

Disseminated Cutaneous Leishmaniasis in Colombia: Report of 27 Cases

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Key Words

Disseminated leishmaniasis · Diffuse cutaneous leishmaniasis · Localized cutaneous leishmaniasis · Post-kala-azar dermal leishmaniasis

Abstract

Disseminated leishmaniasis (DL) is a poorly described disease that is frequently misdiagnosed as other clinical manifestations of cutaneous leishmaniasis (CL) such as diffuse CL or post-kala-azar dermal leishmaniasis. Twenty-seven cases of DL diagnosed between 1997 and 2015 are described. A higher prevalence was observed in men (mean age 32 years). The number of lesions per patient ranged from 12 to 294, distributed mainly in the upper extremities, face and trunk. The lesions were mostly plaques or nodules. Seven patients had nasal mucous damage, 74% of the patients were of mixed race, 92% lived in northwestern Colombia, and *Leishmania (Viannia) panamensis* was identified as the causative agent in 58% of cases. Eighteen patients recovered with pentavalent antimonial. The importance of distinguishing DL from those other clinical presentations is based on the fact that disseminated, diffuse and post-kala-azar CL are very different in etiology, clinical manifestations and response to treatment and prognosis.

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Introduction

Cutaneous leishmaniasis (CL) is an infectious disease caused by the *Leishmania* parasite that is transmitted through the bites of phlebotominae sand flies. CL is characterized by broad clinical polymorphism varying from localized to diffuse and disseminated lesions. Localized CL (LCL) is the most prevalent clinical manifestation worldwide, characterized by

the appearance of a skin lesion at the vector sting site. The lesion occurs after reproduction of the parasites into the dermis, which generates a granuloma. The granuloma is initially manifested as small papule that progressively increases in size to form a rounded nodule. As a consequence of the parasite virulence and host immune response, the nodules show necrosis in the center and become ulcers characterized by a round form, with high and clear borders, an indurated base and granular background, painless and with a scab firmly attached to the base. Overinfection with bacteria or fungi, often caused by empirical treatments, produces purulent and painful ulcers. Characteristic scars with hyper- or hypochromic edges, commonly called 'onion bulb scars', appear after treatment. Nodular lesions sometimes become scaly epidermal plaques or warty lesions [1]. In some patients, the parasite may spread via lymph and blood to the skin of different anatomical regions, particularly the face, chest and upper limbs, where the parasite reproduces widely and causes disseminated leishmaniasis (DL) or diffuse cutaneous leishmaniasis (DCL). Although these two clinical forms can be clearly differentiated (see table 1), some authors consider them as synonymous, which makes a meta-analysis of the literature review difficult.

Here, we report a series of DL patients attended at the PECET, University of Antioquia (Medellín, Colombia). A literature review focusing the attention on the available information to differentiate DL and DCL is also included.

Case Presentation

Between 1997 and 2015, 27 patients who were diagnosed with DL were treated. The patient characteristics are summarized in table 2. Twenty-two patients (85%) were men; 20 patients (77%) were of mixed race, 4 patients (15%) were black, and 2 patients were indigenous; their age ranged from 4 to 61 years (mean 32 years). Twenty-five patients (96%) were from the northwest of Colombia (Antioquia, Choco and Cordoba states), but only 2 patients came from the southeast of the country. Only 1 patient evidenced HIV coinfection. The other patients had a negative HIV serology. Parasite cultures were positive in 16 patients, while the remaining 11 cultures were negative. *Leishmania (Viannia) panamensis* was identified as the causative agent in 15 isolates; the last isolate was identified as *Viannia* subgenus, but no species was determined. This *Leishmania* species distribution is similar to that observed for patients with LCL from the northwestern Colombian region, where 70% of the strains circulating are *L. (V.) panamensis* and 30% correspond to *L. (V.) braziliensis*, whereas in the southeastern region, 80% of the circulating species are *L. (V.) braziliensis* as identified by monoclonal antibody techniques and PCR-RFLP (unpublished data).

