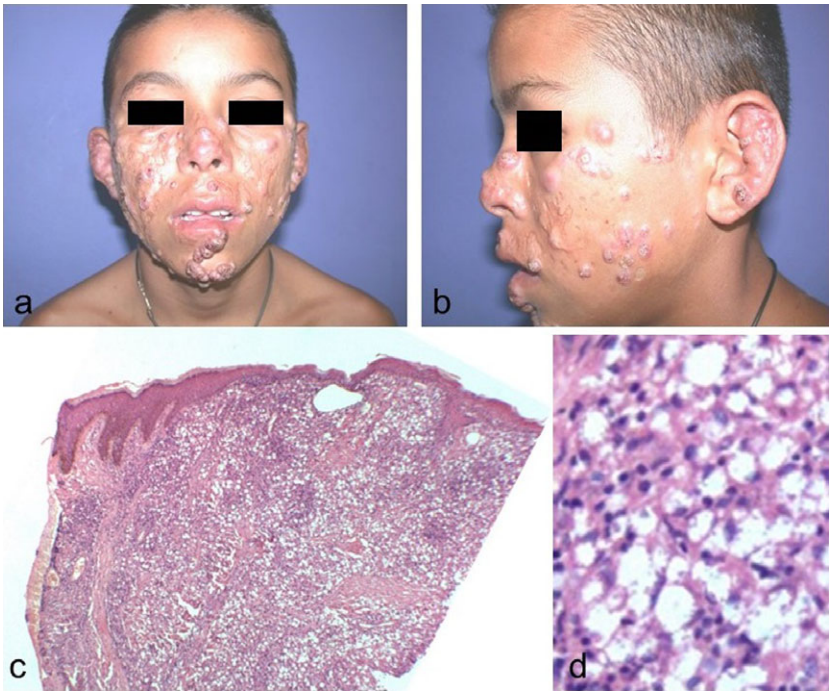

Figure 6 (a–b) A severe case of anergic diffuse cutaneous leishmaniasis with extensive, multiple and confluent non ulcerated nodules and plaques comprising the face. (Instituto de Biomedicina). (c) Section of a lesion from anergic diffuse cutaneous leishmaniasis exhibiting irregular epidermis with moderated acanthosis and an intensely vacuolated macrophagic granuloma occupying almost the entire thickness of the dermis (Hematoxylin-Eosin ×100). (d) Section of the same lesion showing vacuolated macrophages containing abundant amastigotes (Hematoxylin-Eosin ×400)

systemic treatment still generate some debate among different groups; however, there are indubitable criteria on when a patient should receive systemic treatment.[97] Amongst these obligate clinical scenarios are: localization in the face and neck region, chronic ear affection (Chiclero ulcer), evident metastatic spread to lymph nodes, presence of multiple lesions, infection to *L. viannia* complex species (especially *L. braziliensis*), and failure to respond to topical therapy.[13]

Some authors state that isolated ulcers are usually self-limited and that dangers of treatment should be balanced against the possibility of spontaneous cure; thus, it is better to observe them and treat only if they show no signs of improvement over the next 3 or 4 months after diagnosis.[25] In our experience, self-healing lesions are very rare and extremely often are associated to secondary infections that limit the spontaneous healing of the ulcers. On the other hand, parents are usually concerned about the esthetic aspect and prefer a prompt therapeutic solution.

Conventional therapy comprises the utilization of pentavalent antimonials (20 mg antimony/kg per day intravenous (IV) or intramuscular (IM) for 3–4 weeks)[25,98] with careful monitoring of renal and liver function, as well as a previous cardiac evaluation that must include an electrocardiography study due to the antimonials' cardiotoxicity.

