CUTANEOUS LEISHMANIASIS (CL) ASSOCIATED WITH LEPROSY: A NEW AND EMERGING CLINICOEPIDEMIOLOGICAL ENTITY OBSERVED IN THE NORTHEAST OF BRAZIL

LEISHMANIOSE CUTÂNEA (LC) ASSOCIADA À HANSENÍASE: UMA NOVA E EMERGENTE ENTIDADE CLINICOEPIDEMIOLÓGICA NO NORDESTE DO BRASIL

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Cutaneous leishmaniasis (CL) and leprosy are endemic diseases in the state of Maranhão, Brazil, and have some characteristics in common, both affect mucocutaneous tissue, course with a chronic granulomatous response, show a broad clinical spectrum, and affect poor populations. Buriticupu (Amazon of Maranhão) represents an important endemic area for the two diseases in the State. Objective: To report the occurrence of patients with clinical and laboratorial findings of the association of CL and leprosy. Methods: In view of these findings and the scarcity of studies on this subject, we report the clinical and epidemiological characteristics of seven patients from this region. All patients, seen at the health center of the Federal University of Maranhão-UFMA, Buriticupu municipality, during March 2003 to December 2004, had their diagnosis confirmed after clinical and laboratorial findings. Results: Patient age ranged from 9 to 64 years, there was predominance of males (71.3%), 57.1% was laborers, and their socioeconomic situation was considered poverty. All patients had borderline leprosy and 90% had ulcerated lesion of CL. Treatment with meglumine antimonate (Glucantime®) + anti-leprosy drugs (polychemotherapy) had good response. Conclusions: The association of CL + leprosy represents a new entity in northeast of Brazil, which however, is predictable since there is reports of an association among diseases which course with a granulomatous response caused by distinct parasitic agents.

Key words: Leprosy, cutaneous leishmaniasis, association of diseases, Northeast of Brazil.

A leishmaniose cutânea (LC) e a hanseníase são doenças endêmicas no estado do Maranhão, Brasil, e apresentam algumas características em comum: ambas afetam o tecido mucocutâneo, cursam com resposta crônica granulomatosa, apresentam um largo espectro clínico e acomete populações com baixas condições sócio-econômicas. Buritiucpu (Amazônia do Maranhão) constitui-se em área endêmica da maior importância para ambas às doenças no Estado. Objetivos: Relatar a ocorrência de pacientes com quadro clínico e laboratorial compatíveis com a associação LC x hanseníase. Métodos: Pretende-se relatar as observações clínicas e epidemiológicas encontradas em 7 pacientes procedentes da região de Buriticupu (Amazônia do Maranhão). Todos tiveram diagnóstico clinico e laboratorial confirmados, após exames realizados no posto de saúde da Universidade Federal do Maranhão, município de Buriticupu (MA), de março de 2003 a Dezembro de 2004. Resultados: Houve predomínio do sexo masculino (71,3%), idade entre 9 a 64 anos, 57,1% lavradores, situação sócio-econômica considerada precária. Todos os pacientes apresentavam a forma dimórfica da hanseníase, 90% tiveram lesões ulceradas da LC. Instituiu-se como terapêutica o antimoniato-N-metilglucamina (Glucantime®) associado a polioquimioterapia hansência com bons resultados. Conclusões: Trata-se de um fato novo, a associação LC x hanseníase, embora previsível, pois existem relatos na literatura da associação de doenças granulomatosas causadas por agentes parasitários distintos.

Palavras-chave: hanseníase, leishmaniose cutânea, associação de doenças, Nordeste do Brasil.

According to the World Health Organization (WHO), both leishmaniasis and leprosy are among the main diseases for demanding intensive research and training. The incidence of leishmaniasis is 600,000 cases/year and the prevalence is 12 million cases, with a population of 350 million being at risk of acquired the infection[1-4].

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Leprosy is still one of the major health problems of developing countries. More than 1.6 billion of people live in countries where the estimated prevalence is greater than 1 case/1,000 inhabitant. Over 83% of all leprosy cases in the world are concentrated in five countries (India, Brazil, Nigeria, Myamar and Indonesia)[3,5]. Brazil accounts for 85% of the cases in the Americas and is considered an area of high endemicity, with prevalence higher than 1 case/1,000 inhabitants[6-8].

