

American cutaneous leishmaniasis: epidemiological profile of patients treated in Londrina from 1998 to 2009*

Leishmaniose tegumentar americana: perfil epidemiológico dos pacientes atendidos no município de Londrina entre 1998 e 2009

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Abstract: BACKGROUND: American cutaneous leishmaniasis is a dermatozoonosis of compulsory notification with relevant morbidity. The disease is considered endemic in northern Paraná. OBJECTIVES: To evaluate the clinical, laboratory and epidemiological aspects of patients with American cutaneous leishmaniasis treated at Clinics Hospital, State University of Londrina, Brazil (Paraná). METHODS: This was an observational, cross-sectional, retrospective and descriptive study. The medical records of patients with American cutaneous leishmaniasis treated at the University Hospital of Londrina - Paraná, from 1998 to 2009 were evaluated. RESULTS: A total of 470 patients, with prevalence of 8.72 cases / 100,000 inhabitants, participated in the study. Most patients were male, aged 21-40 years, with a single ulcerated lesion as the most common clinical presentation, located mainly in an exposed area of the body. With regard to immunological tests, the Montenegro intradermal reaction was positive in 84.4% of cases. Treatment with pentavalent antimony was well tolerated, and patient follow-up for a year occurred in 59% of cases. CONCLUSION: American cutaneous leishmaniasis is still an endemic disease in the region, with a high potential for morbidity, but with a cure rate of around 95% after treatment. The use of immunological techniques facilitates the diagnosis of clinically suspicious cases.

Keywords: Endemic diseases; Epidemiology; Leishmania; Skin ulcer

Resumo: FUNDAMENTOS: Leishmaniose tegumentar americana é uma dermatozoonose de notificação compulsória com morbidade relevante, considerada endêmica no norte do Paraná. OBJETIVOS: Avaliar os aspectos clínicos, laboratoriais e epidemiológicos de pacientes com leishmaniose tegumentar americana atendidos no Hospital das Clínicas da Universidade Estadual de Londrina, Brasil (Paraná). MÉTODOS: Estudo observacional, transversal, retrospectivo com caráter descritivo. Realizada a avaliação dos prontuários médicos dos pacientes com leishmaniose tegumentar americana atendidos no Hospital Universitário de Londrina - Paraná, no período compreendido entre 1998 e 2009. RESULTADOS: Incluídos no estudo um total de 470 pacientes com uma prevalência de 8,72 casos/ 100.000 habitantes. A maior parte dos pacientes eram do sexo masculino, na faixa etária de 21 a 40 anos, com lesão única ulcerada como apresentação clínica mais comum, com localização principal em área descoberta. Dentre os testes imunológicos, a intradermoreação de Montenegro apresentou positividade em 84,4% dos casos. O tratamento com antimonial pentavalente foi bem tolerado, e o seguimento dos pacientes por um ano ocorreu em 59% dos casos. CONCLUSÃO: Leishmaniose tegumentar americana ainda é uma doença com caráter endêmico na região, com potencial mórbido elevado, porém com percentual de cura com o tratamento usual em torno de 95%. O uso de técnicas imunológicas facilita o diagnóstico de casos clinicamente duvidosos.

Palavras-chave: Doenças endêmicas; Epidemiologia; Leishmania; Úlcera cutânea

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INTRODUCTION

American cutaneous leishmaniasis (ACL) is a zoonosis caused by protozoa of the genus *Leishmania* of the Trypanosomatidea family. Transmission usually occurs by inoculation of promastigotes through the bite of female phlebotomine sandflies, whose species vary according to geographical location. They are classified into seven species of the genus leishmania capable of causing ACL: *Leishmania (Leishmania) amazonensis*, *Leishmania (Viannia) guyanensis*, *Leishmania (Viannia) braziliensis*, *Leishmania (Viannia) lainsoni*, *Leishmania (Viannia) naiffi*, *Leishmania (Viannia) shawi* and *Leishmania (Leishmania) infantum*.^{1,2} After being phagocytosed by macrophages of the endothelial reticular system, promastigotes lose their flagella, becoming amastigotes and infecting new macrophages. Clinical presentations of the disease can range from localized cutaneous, disseminated cutaneous, mucocutaneous, and even diffuse cutaneous leishmaniasis.