All patients met the diagnostic criteria of having 10 or more polymorphic lesions in at least 2 parts of the body surface. The number of lesions for each patient varied between 12 and 294 (21 patients with 100 lesions or less, 3 patients had more than 100 lesions and less than 200, and 4 patients had more than 200 lesions; table 3). The evolution time since the appearance of the first lesion to the spreading was more than 2 weeks. In most patients, the primary lesion was plaque, and the secondary lesions (disseminated) were nodules, papules and plaques, with different sizes but smaller than 2.0 cm in diameter. Only 1 patient had frank ulcers (fig. 1, fig. 2, fig. 3, fig. 4). Lesions were present mainly on the face, trunk and upper limbs. Seven patients (25%) had nasal mucosal involvement consisting of ulcers, scabs or septal perforation indicating an important frequency of mucosal involvement.

The Montenegro skin test was positive in 18 of 21 patients (84%) with an induration size that varied between 5 and 12 mm (average 6.8 mm; table 2), suggesting no complete anergy of cellular immune response. Cell proliferation and T cell subpopulation in peripheral

blood samples were evaluated only in 4 patients who had absolute values of T cell and lymphoproliferative response within the reference values. However, the percentages of T cell CD3+, CD4+ and CD3+CD4+ subpopulations were below the reference values, whereas the percentage of naturally occurring regulatory T cells (CD4+CD25+Foxp3+) were increased. Five of the 27 patients (19.3%) had diabetes mellitus, obesity, vitiligo, HIV/AIDS and leukemia as baseline comorbidities, which could favor the spread of the parasite. In 92%, their immunosuppressive condition was not identified, which could facilitate the spread of the parasite since most of patients were farmers from rural areas. Only 2 patients had a clinical condition-based immunosuppression (HIV and leukopenia).

Twenty-two patients were treated with intramuscular meglumine antimoniate at a dose of 20 mg/kg/day for 20 days (table 3). Treatment was extended to 28 days for those patients that had mucosal involvement. Nineteen of these 22 patients (86.3%) were cured with a single treatment cycle of meglumine antimoniate, while 3 patients did fail. One of these 3 patients was cured with a second cycle with topical amphotericin B (Anfoleish®) applied twice daily for 28 days, and the other 2 patients were cured with a second cycle with oral miltefosine at doses of 2–2.5 mg/kg/day for 28 days. One of these 2 patients had been treated before with amphotericin B deoxycholate 1 mg/kg daily only for 9 days because of renal toxicity. Among the remaining 7 patients, 2 of them were cured with 4 applications of intramuscular pentamidine at a dose of 3 mg/kg/day (table 3); another patient, who had 103 lesions, was cured after treatment with pentamidine combined with topical amphotericin B applied as before. Another patient was cured with miltefosine alone, and the last patient, who had HIV/AIDS coinfection, drug abuse, Kaposi's sarcoma, extrapulmonary tuberculosis, cryptococcal meningitis and poor adherence to antiretroviral therapy, was treated with liposomal amphotericin B combined with miltefosine; this patient showed partial clinical improvement but subsequent appearance of new skin lesions and extensive mucosal involvement.

Discussion

DL is characterized by an initial injury into the dermis followed by a high number of skin lesions (>10 polymorphic lesions) in at least two parts of the body surface, with or without mucosal involvement [2, 3]. DL has been described in Brazil, Venezuela, Guyana and Colombia, with a significant increase in the number of cases in highly endemic places as the Brazilian north, Colombo-Brazilian Amazon and Colombian northwest. This clinical manifestation is caused by *Leishmania* species of the subgenus *Viannia*, mainly *L. (V.) panamensis*, *L. (V.) braziliensis* and *L. (V.) guayanensis*. The higher incidence occurs in men, young adults and farmers [2]. Patients suffering DL describe the initial appearance of a single lesion (nodule or ulcerative plaque), presumably located in the vector bite site. Weeks or months later, as a consequence of parasite dissemination, polymorphic lesions (isolated or confluent), different in size and growth rate, appear in remote anatomic areas from the initial lesion that may cover the entire body surface, except armpits and inguocrural region; lesions in the face may become disfiguring. Associated to the skin lesions, mucosal involvement or symptoms such as fever, chills and lymphadenopathy may occur [2, 4]. Dissemination may occur after therapy with immunosuppressive drugs [5].