In Brazil, cutaneous leishmaniasis (CL) and leprosy represent a major public health problem due to their wide distribution, with predominance in the North, Northeast regions, with the states of Pará, Amazonas and Maranhão

being the most important in relation to the number of cases of these diseases[9,10]. The epidemiological pattern of CL in the State of Maranhão is related to the process of deforestation for agricultural projects, highway and railroad, as demonstrable by the outbreak that occurred after implantation of the agricultural colony of Buriticupu (Maranhão Amazon region). Notably, even 30 years after the implantation and settlement of populations in this region, hundreds of cases of CL continue to be observed annually[11].

In relation to leprosy, cases continue to increase in some states even after the implementation of a control program by the Brazilian Ministry of Health. Maranhão is one of the states in which leprosy is clearly expanding. Although the program has been implemented in 90% of the municipalities, the disease is found to be out of control in certain areas such as the Maranhão Amazon region[12]. Leprosy and CL have characteristics in common, both affect mucocutaneous tissue, involve a chronic granulomatous response, present a broad clinical spectrum, and resemble each other from an epidemiological point of view, both occur in poor populations[11,12].

Despite the importance of the two diseases in Buriticupu, Maranhão, only recently have cases of an association between CL and leprosy been observed. In view of the scarcity of reports in the world literature on this subject, the aim of the present study was to discuss the epidemiological, clinical and social aspects of the association of these two diseases.

Material and Methods

Study design

A prospective study was conducted on seven patients with CL + leprosy from an endemic area for the two diseases (Buriticupu, Maranhão Amazon region – Map 1), who were seen at a health station of the Federal University of Maranhão-UFMA in this municipality, between March 2003 to December 2004[11,12].

The study was carried out in two steps. The first consisted of clinicoevolutive assessment of patients, including: identification, age, sex, race, profession, housing and sanitary conditions, time of residence, duration of the disease, location and number of the lesion(s), probable place of contamination, and presence of mucosal lesions (location, extension, duration, type, septum perforation). Diagnosis was confirmed by Montenegro skin test (DTH), indirect immunofluorescence (IFA), lesion smears (*Leishmania* detection), and skin biopsies. Leprosy was identified by bacterioscopy and skin biopsy. The material was collected at the Buriticupu health center and processed and analyzed in the laboratories of the Nucleus of Tropical Pathology-UFMA. Exams DTH and IFA were analyzed on the basis of the criteria by Cuba *et al*.[13]. Skin biopsies were obtained from the active border of the lesion with a punch-type surgical knife measuring 4mm after local infiltration of anaesthetic. The histopathological specimens were analyzed on the basis of Magalhães *et al*.[14] for CL and Riddley and Joppling for leprosy[35,36].

All patients received N-methylglucamine antimonate (Glucantime®) at doses of 15mg/Sb^{5+}/day/20 days, with final post-therapy assessment after 6 months + polychemotherapy performed according to the standards of the Brazilian Ministry of Health[4-7].

In the second step, field assessment involving relatives of the patients was carried out. The person responsible for the dwelling under investigation was interviewed using a questionnaire card consisting of open and closed questions, and data regarding identification and epidemiological (socioeconomic and housing conditions, type of activity) and preventive aspects of the two diseases were recorded.

Results

Patients ages ranged from 9 to 64 years, there was predominance of males (71,3%), 57,1% was laborers, and their socioeconomic situation was considered poverty. The time of actual residence (Buriticupu) ranged from 1 to 15 years. Regarding clinical aspects, cutaneous lesions were observed in all patients studied. Four had more than one lesion. Patient J.R.L, who had a 5 year old scar, also presented a new recent lesion on the posterior side of the right forearm located above the leprosy lesion close to a site of satellite adenomegaly (Figures 1, 2). The duration of the CL lesions since diagnosis ranged from 1 to 2 months and the lesions ranged in diameter from 1 to 3cm.

Three patients also presented old scars which ranged in size from 1x1 to 5 x 3cm, while duration ranged from months to 5 years. The lesions were predominantly located on the upper limbs, while in patients with old scars the lower limbs were more frequently involved. In all cases, the lesions were found in exposed body areas. None of the patients presented mucosal lesions.