Some authors have reported clinical success using a dose of 10 mg/kg/d in children in order to prevent cardiac side effects.[99–101] Intralesional injections of antimonials (accepted therapy for disease in the Old World) have not seen wide use in America except in Brazil;[1,102] we have used it as a complementary treatment in scarce patients with severe refractory lesions. Although there are few studies using intralesional injections of antimonials in Brazil, this is not accepted as a standard therapy by the local Ministry of Health and most of Brazilian researchers studying Leishmaniasis do not agree with this therapeutical approach. On the other hand, antimony therapy combined with pentoxifylline has proved to be effective in the treatment of cases of refractory mucosal leishmaniasis by decreasing the exaggerated inflammatory response based on the well-known inhibitory action of the latter over TNF-α production and leukocyte function.[103]

In Colombia, clinical response to supervised treatment of children with cutaneous leishmaniasis was evaluated in a randomized controlled trial comparing 10 days vs. 20 days of treatment with meglumine antimonate (20 mg Sb/kg/d).[104] Masked examiners evaluated clinical response defined as 100% re-epithelialization of all lesions at 13 weeks and no relapses during 52 weeks of follow-up. The efficacy of meglumine antimonate for 10 days treatment was 61% (28 of 46) compared to 67% (24 of 36) for 20 days. There was a significantly lower clinical response for children <5 years in both 10-day (11%) and 20-day (25%) groups compared to patients aged 5–14 years (67% and 75%, respectively) and 15 years or more (81% and 83%, respectively). Overall efficacy of treatment schedules was comparable but lower than expected mainly because of low efficacy in children. Pathogenicity of infection and pharmacokinetics may affect the treatment response in children. New therapeutic alternatives should be evaluated in trials that include children and women.[104]

Pentamidine should be considered as an alternative therapy[1,105]; the pediatric dosage is 2–3 mg/kg IV or IM daily or every second day for 4–7 doses.[106,107] Recently, a single dose of 7 mg/kg of pentamidine for cutaneous leishmaniasis due to *L. guyanensis* showed the same effectiveness as the regimen of three injections of 4 mg/kg (adults).[35] Amphotericin B deoxycholate is sometimes effective in patients unresponsive to antimonials[1] and is considered a drug of choice in cases with mucosal involvement at a dosage of 0,5-1 mg/kg IV daily or every other day for up to 8 weeks;[1,108,109] as well as in refractory cases of diffuse cutaneous leishmaniasis.[110] There is insufficient information on which to make confident recommendations for the lipid-associated amphotericin B compounds, and although there are case reports of failure[1,110] an increasing number of reports have started to demonstrate their good safety profile and efficacy, especially in cases of mucocutaneous leishmaniasis.[111] It is important to quote that the use of intravenous and oral rehydration solutions has proven to be effective in preventing both glomerular damage and hypokalemia during the administration of amphotericin B.[112]

Although there is scarce evidence on which to make reliable considerations on azole therapy, ketoconazole 100 mg/d p.o. for several weeks has proven to be effective[25] as well as other azole agents such as fluconazole.[113,114] Fluconazole, for example, has proven effective in the management of intermediate borderline and extensive forms of the disease.[115] However, azoles seem to exhibit species-specific responsiveness which can limit their use for certain species.[115]

The lack of comparative studies between systemic and local agents hampers appropriate recommendations, however local agents may be secure and cost-effective therapeutical approaches in uncomplicated cases of cutaneous leishmaniasis.[116] Topical application of paromomycin formulations is among the alternative drugs of choice[1] but should be used only in geographic regions where cutaneous leishmaniasis species have low potential for mucosal spread.[117] A formulation of 15% paramomycin/12% methylbenzethonium chloride has been reported to be partially effective in some patients against cutaneous leishmaniasis due to *L. mexicana, L.(V). braziliensis,* and *Leishmania panamensis.*[116,117]Topical formulations of amphotericin B have also emerged as an attractive alternative in order to avoid systemic toxicities while providing a rapid painless route for treatment, which is ideal for the pediatric population.[118–121]

Imiquimod, an imidazoquinoline amine with immunomodulatory effects, has also proven to be effective, exhibiting a synergistic effect when used in combination with antimonials.[116,122,123] Also, intralesional injections with zinc sulfate and hypertonic sodium chloride have also been reported to be effective in Iran,[124,125] however there is a lack of experience with this approach on new world species.