The pathogenesis of DL is not well established. However, partial inhibition of specific cellular immunity against the parasite has been demonstrated. A decrease in CD4+ T cells in peripheral blood with partial absence of T cell response to *Leishmania* antigen, evidenced by a mildly reactive (3 or 4 mm induration) or positive (>5 mm) Montenegro skin test, is ob-

served [6]. A low production of the type Th1 cytokines IFN- γ , TNF- α , IL-10 and IL-5, which favor the spread of the parasite, is also registered.

Histological examination of the lesions can reveal the presence of a granuloma composed of lymphocytic infiltrates with very few or no parasites [4, 7, 8]. A decrease in the percentage of CD3+CD4+ T cells and an increase in the percentage of regulatory T cells could affect the immune response mediated by T cells because it has been shown that the regulatory T cells CD4+CD25+Foxp3+ (known as natural regulatory T cells) are potent suppressors of acquired immune response, as is the immune response mediated by T cells [9, 10]. A decrease in the percentage of activated CD4+ T cells in the blood of patients may affect the cellular immune response associated with a decrease of the specific local cellular response against some *Leishmania* species.

The diagnosis of DL as well as other clinical forms of CL is based on the observation of the parasite in smears or aspirates from the lesion. In most cases, abundant amastigotes are observed [11]. The treatment of DL is based on systemic administration of pentavalent antimonials (20 mg/kg/day for 20 days), miltefosine (2–2.5 mg/kg/day for 28 days) and amphotericin B both deoxycholate (0.7–1 mg/kg/day for 30 days) or liposomal (3 mg/kg/day for 10–14 days), although the liposomal form is preferred for the lower toxicity [11]. Therapeutic response may also vary from poor to good, depending on the *Leishmania* species. Thus, for example, the percentage of cured patients with DL by *L. (V.) braziliensis* treated with 1 course of antimony therapy for 30 days in its highest dosage (20 mg/kg/day) is 24% [7], while in patients with DL by *L. (V.) panamensis*, the cure rate is 86.3%, as shown here. With liposomal amphotericin use (dose ranging from 17 to 37 mg/kg, used in 7–14 days of treatment), the final cure rate was 65% [12]. As shown in this work, pentamidine at a dose of 3 mg/kg/day (4 applications) is also a good option to treat DL even in cases having a high number of lesions.

In endemic areas for leishmaniasis, DL is considered as an opportunistic infection mainly in HIV positive patients in whom therapeutic failures and relapses are frequent [13]. Differential diagnosis of DL include diseases such as psoriasis, histoplasmosis (and other relevant deep mycoses in immunosuppressed patients), pemphigus, pityriasis rosea and lupus [14] but also other cutaneous forms of leishmaniasis such as DCL and post-kala-azar dermal leishmaniasis (PKDL) [15].

DCL was described for the first time in Venezuela by Convit and Lapenta [16] in 1948. This clinical manifestation of DCL is associated with *Leishmania* species of the *Leishmania* subgenus, mainly *L. (L.) amazonensis* (in the New World) and *L. (L.) aethiops* (in the Old World) [17, 18]. DCL appears during the first decades of age, with periods of remission and frequent relapses. The lesions are mostly papules and nodules; they do not ulcerate [11]. The Montenegro skin test is predominantly negative, and histologically, granulomas with few lymphocytes and abundant parasites are observed. DCL is more severe because a complete inhibition of specific cellular immunity occurs and the therapeutic response is poor and therefore, relapses occur more frequently [19, 20]. In DCL, the inhibition of cellular immune response is complete. Contrary to DL, there is no fully effective treatment against DCL. Temporary improvement has been observed in Venezuela using immunotherapy with BCG and heat-dead *L. (L.) amazonensis* promastigotes [21], combined with other drugs such as pentavalent antimonial, amphotericin B and miltefosine. However, relapses of lesions make it necessary to use multiple schemes of treatment [22–24].