In relation to leprosy, the most diverse clinical aspects were observed, including: multiple plaques (some showing hyperchromia scattered throughout parts of the body), absence of tactile and pain sensitivity, infiltration of the face, and auricles (Figure 3,4). Table 1 summarizes the clinical aspects as well as the results of the laboratory exams. All patients were treated with Sb^{+5} + polychemotherapy. Table 2 shows the therapeutic regimens, the response obtained and the evolution of the patients up to the last assessment.

Analysis of the dwellings revealed the presence of domestic and wild animals belonging to the following orders: **Carnivora** (dog, cat, fox), **Primates** (monkey), **Rodentia** (rat), **Artiodactyla** (ox and pig), **Marsupialia** (opossum), and **Perissodactyla** (horse and donkey). All patients reported the presence of insects in the domiciliary and peridomiciliary area. The dwellings were located close to the forest and were surrounded by abundant vegetation, resulting in humid shadowed. The number of household dwellers ranged from 2 to 8 persons (mean 5.1), with the predominant age groups being adolescents (13 to 18 years), followed by children (6 to 10 years) and pre-adolescents (10 to 13 years).

Figure 1. Patient JRL - Ulcer caused by CL located above the leprosy plaque, associated with satellite adenomegaly.

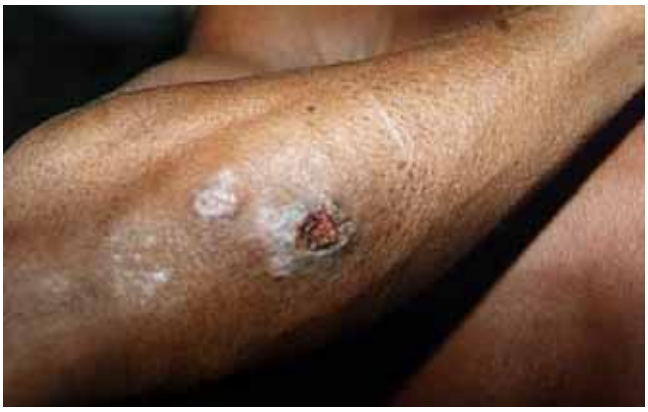


Figure 2. Same patient with old scar of CL above leprosy plaque in right leg.

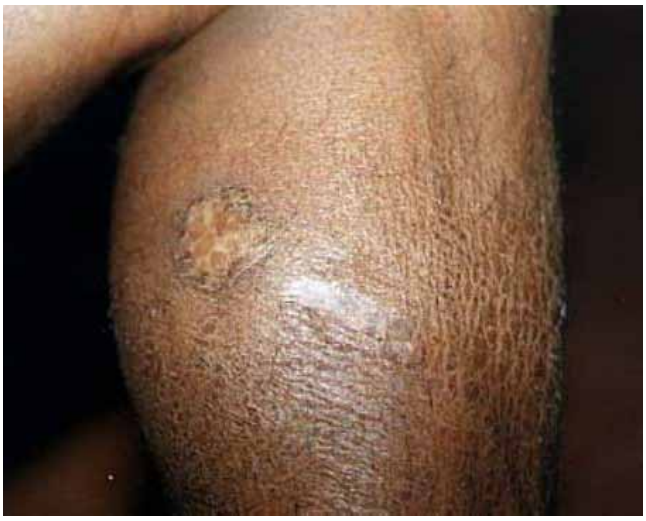


Figure 3. Patient JSS - Ulcerated lesions of CL located above a leprosy plaque at one third the level of the leg.