In Brazil, from 1988 to 2009, ACL presented an annual average of 26,021 registered cases and a mean detection rate of 14.1 cases per 100,000 inhabitants.² A geographical expansion is observed; in the early 80s, autochthonous cases were registered in 19 federative units of the country; in 2003, autochthonous cases were confirmed in all federative units of the country. The northern region has more cases of the disease (about 37.3% of the total cases registered in the period), followed by the Central West region (32.6 cases per 100,000 inhabitants) and Northeast region (16.1 cases per 100,000 inhabitants).²

The state of Paraná accounts for 98% of the cases in southern Brazil, with a coefficient of 3.8 cases per 100,000 inhabitants. This ratio is considered average by the National Foundation of Health.² The northern region of Paraná has a coefficient similar to that of the rest of the state.

The present study aims at evaluating the main clinical, epidemiological and laboratory characteris-

tics of ACL in the metropolitan region of Londrina (Paraná).

MATERIAL AND METHODS

We reviewed the records of all cases with confirmed diagnosis of ACL treated at the outpatient clinic of the Clinics Hospital, State University of Londrina, from January 1998 to December 2009.

This service is responsible for the treatment of all suspicious cases of ACL, referred by basic health units in the municipalities of the 17th Regional Health Facility of Londrina, comprising 21 municipalities in northern Paraná, according to figure 1.

Patients referred to the service are clinically assessed by dermatologists and residents. Laboratory workout includes Montenegro skin test (MST), with inoculation in the right forearm of 0.1 ml of antigen provided by the Health Department of the State of Paraná, with readings taken within 48-72 hours. The results were considered positive when they were equal to or above 5mm. Biochemical tests such as blood count, C-reactive protein, renal and hepatic function, and immunofluorescence for ACL could be performed during the investigation. In doubtful cases, a wedge biopsy of the border of the lesion is done.

Diagnosis is considered positive based on the clinical aspect of the lesion, positive Montenegro skin test, positive serology (titers equal to or greater than 1/40) or a wedge biopsy of the border of the lesion showing the parasite.

N-methyl glucamine administered intravenously in a dose of 15 - 20 mg SbV / kg/day is the first-choice treatment, respecting the limit imposed by the Ministry of Health of 3 ampoules per day. In case of failure in the first 20-day cycle, the cycle is repeated for 30 days using the same doses, according to clinical and laboratory data. In case of contraindication to pentavalent antimony, pentamidine is administered at a dose of 300 mg every three days, totaling five doses.

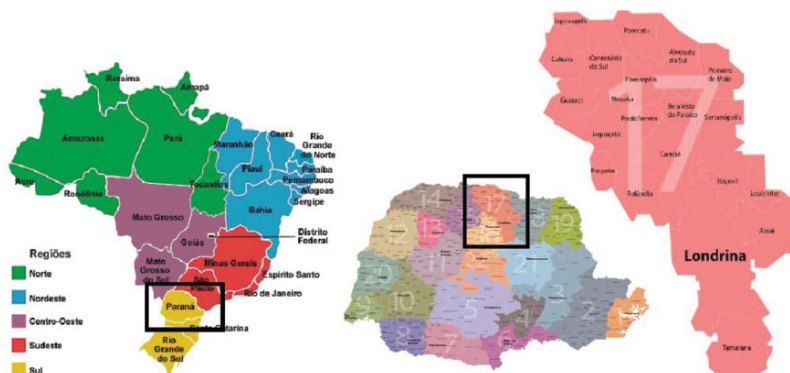


FIGURE 1: Location of the 17th Regional Health Facility of Londrina in the State of Paraná and Brazil

In special cases, in which the use of these drugs was contraindicated, immunotherapy vaccine (Leishvacin®) was used.

RESULTS

In the period studied, four hundred and seventy cases of leishmaniasis were diagnosed (Graph 1).

Three hundred and twelve patients were from Londrina, 136 were from neighboring municipalities and twenty-two had an unknown origin.

