Clinical Picture of Cutaneous Leishmaniases Due to *Leishmania (Leishmania) mexicana* in the Yucatan Peninsula, Mexico

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Localized cutaneous leishmaniasis (LCL), known as "chiclero´s ulcer" in southeast Mexico, was described by Seidelin in 1912. Since then, the sylvatic region of the Yucatan peninsula has been identified as an endemic focus of LCL. The purpose of the present work was to describe the clinical picture of LCL caused by Leishmania (Leishmania) mexicana *in the Yucatan peninsula. A total of 136 cases of LCL, based on isolation and characterization of* L. (L.) mexicana *by isoenzymes and/or monoclonal antibodies, were selected. Some variability of clinical features regarding number, type, size, form, location and time of evolution of the lesions was observed. The most frequently observed presentation was a single, ulcerated, rounded small lesion, located on the ear, with an evolution time of less than three months, with neither cutaneous metastases nor lymphatic nor mucosal involvement. This picture corresponds to previous studies carried out in the same endemic area where an organism of the* L. mexicana *complex has been incriminated as a major aetiological agent of classical "chiclero´s ulcer", confirming that in the Yucatan peninsula LCL due to* L. (L.) mexicana *when located on the pinna of the ear is a remarkable characteristic.*

Key words: *Leishmania (L.) mexicana* -"chiclero´s ulcer"- Yucatan peninsula

Human leishmaniases include a spectrum of diseases of variable severity ranging from cutaneous ulcer to a fatal visceral disease, all of them caused by intracellular protozoan parasites of the genus *Leishmania* Ross, 1903. Cutaneous leishmaniases in the New World are zoonoses caused by at least ten species of *Leishmania*, of the *mexicana* and *braziliensis* complexes (Marinkelle 1980, Dedet 1999). The disease is polymorphic in its clinical presentation and evolution. Differences may be due to *Leishmania* species or strains, host´s genetic background and immune response. Localized cutaneous leishmaniasis (LCL) known as "chiclero´s ulcer" (collector of natural chewing gum) in southern Mexico, was described by Seidelin (1912). Since then, the sylvatic region of the Yucatan peninsula has been considered an endemic focus of LCL (Shattuck 1933, Beltran & Bustamante 1942, Biagi et al. 1957, Andrade-Narváez et al. 1988, 1990, 1992). Clinical picture of "chiclero´s ulcer" is characterized by cartilage involvement of the pinna of the ear (Martínez 1951, Biagi 1953, Lainson & Strangways-Dixon 1963, Walton 1987). Very recently, we have demonstrated that *Leishmania (Leishmania) mexicana* Biagi, 1953, *emend.* Garnham, 1962, is the main agent causing LCL in this focus, although, *Leishmania (Viannia) braziliensis* Vianna 1911, *emend.* Matta, 1916, has also been isolated from a few cases (Canto-Lara et al. 1998, 1999). Moreover, *L. (V.) braziliensis* has been predominantly isolated from LCL cases occurring in Belize (Evans et al. 1984) and in Guatemala (Herwaldt et al. 1992), both recognized endemic areas of LCL attributed to the *Leishmania mexicana complex* (Zeledón 1985). Hence, we decided to report in here the clinical findings of LCL cases caused by *L. (L.) mexicana* in the Yucatan peninsula.

In the present study, *L. (L.) mexicana* isolated from 136 patients suffering of LCL ("chiclero´s ulcer") in southeast Mexico was identified by molecular methods. It was confirmed that "chiclero´s ulcer" – LCL caused by *L. (L.) mexicana* in the Yucatan peninsula – is a clinical polymorphic disease characterized by predominantly single ulcer-

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ative lesions, located mainly on the ears and with no tendency to produce either cutaneous metastases or lymphatic or mucosal involvement.

MATERIALS AND METHODS

Patient population - Patients from the Yucatan peninsula, Mexico, with a suggestive clinical picture of LCL, who sought treatment between January 1990 and December 1995, were evaluated in a long-term clinical-epidemiological study to define dynamics of transmission of *L. (L.) mexicana* in that focus. This study was reviewed and approved by the Ethical Committee of the Universidad Autónoma de Yucatán, in agreement with international ethical guidelines for biomedical research involving human subjects (Ley General de Salud, Mexico). Written informed consent to participate was obtained from each patient. Eligibility for this study included a confirmed diagnosis of LCL based on visualization of the parasite by smear, biopsy, and/or isolation-culture (Garcia-Miss et al. 1990). A complete clinical history was performed in all cases recording age, sex, occupation, as well as clinical presentation through dermatological examination (number, size, form, and location of lesion(s), suggestive signs of secondary infection, time of evolution prior to diagnosis and metastases), and searching for lymphatic involvement. Mucosal were examined by means of direct examination of oropharynx with a frontal light and a tongue depressor.