Miltefosine is recommended for New World cutaneous disease to diminish the time to cure the ulcer and to attempt to prevent metastasis.[117–126] It is an oral agent administered at a dose of 2.5 mg/kg/d for approximately 28 days, and with very few side effects such as nausea, vomiting, and mild elevation of serum creatinine;[127–130] relapses have been described in cases of anergic diffuse cutaneous leishmaniasis.[131] Recently in Colombia, a randomized, noninferiority clinical trial with masked evaluation was conducted at three locations in Colombia where *L. panamensis* and *L. guyanensis* predominated.[132] A total of 116 children aged 2–12 years with parasitologically confirmed cutaneous leishmaniasis were randomized to directly observed treatment with meglumine antimoniate (20 mg Sb/kg/d for 20 days; intramuscular) ($n = 58$) or miltefosine (1.8–2.5 mg/kg/d for 28 days; by mouth) ($n = 58$). Primary outcome was treatment failure at or before week 26 after initiation of treatment. Miltefosine was noninferior if the proportion of treatment failures was ≤15% higher than achieved with meglumine antimoniate (1-sided test, $\alpha = 0.05$). Then, 95% of children (111/116) completed follow-up evaluation. By intention-to-treat analysis, failure rate was 17.2% (98% confidence interval [CI], 5.7–28.7%) for miltefosine and 31% (98% CI, 16.9–45.2%) for meglumine antimoniate. The difference between treatment groups was 13.8%, (98% CI, −4.5 to 32%) ($P = 0.04$). Adverse events were mild for both treatments.[132]

The concomitant implementation of nonpharmacological alternatives should be considered. In children cryotherapy, used as an adjunct to low-dose systemic antimonials has proven to induce complete and sustained remission of the disease[133,134] particularly in Old World cutaneous leishmaniasis[116,135,136]; nevertheless pain, hypopigmentation, and scarring limit their use in the pediatric population. In addition, localized control heat has also been found to be effective,[137] especially against *L. mexicana*, but its use is also limited due to its painful nature, often requiring the use of local anesthetics.[137]

Concerning immunotherapy, the addition of interferon gamma (as supplementary treatment or as single therapy in cutaneous lesions) has proven to be effective.[25] Also, studies in Venezuela have shown that treatment with three injections of heat killed *Leishmania mexicana amazonensis* promastigotes mixed with viable bacilli Calmette-Guerin (BCG) given intradermally for 6–8 weeks is as effective as Glucantime® in achieving clinical cures of localized cutaneous leishmaniasis.[1,138] More recently, we have treated patients with severe forms of cutaneous leishmaniasis with a novel formulation containing promastigotes of L. (V.) *braziliensis* killed by pasteurization and associated with viable BCG obtaining favorable clinical response without significant side effects.[138,139] Unfortunately, anergic diffuse cutaneous leishmaniasis is poorly responsive to treatment and although patients in Venezuela usually improve after initial treatment with antimonials, relapse is invariable.[1,110] The experience at our institutions reveals that treatment combining chemotherapy and immunotherapy produces prolonged remissions as well as positive cell-mediated responses, suggesting a clinical cure in 50% of patients that have been followed for many years.[38]

A very important aspect to consider when treating cutaneous leishmaniasis is the intrinsic sensitivity between *Leishmania* species to several chemotherapeutic agents.[140] Even though some species may exhibit intrinsic variation due to their molecular and biochemical differences, selection due to drug pressure is becoming another important element of inter-species variation.[140] For detailed information on species-specific treatment and clinical and parasite resistance, we refer the reader to the comprehensive review by Croft et al, on drug resistance in leishmania.[140]

Although the current situation for the chemotherapy of leishmaniasis is more promising than it has been for several decades with both new drugs and new formulations of old drugs,[140] chemotherapy must be managed under strict and rational clinical criteria in order to prevent the emergence of parasite resistance to drugs as well as its spread and the development of resistance to new antileishmanial drugs.[141]

Concluding remarks

American cutaneous leishmaniasis is a widely spread parasitic disease in Latin America with a broad and pleomorphic spectrum of clinical manifestations and a complex epidemiological behavior.[142] The objective to approach an adequate management of this infectious cutaneous pathology includes not only the knowledge of all the complexities of childhood diseases seen in the tropics but also the awareness about the challenge that this disease offers at the time of diagnosing and treating individuals in the pediatric population with this disease.

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