There was predominance of males (62.62% of cases) (Graph 2). The age range of greatest prevalence of the disease was 21-40 years (35.1% of cases). Male subjects predominated in the age range from 21 years up to above 50 years (Graph 3). With regard to the clinical forms of the disease, localized cutaneous leishmaniasis corresponded to 83.4%, the mucous form to 10.6%, the mucocutaneous form to 4.5%, and unknown 1.1%. There were no cases of disseminated or visceral leishmaniasis.

With regard to the clinical presentation of ACL, a single lesion was found in 71% of cases; ulcers with raised borders were present in 59.7% of cases (Graph 4). The second most prevalent clinical form was crusty-ulcerated, accounting for 16% of lesions. Nasal septum perforation without cutaneous lesion was found in 37 patients, which represents only 7.88% of patients.

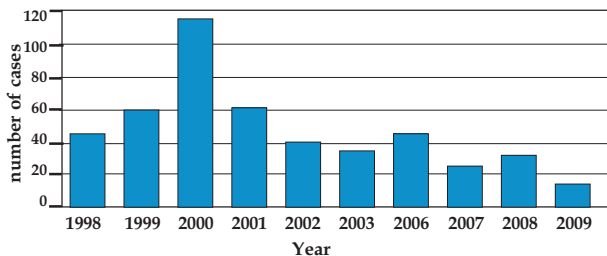
Taking into account the number of lesions and their location, the single form affected 71.2% of patients with predominance of lesions in the upper limbs, followed by the lower limbs (Graph 5).

Montenegro skin test was performed in 397 cases, and 84.4% of cases were positive.

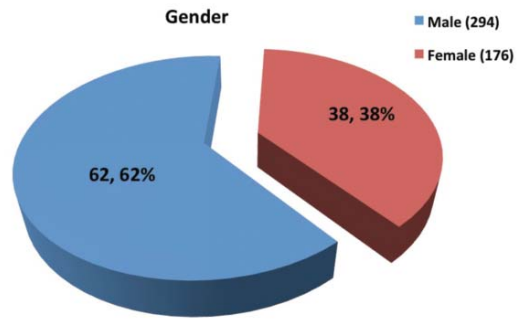
Indirect immunofluorescence was performed in 334 patients; 82% had titers above 1:40. Skin biopsy was needed to confirm the diagnosis of 108 patients (26.5%)(Graph 6).

With respect to drug use, 91.7% received glucantime, 5.6%, pentamidine, and 2.8%, vaccine. Ninety-eight percent of patients finished their treatment regimen.

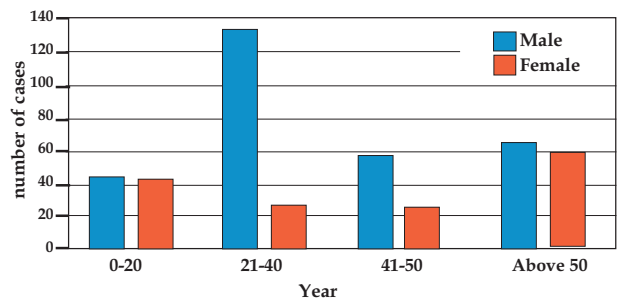
With regard to the number of glucantime cycles, 49.1% of patients underwent only one cycle, 27.3% two cycles, and 23.3% three cycles.



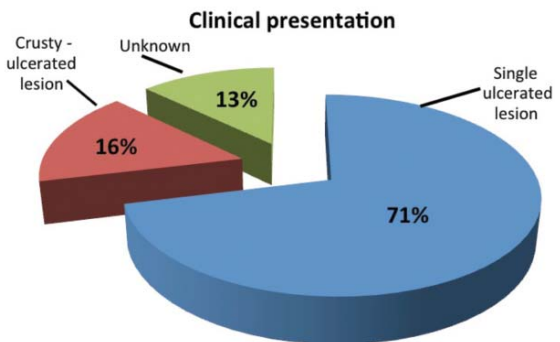
GRAPH 1: Number of ACL cases treated at the Clinics Hospital, State University of Londrina, municipality of Londrina, 1998-2009