Characterization of parasites - Parasites isolated by needle aspirates from the edge of the lesion were inoculated into a tube of Senekjie´s modified medium and kept at 22ºC. After initial growth in culture tubes, the parasites were mass cultivated for isoenzyme electrophoresis and analyses with monoclonal antibodies as described previously in Chablé-Santos et al. (1995) and Canto-Lara et al. (1998, 1999).

RESULTS

Between January 1990 and December 1995, a total of 683 patients with cutaneous lesions suggestive of LCL were studied. Parasite demonstration by smear, biopsy, and/or isolation-culture was positive in 445 of them (65.1%). From these, *L. (L.) mexicana* was successfully isolated, cultured, and identified by isoenzyme characterization and/or monoclonal antibodies in 136/445 cases (30.5%). Males (128/136, 94.1%) between 10 to 40 years old (116/136, 85.3%) were mainly affected. The most common lesions were single (84.5%), rounded (52.6%), ulcerated (72.5%), and located on the ear (39.9%). However a great variability in clinical presentations was observed (Table). Four patients had 3 lesions and only three men had 4, 7, and 8 lesions respectively. Time of evolution varied from seven days to 30 years (average=9.9 months). The average area of the lesions was 2.6 cm^2 (ranging from 0.03-29.6 cm^2). Secondary infection was observed in 43/136 lesions (31.6%). There was no cutaneous metastases and lymphatic involvement as so mucosal involvement was not observed in any of the 136 cases even after ten years of monthly follow-up.

TABLE

Clinical features of 136 cases of localized cutaneous leishmaniases due to *Leishmania (Leishmania) mexicana*

Characteristic	Number	%
Time of evolution		
0-3 months	99	72.8
3-6 months	23	16.9
>6 months	14	0.3
Shape of lesion		
Rounded	71	52.6
Oval	32	23.7
Geographic	32	23.7
Type of lesion		
Ulcerated	98	72.0
Nodular ulcerated	29	21.3
Nodular	9	6.6
No. of lesions		
One	115	84.5
Two	14	10.3
Three or more	7	5.1
Location		
Ear	57	39.9
Head-neck	44	30.8
Upper limb	29	20.3
Limb	7	4.9
Trunk	6	4.1

DISCUSSION

This paper is the first report in which clinical presentation of LCL, related to *L. (L.) mexicana* identified by molecular methods, is offered in southeast Mexico. The clinical picture was polymorphic but characterized by a predominantly single, painless, small rounded, ulcerative, ear-located lesion, without cutaneous metastases, lymphatic or mucosal involvement, confirming "chiclero´s ulcer" clinical presentation attributed to *L. mexicana complex* described in previous studies carried out in the same endemic area.

In the Yucatan peninsula, previous studies (Seidelin 1912, Shattuck 1933, Biagi 1953) reported the typical "chiclero´s ulcer" but precise identification techniques of species of *Leishmania*

were not available yet. Seidelin (1912) was the first to describe the disease in the Yucatan peninsula in "two young natives, chicleros, with extensive ulcers located on the upper part of the helix of one ear, with somewhat elevated irregular borders, granular surface beset with minute vesicles, considerable destruction of the tissues and beginning deformation due to cicatricial retraction". Laymen knew the affection as a typical one, the ear "ulcer of the chiclero". Shattuck (1933) described 17 cases reporting for the first time the affection in two women and two children. Single lesion (88.2%) located on the ear (76.5%) was the most common clinical presentation. He mentioned that "such lesions persist for years and ultimately heal leaving a well-marked scar". Biagi (1953) working in Escárcega, Campeche, southwest of the Yucatan peninsula, studied 70 cases of LCL. Male were predominantly affected (94.3%). Clinical picture was characterized by a single (76.2%), nodular subcutaneous ulcerated lesion (67.5%), located predominantly on the ear (48.4%), where it usually became chronic with a time of evolution of more than 12 years. Walton (1987) pointed out that in the Yucatan peninsula, cartilage involvement of the pinna of the ear is such a common occurrence that it might be considered as a special feature of "chiclero´s ulcer".