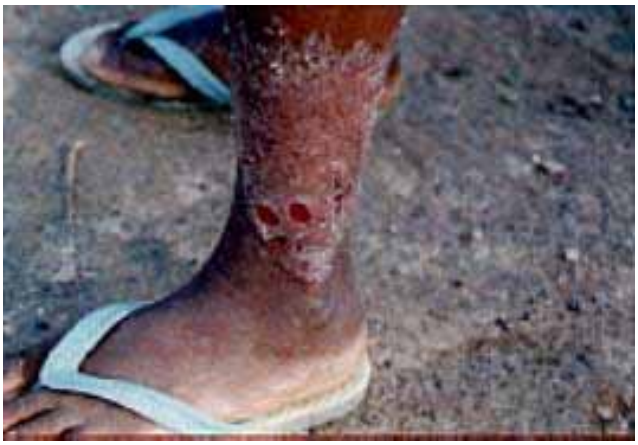
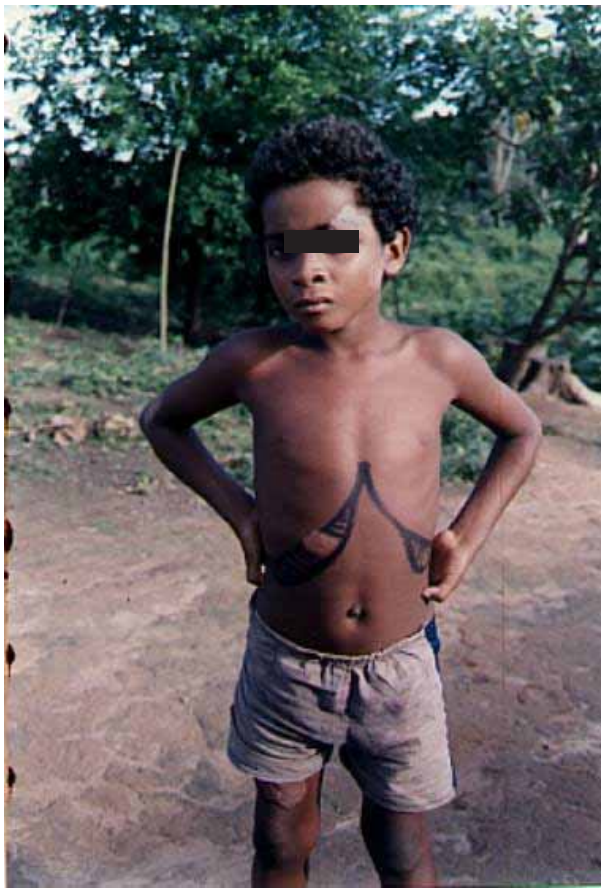


Figure 4. Same patient, with hypercromia plaques of leprosy located in the face and body.



The number of persons in the household with a job ranged from 1 to 5. The family income was generally maintained by only one person (4 patients) and ranged from less than US$ 100 (3 patients) to US$ 100 to 200 (2 patients), with the family income being unknown in two cases because the patients only worked on subsistence farming. In addition, five patients were directly responsible for the support of their family.

The absence of CL or leprosy in relatives was reported by five patients. One patient (I.S.S.) had a daughter with leprosy who had been treated for 2 years. However, in the family of one of the patients (J.S.S.), three relatives had CL and 2 leprosy and had been treated irregularly; of these, one also had CL and was undergoing leprosy treatment when assessed the last time. Three patients reported to know persons with leprosy, 3 knew persons with CL or leprosy, and one did not know persons with either disease. One patient (M.O.O.) reported to have lived with a person that had leprosy 8 years before. The other patients did not have intimate or prolonged contact with persons with the disease. In relation to water supply, the main source consisted of collective wells devoid of minimum sanitary conditions. Only one patient reported to have a well in his dwelling and three reported to filter water for drinking. No toilet existed inside the houses and the dejecta were eliminated in cesspools (2 patients) or in the open (5 patients).

Table 1. Clinical data and results of the laboratory exams for the diagnosis of the association between cutaneous leishmaniasis (CL) and leprosy.