In turn, PKDL is caused by *L. (L.) donovani* in East Africa and India. This disease is characterized by the appearance of rash during weeks or months, followed by macules and plaques especially in the face, upper chest and upper limbs. Sometimes, mucosal involvement may occur. PKDL occurs in patients who previously had visceral leishmaniasis. In In-

dia, PKDL requires specific treatment, while in African countries, the disease usually heals spontaneously [25].

Although DL has been showing an increase in the number of cases in recent years in countries such as Brazil and Colombia, this is a rare entity and poorly described in the literature. In this clinical manifestation, anergy is not absolute, lesions heal easily and patients show good response to drugs recommended by the WHO to treat LCL such as pentavalent antimonials and miltefosine, and therefore, patients have good prognosis. It is very important to distinguish it from other cutaneous manifestations, mainly from DCL and PKDL, because there are significant differences in etiology, treatment response and prognosis.

Statement of Ethics

The authors state that the patients gave their informed consent complying with all ethical guidelines for human studies.

Disclosure Statement

The authors declare no conflicts of interest.

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Table 1. Parasitological and clinical differences between DL and DCL

Clinical form	DL	DCL
Species	<i>L. braziliensis</i> , <i>L. panamensis</i> and <i>L. guayanensis</i>	<i>L. amazonensis</i> and <i>L. aethiopicum</i>
Clinical signs	Papules, superficial nodules and ulcerations	Infiltrated papules and nodules, infiltrated plaques resembling lepromatous leprosy
Mucosal involvement	Almost half of patients	Absent
Inhibition of cellular immune response	Partial	Total
Montenegro skin test	Positive or negative	Negative
Histopathology	Granuloma composed of lymphocytic infiltrates with very few parasites	Macrophage granuloma with abundant parasites
Therapeutic response	Variable*	Poor
Recommended treatment	Pentavalent antimonials, miltefosine and amphotericin B	Immunotherapy combined with pentavalent antimonials and/or miltefosine or pentamidine

* Therapeutic response varies according to the *Leishmania* species involved.

Table 2. Demographic and clinical characteristics of patient with DCL

Patients	27
Region of origin	
Northwest	25
Center	1
South	1
Median age [range], years	34 [4–75]
Sex, male/female	23 (85)/4 (15)
Race	
Mixed	20 (74)
Black	5 (18)
Amerindian	2 (7)
Baseline comorbidities*	18 (15)
Range of number of lesions	12–294
Nasal mucosal involvement	7 (25)
Montenegro skin test	
Done	20
Positive/negative	18/3
Average size [range], mm	6.8 [5–12]
<i>Leishmania</i> spp.	
<i>L. panamensis</i>	15/16
Treatment	
Meglumine antimoniate	18
Miltefosine	1
Miltefosine + meglumine antimoniate	2
Meglumine antimoniate + amphotericin B + miltefosine	1
Pentamidine	2
Pentamidine + topical amphotericin B	1
Amphotericin B + miltefosine	1
topical amphotericin B	1

Figures are n (%), unless otherwise indicated. * Diabetes mellitus, obesity, HIV/AIDS, leukemia, vitiligo, hypertension.

Table 3. Clinic, demographic and therapeutic characteristic of patients with disseminated cutaneous leishmaniasis