In Belize, Lainson and Strangways-Dixon (1963) in a three-years study on the epidemiology of dermal leishmaniases, studied in detail a total of 46 human cases. They found that the disease was characterized by a single dermal lesion commonly located on the ear (40%), without evidence of any cutaneous dissemination of infection or visceral involvement. Moreover, they highlighted that lesions on the ears were a particular characteristic due to their extreme chronic destruction of the cartilage and overlying tissues. The parasite was isolated in 27 instances and cultured in NNN media. It was identified as *L. mexicana* based on the behaviour of strains isolated in cultures and in hamsters.

In Guatemala, Herwaldt et al. (1992) evidenced the importance of species of *Leishmania* identification. In their study on the natural history of LCL caused by *L. (L.) mexicana*, 22 of the 25 lesions (88%) completely re-epithelialized in 14 weeks. In contrast, only 2/32 (6%) lesions caused by *L. (V.) braziliensis* cured spontaneously. They concluded that the species of *Leishmania* is the primary determinant of both the clinical course and the outcome of untreated lesions. It is interesting to point out that the most common location of lesions was not the ear, but the upper limbs (43%).

In Texas, McHugh et al. (1996) studied 27 cases of LCL in which the clinical presentation was characterized by a single lesion (74.1%) with an area less than 3 cm^2 (96.3%), located on the head predominantly (96.3%), and from these only 6/20 (30%) were located on the ear. The parasite was isolated in eight cases and was identified by isoenzymes as *L. (L.) mexicana*.

All these studies demonstrate the variability of the clinical presentation of LCL caused by *L. (L.) mexicana* regarding the number, form, size, and location of lesions as it has been described in other species of *Leishmania* (Louzir et al. 1998). Various hypotheses have been proposed to explain such variability: (a) differences in parasite´s virulence; (b) differences in skin permeability; (c) individual variation in the host´s genetic susceptibility; (d) individual human differences of attraction for phlebotomine sand flies (Llanos-Cuentas & Campos 1988). Inter- and intraspecific variations of parasite virulence have been demonstrated (Chang et al. 1990) and human susceptibility is likely to have a genetic basis (Lara et al. 1991). The skin permeability hypothesis to the sand fly bite was evaluated by Esterre et al. (1987), however, they did not show convincingly that the differences between the patients and controls were significant. Louzir et al. (1998) studying the immunologic determinants of disease evolution in LCL due to *L. major*, found that an unfavorable clinical outcome was not related to an inadequate Th1 cell response, and suggested that the macrophage-activating effect of IFN-γ may be inhibited by the concomitant expression of IL-10. Finally, McHugh et al. (1996) pointed out that although the *Leishmania* parasites infesting humans in Texas share a high genetical similarity with *L. (L.) mexicana* isolates from southeast Mexico, the epidemiology and ecology of the disease in Texas and Mexico are different. This emphasizes the importance of dynamics of transmission on the clinical presentation.

The most remarkable characteristic of "chiclero´s ulcer" [LCL caused by *L. (L.) mexicana* in the Yucatan peninsula] is the predominant location of lesions on the ears. Lainson and Strangways-Dixon (1963) proposed that it was "simply owing to the almost constant exposure of this part of the body, day and night, to the bite of the vector. Moreover, they mentioned, according to Professor Adler, that extensive sweating of the face compared with that of the ears might be an important factor. Finally, the slightly lower temperature of the ears conceivably might lead to a faster development of *L. (L.) mexicana* on that site.

On the other hand, it is important to consider the possible role of the vector in determining the biting site selection. Although variability of attractiveness of human hosts has been shown for several species of mosquito (Brouwer 1960, Khan

et al. 1965), at present little is known about the biting site selection of sand flies and human attractants for sand flies. Very recently, biting site distribution of three members of the *Lutzomyia longipalpis* complex (Diptera: Psychodidade: Phleobotominae) was documented on a male human volunteer aged 29. Female sand flies from Jacobina, State of Bahia, Brazil, displayed a marked preference for biting on the ears. Biting selection behaviour seemed to be odour-mediated as revealed by female sand fly responses to ear extracts (Rebollar-Tellez 2000). The possible role of odour-mediated biting selection behaviour of *Lu. olmeca* and *Lu. cruciata* – incriminated vectors of *L. (L.) mexicana* – is under study in order to explain the frequency of ear lesions.

In summary, the clinical outcome and evolution of the infection by *Leishmania* parasites depends on multiple factors. The study of these factors is of paramount importance to identify markers for population at risk that could be used as targets for a direct intervention leading to a better control of the disease.

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