Cutaneous Leishmaniasis						Leprosy			
Patient	Clinical data	Immunological Exams			Parasitological	Clinical data	Parasitological Exams		
		DTH (mm)	Serology (IFA)	Smear Exams	Histopathology		Bacilloscopy	Histopathology	
LS.	Nodules and ulcers	10x10	Negative	Positive	Exudative and granulomatous reaction, with marked fibrosis	Borderline	Negative	Chronic dermatitis compatible indeterminate with lesions produced by leprosy	
JRL	Ulcers	29x20	Negative	Negative	Chronic fibrous inflammatory reaction, with the presence of Langhans type giant cells	Borderline	Negative	Chronic fibrous inflammatory reaction, with the presence of a Langhans type giant cell	
MOO.	Ulcer	8x9	Positive	Negative	Exudative and granulomatous reaction, with marked fibrosis	Borderline	Positive	Chronic inflammatory reaction with the presence of Langhans type giant cells	
BRS	Ulcers	15x19	Positive	Positive	NP	Borderline	Positive	NP	
JSS	Ulcers	10x11	Negative	Positive	Chronic exudative, necrotic and granulomatous inflammatory reaction	Borderline	Positive	Chronic inflammatory reaction with an aspect of chronic dermatitis, presence of Langhans type giant cells	
FGA	Ulcer	6x6	Positive	Positive	NP	Indeterminate	Positive	Chronic dermatitis compatible with lesions produced by leprosy	
ISS	Ulcers	18x15	Negative	Positive	Chronic fibrous inflammatory reaction	Borderline	Positive	Chronic dermatitis compatible with lesions produced by leprosy, with presence of Langhans type giant cells	

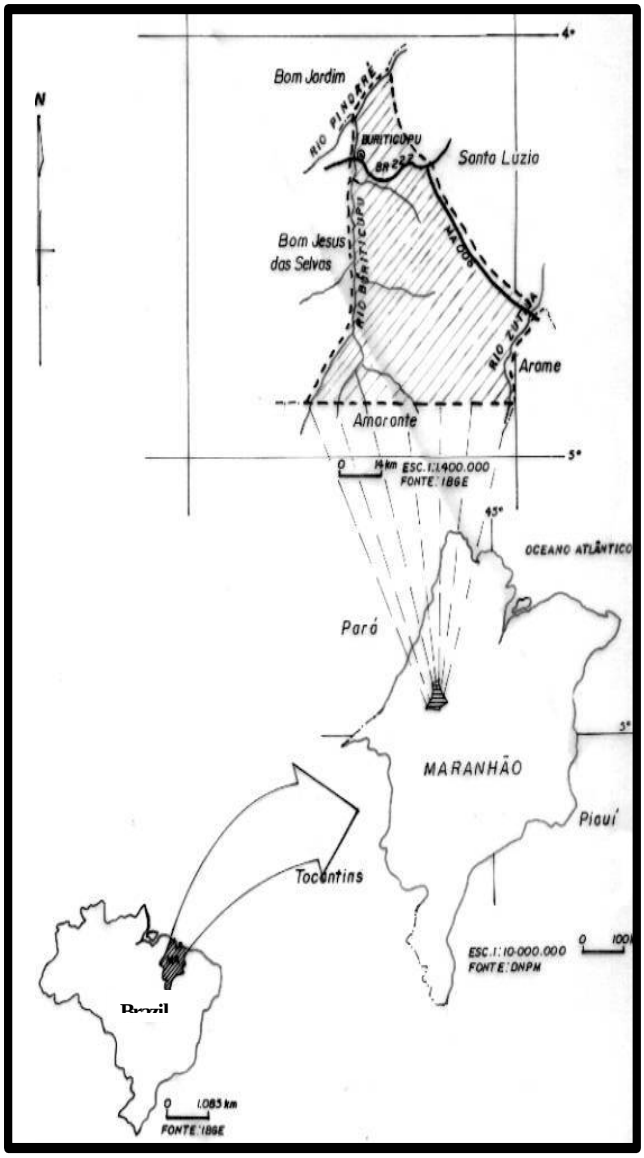
NP = not performed. DTH = positive (≥ 5mm); negative (≤ 4mm).

Table 2. Therapeutic used in patients with CL and leprosy from the municipality of Buriticupu, Maranhão, Brazil.