Patient code	Provenience	Gender	Age, years	Race	Comor-bidity	Lesions	Mucosal involvement	MST	Treatment	Outcome
001	Choco	Male	28	Black	D	85	–	+	1st MA (i.m.), 2nd miltefosine (o)	1st: failure, 2nd: cure
002	Antioquia	Male	61	Mestizo	H, O	103	–	–	Pentamidine (i.m.) + AmB (t)	Cure
003	Tolima	Male	45	Mestizo	H	56	+	+	1st MA (i.m.), 2nd AmB (t)	1st: failure, 2nd: cure
004	Antioquia	Male	55	Mestizo	H	17	–	ND	MA (i.m.)	Cure
005	Antioquia	Male	34	Mestizo	HIV/AIDS, TB, KS	200	+	–	lAmB (i.v.) + miltefosine (o)	Improvement
006	Caquetá	Male	21	Mestizo	None	32	+	ND	MA (i.m.)	Cure
007	Antioquia	Female	55	Mestizo	LKP	70	–	+	MA (i.m.)	Cure
008	Choco	Male	19	Mestizo	None	16	+	+	MA (i.m.)	Cure
009	Antioquia	Male	21	Black	None	136	+	+	MA (i.m.)	Cure
010	Antioquia	Male	28	Mestizo	None	27	–	+	MA (i.m.)	Cure
011	Antioquia	Male	29	Mestizo	None	41	–	+	MA (i.m.)	Cure
012	Antioquia	Male	26	Black	None	294	–	+	Miltefosine (o)	Cure
013	Antioquia	Male	22	Mestizo	None	13	–	ND	MA (i.m.)	Cure
014	Antioquia	Male	22	Mestizo	None	14	–	+	MA (i.m.)	Cure
015	Cordoba	Female	30	Mestizo	None	17	–	ND	MA (i.m.)	Cure
016	Antioquia	Female	4	Mestizo	None	50	–	ND	MA (i.m.)	Cure
017	Antioquia	Male	23	Mestizo	None	12	–	+	MA (i.m.)	Cure
018	Antioquia	Male	22	Mestizo	None	13	–	ND	MA (i.m.)	Cure
019	Antioquia	Male	41	Mestizo	V	12	–	ND	MA (i.m.)	Cure
020	Choco	Male	27	Mestizo	A	17	–	+	MA (i.m.)	Cure
021	Antioquia	Male	43	Indian	Dy	50	–	+	Pentamidine (i.m.)	Cure
022	Antioquia	Male	32	Mestizo	None	46	–	+	MA (i.m.)	Cure
023	Choco	Male	12	Indian	LKM	21	–	+	MA (i.m.)	Cure
024	Antioquia	Female	55	Mestizo	E	17	–	+	MA (i.m.)	Cure
025	Antioquia	Male	46	Mestizo	None	46	+	+	MA (i.m.)	Cure
026	Choco	Male	44	Black	None	250	–	+	1st MA (i.m.), 2nd miltefosine (o)	1st: failure, 2nd: cure
027	Antioquia	Male	75	Black	H, CKD	143	+	+	Pentamidine (i.m.)	Cure

D = Diabetes; H = hypertension; O = obesity; TB = tuberculosis; KS = Kaposi's sarcoma; LKP = leukopenia; V = vitiligo; A = anorexia; Dy = dyslipidemia; LKM = leukemia; E = epilepsy; CKD = chronic kidney disease; MST = Montenegro skin test; ND = not done; MA = meglumine antimoniate; AmB = amphotericin B; lAmB = liposomal amphotericin B; i.m. = intramuscular; i.v. = intravenous; o = oral; t = topical.



Fig. 1. Male with 294 lesions with good response to treatment with miltefosine. Previously, the patient had failed to respond to amphotericin B plus one scheme of intramuscular meglumine antimoniate treatment showing toxicity and worsening clinical disease with new lesions. Lesions before (**a, c**) and after treatment (**b, d**).



Fig. 2. Male with 250 lesions. This patient was treated with intramuscular meglumine antimoniate. After failure, the patient was treated with miltefosine and was cured. Lesions before (a–c) and after treatment (d–f).



Fig. 3. Patient with 143 lesions and mucosal involvement, who had previously received systemic management with glucantime and miltefosine. He presented renal toxicity and reactivation and was treated with pentamidine. He had complete resolution of lesions without systemic toxicities. Lesions before (a–c, f) and after treatment (d, e).



Fig. 4. Patient with 56 lesions who showed good response to treatment with topical amphotericin B.