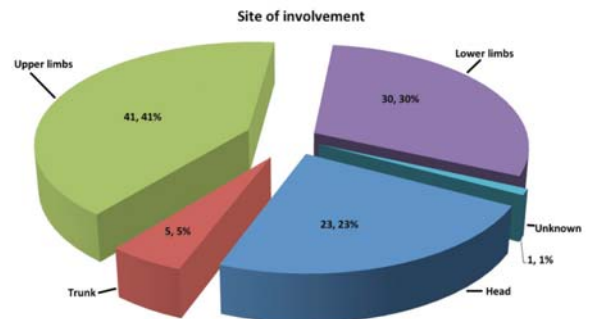
GRAPH 2: Distribution of cases of ACL by gender, Clinics Hospital, State University of Londrina, municipality of Londrina, 1998-2009



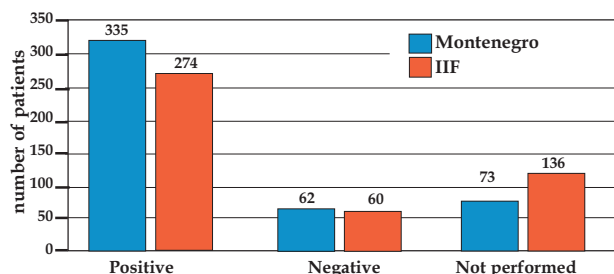
GRAPH 3: Number of cases of ACL by age range, Clinics Hospital, State University of Londrina, municipality of Londrina, 1998-2009



GRAPH 4: Clinical presentation of patients with ACL seen at the Clinics Hospital, State University of Londrina, municipality of Londrina, 1998-2009



GRAPH 5: Body parts affected by ACL lesions in patients treated at the Clinics Hospital, State University of Londrina, municipality of Londrina, 1998-2009



GRAPH 6: Results of Montenegro skin test and indirect immunofluorescence in patients with ACL treated at the Clinics Hospital, State University of Londrina, municipality of Londrina, 1998-2009

Adverse reactions to the drugs were mild and did not prevent any patient from completing their treatment.

The total percentage of patients discharged from the hospital due to clinical cure, that is, use of medication with complete epithelialization of the lesion, absence of local infiltration or erythema and follow-up for one year was 59.1%. Of the remaining patients, 34% underwent full treatment, but abandoned clinical follow-up before completing one year and were not considered as documented cure. In the remaining 6.9% of cases, medical records were incomplete, which made an accurate analysis of the recovery process impossible.

DISCUSSION

The municipality of Londrina is located in the northern region of the state of Paraná, located between latitude 23 08 '47" and 23 55' 46" S and longitude 50 52 '23" and 51 19' 11" °. It has an area of 1724Km and total population of 447,065 inhabitants. The population of the metropolitan area is 662,885 inhabitants.

The first cases of leishmaniasis in Paraná were reported in the mid-nineteenth century, and the disease became endemic in 1980.³ Two large outbreaks of the disease occurred in the State of Parana, in the cities of Jussara and Terra Boa. They were associated with infestation in dogs and deforestation in the 20s and 30s.^{4,5} Recently, Lima *et al* (2002), through the use of orbital remote sensing images and the study of 4416 cases of ACL in Parana from 1993 to 1998, conducted with information from the Health Department of the State of Parana, observed that approximately 94% of cases of ACL in the State of Parana occurred in subtropical regions, with predominance in the north and west regions, but with diffuse notification in 276 municipalities, specially in areas with a high degree of destruction of native vegetation.⁶

Nowadays, the increased number of cases in Northern Paraná has confirmed that leishmaniasis is an endemic disease. In fact, there have been true epidemics, such as the one observed from 1993 to 1995.

These data confirm transmission in peridomestic environments and reports of infected pets, as few areas of native vegetation remain in our region due to intense land use.^{4,7,8} In this study, we observed an average of 39 cases diagnosed for a year in a population of 447,065 inhabitants, with a prevalence of 8.72 cases/100,000 inhabitants in the municipality of Londrina. Prevalence in neighboring municipalities could not be estimated because not all of these cases are treated in our service.