Patients	Cutaneous Leishmaniasis		Leprosy	
	Clinical (Form)	Drug Sb^5/Kg/dose	Clinical (Form)	Drug
LS	Nodules and ulcers	15 mg	Borderline	DDS + Clofazimine + Rifampicin
JRL	Ulcers	15 mg	Borderline	DDS + Clofazimine + Rifampicin
MOO	Ulcer	15 mg	Borderline	DDS + Clofazimine + Rifampicin
BRS	Ulcer	15 mg	Borderline	DDS + Clofazimine + Rifampicin
JSS	Ulcers	15 mg	Borderline	DDS + Clofazimine + Rifampicin
FGA	Ulcers	15 mg	Indeterminate	DDS + Clofazimine + Rifampicin
ISS	Ulcers	15 mg	Borderline	DDS + Clofazimine + Rifampicin

Regimen used for the treatment of leprosy: Borderline form - DDS - 2 mg/kg/day x 6 months + clofazimine - 50 mg/day or 100 mg on alternate days + rifampicin - 600 mg for adults; 450 mg for children and clofazimine - 300 mg once a month. Indeterminate form - DDS - 2 mg/kg/day + rifampicin - 600 mg for adults x 6 months; rifampicin 450 mg for children once a month for 6 months.

Map 1. Schematic map of the situation and location of the municipality of Buriticupu, Maranhão, Brazil – endemic area of the study.



Garbage was generally disposed of on wastelands and in the forest itself, and only one dwelling had access to weekly public collection.

When asked about notions of hygiene, the patients answered with insecurity. A single daily shower seemed to be a usual habit among them. Table 3 shows the level of knowledge about CL and leprosy.

Discussion

The most important epidemiological pattern of CL in Brazil is its close relationship with deforestation, with a high prevalence of the disease being observed among colonizing pioneers. In the Amazon region of Maranhão, CL maintains characteristics of a forest disease[11].

Leprosy, in turn, is a disease clearly related to poor conditions. The degree of dissemination depends on the proportion of susceptible individuals in the population and the potential risk of contact with the *M. leprae*. Poor conditions, an increased number of household contacts and inadequate nutrition are factors that contribute to the dissemination of leprosy. The fact that many individuals share the same space during the night favors skin contact between them or dispersal through inspired air[10,15].

In the study, the main profession was laborer (4 patients), followed by housewives (2 patients) and one student, in agreement with other studies on the two diseases[15,16]. It should be noted that the student and the housewives were also engaged in activities in subsistence farming. All patients were from the rural area and only one person was born in Buriticupu. The remaining individuals had migrated from other places in search of work and of better financial conditions. This finding was supported by the time of residence in Buriticupu (1 to 23 years), confirming the clear relationship between the migratory process and construction of highways and railroads[11].

In Brazil, animals involved in the transmission of CL include rodents, edentates and marsupials, with domestic dogs tending to be important in the cycle of domiciliary and peridomiciliary transmission[9,11,18]. In our study, the presence of animals in the dwellings and their surroundings was

Table 3. Determination of the cutaneous leishmaniasis (CL) in contacts and the level of knowledge of the patients about the two diseases.

Patient	Leprosy in the family	CL in the family	Close persons with CL or leprosy	Knowledge about CL or leprosy	Source of knowledge	Other names for leprosy	Other names for CL	Knowledge about the mode of transmission
LS	No	No	No	No	-	"Lepra" or skin disease	Leish	No
JRL	No	No	CL and leprosy	Leprosy	Relatives	"Lepra"	Leish	No
MOO	No	No	CL and leprosy	Leprosy	Friends	"Lepra"	Leish	No
BRS	No	No	CL and leprosy	CL and leprosy	Friends	"Lepra"	Leish, severe wound	No
JSS	2 members	3 members	Leprosy	No	-	Does not know	Leish	No
FGA	No	No	Leprosy	Leprosy and CL	Friends	Does not know	Leish	No
ISS	Daughter	No	Leprosy	No	-	Does not know	Leish	No

CL = Cutaneous lesion.

considered to be an important fact, with these animals probably playing a role in the transmission cycle of CL in the region.

It should be emphasized that, although leprosy is regarded as a disease exclusively affecting humans, some studies have labeled it as a zoonosis since there are reports of naturally acquired leprosy in armadillos, chimpanzees and Manbey monkeys[19,34]. In addition, the disease has been reported in five armadillo breeders from Texas, USA, all of them born in the region and without a history of contact with leprosy patients[19]. The predominance of children and adolescents among the persons with direct contact with the patients studied indicates the severity of the problem[6,20]. In relation to leprosy, studies have suggested that children are more susceptible than adults since almost 60% of children at risk due to contact with leprosy patients develop the disease during childhood or at the beginning of adult life after an incubation period of 3 to 5 years[6,7,10].