There was a higher percentage of male involvement, with a single lesion, which is similar to data found in the literature. The age range from 21-40 years was the most affected. These results differ a little from those from other studies, in which older patients prevail, but this is still within expectations.^{9,10} Murback *et al* (2011) conducted a review of the medical records of 47 patients with suspected ACL and noticed that the most affected group was represented by adult males (72.3% of cases), and in smaller proportions, there was involvement of children and women (8.5% and 27.7%, respectively).¹¹

Involvement of individuals under 20 years old and of women is observed, in agreement with what has been observed in other regions of the country. This fact is attributed to a possible change in the epidemiological profile of the disease, with an increasing number of cases in peridomestic regions.^{12,13} Silvia *et al* (2007) conducted an epidemiological study in the macroregion of Campinas-SP. The authors obtained data from the Brazilian National Disease Notification System (SINAN) from 1998-2004. They identified 458 cases, with predominance in urban areas (57%), of males (62%), with higher prevalence in the age range from 30 to 50 years (34%). This shows the growing adaptability of the vector to peridomestic regions.¹³

Although the study was conducted in a tertiary and reference hospital, only 4.5% of reported cases involved the mucocutaneous form. This is due to the compulsory notification of cases to this center of study, without previous triage, despite the fact that mucous cases are more resistant to the usual treatment.^{12,14} More than 70% of patients presented a single ulcerated lesion, and this result was also found in many studies.^{1,9,14,15} Name *et al* (2005) evaluated 402 medical records of patients seen in a tertiary hospital and verified predominance of men (65.6%), farmers (23.9%), 20-39 years old (41.8%), cutaneous form (59.2%), with the most frequent type of lesion being an ulcer with infiltrated borders and granular base (72.4%), and the most common location being the lower limbs (56.5%).¹⁰

A high positivity was observed in immunological tests, Montenegro skin test or immunofluorescence, with 84.4% and 82% positivity, respectively. In

patients with suggestive symptoms, findings of a serological test associated with IDST lead to diagnosis with relative accuracy. However, it should be emphasized that when these tests are conducted in endemic areas, such as the one reported, they can be considered positive in cases of previous exposure to the antigen, such as IDST or previous leishmaniasis.^{14,7} Polymerase chain reaction (PCR) was not performed due to its high cost, whereas histopathological examination was not properly described in suspicious cases. For this reason, it was not included in this study. A recent study by Andrade *et al* (2011) employed PCR in a sample of 90 biopsies in which histopathological findings were compatible with ACL, but a conclusive diagnosis could not be established due to the non-visualization of amastigotes. Leishmania DNA was found in 96.7% of samples, and the most common histological pattern was granulomatous exudative. This shows the high sensitivity of PCR in cases in which histopathology is compatible with ACL.¹⁶ This is confirmed by Benicio *et al* (2011), who evaluated diagnostic methods in an endemic area for *Leishmania (Leishmania) amazonensis* in the Brazilian Amazon. The authors studied 180 patients and conducted skin biopsy, histological examination, PCR and culture. Histopathology, through biopsy, was only 50% sensitive, and its association with PCR was the best combination, with a sensitivity of 94%.¹⁷

Treatment with the drugs recommended by the Ministry of Health was highly effective. Glucantime was used in most cases. Name *et al* (2005) obtained similar results; 81.6% of patients with cutaneous leishmaniasis received 20mg SbV/kg/day for 20 days and

were cured. This result lasted for at least a year or more. Pentamidine was the second-choice drug due to the side effects of amphotericin B, and despite the fact that the one-year follow-up was restricted to 59.1% of cases, complete epithelialization of the lesion and absence of infiltration or erythema immediately after treatment was finished were achieved in approximately 96% of patients with the adoption of these two regimens. These numbers are similar to those found in the literature.

CONCLUSION

The results of this study suggest that ACL is highly prevalent, with high rates of the disease in urban areas and the involvement of children and women, groups that were previously unaffected. The involvement of exposed areas, especially the limbs, was the main finding, which is expected due to the natural activity of the mosquito.

Laboratory tests aided clinical diagnosis, shortening the time between an appointment with the doctor and the start of treatment. Indirect immunofluorescence showed the highest positivity. The association of symptoms with complementary exams makes diagnosis safer and more reliable, allowing patients to be immediately treated with the use of N-methyl-glucamine, which may have contributed to the high rate of cure, above 95%, since cutaneous forms respond better than mucocutaneous forms.

Despite the constant effort, it must be emphasized that ACL is still endemic in Brazil, and early clinical and laboratory diagnosis is one of the pillars to control the disease. □

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