In relation to the socioeconomic situation of the seven patients studied, 5 were directly responsible for supporting their family and contributed actively to the family income. In 3 families, the patients themselves were the only ones responsible for maintaining the household, a serious fact which demonstrated that CL and leprosy, more than other organic illnesses, are social diseases disrupting the economic structure of the family since they affect individuals during the productive phase of life[15,17,21]. The family of patient J.S.S. lived under the poorest conditions. All men in the dwelling (4 persons), except for the father who suffered from the sequelae of leprosy, worked on subsistence farming. Two of them already had CL. The area surrounding the dwelling was the forest itself harboring armadillos, foxes, opossums, rats, horses and dogs which might have been involved in the transmission chain of CL as reservoirs or as food source for sandflies such as *Lutzomya whitmani*, one of the most common species in the region.

The lack of a drinking water supply reported by the patients is one of the major public health problems in the region because it makes personal and collective hygiene difficult. Well water (collective or private) is inappropriate for consumption and the population is completely unaware of the need to filter or boil water before drinking, a fact that perpetuates the cycle of intestinal parasitoses which are highly common in the region[11,24].

Regarding the level of knowledge about the diseases, in general the patients and their relatives did not know either disease. In addition, in the case of individuals with some knowledge, it was superficial. In relation to leprosy, this finding is worrisome since patients continue to hide because the fear of "an incurable disease that makes the fingers fall" is still great, the social stigma persists and the endemic disease continues to expand[3,7,22]. About CL, the level of knowledge was also considered to be incipient despite the efforts of the UFMA team which has been trying to control the disease since the founding of the municipality. The families know the disease by the name "léish", which seems almost like a diminutive of the scientific term leishmaniasis. This denomination was the result of an outbreak of CL recorded in 1979, when the studies of the UFMA researchers began in the region, with no opportunity to formulate a regional term but rather an adaptation facilitating the use by doctors and technicians working with the disease in the region[11, 12, 24].

In the study, all patients presented cutaneous lesions, a finding confirming those reported by Costa *et al.*[11]. According to these authors, the scarcity of mucosal lesions is probably due to the presence of at least 3 leishmanias species circulating in the region (*L. braziliensis*, *L. amazonensis* and *L. shawi*), in contrast to data reported by Barnetson and Bryceson[23], in Ethiopia who, studying eight patients with the CL + leprosy association, observed mucosal lesions in their patients.

Diagnosis of CL, the DTH (hardening ≥5mm) was positive in 100% of cases, a positive smear was obtained for 5(72%) patients, and IFA was reactive in 3 cases. Some authors reported that smears on slides contributed little to the diagnosis of CL in their series. Cuba *et al.*[13], had 31.8%

studying an area where *L. braziliensis* predominates, while Silva *et al*.[24] obtained 17% positivity for the region of Buriticupu. Regarding IFA, Cuba *et al*.[13], considered this approach to be only a complementary diagnostic method which could never replace the DTH, since the use of the former for the diagnosis of CL is largely undefined. Using IFA positivity was 86% in the study in area where *L. braziliensis* predominates.

All histopathological exams regarding CL lesions were compatible with the criteria by Magalhães *et al*.[14]. It should be emphasized that this classification is strictly morphological and of easy practical application during diagnosis, but this approach is of little help in the prognostic assessment of the disease. Despite the elevated frequency of the two diseases in the region, their simultaneous occurrence was rare, a fact also observed in Ethiopia[23]. Goble *et al*.[25], in an experimental study on rats, provided evidence for cross-protection against *Mycobacterium* and *Leishmania* and observed that rats immunized with BCG or rats previously infected with *M. tuberculosis* were resistant to *L. donovani* infection and vice versa. One possible explanation may be an increase in macrophage activity as demonstrated by Mackaness and Blanden[26], in experiments with BCG and *Listeria*. An alternative route might exist in which *M. leprae* acts as an adjuvant factor, supporting the immune response of leprosy patients in the presence of leishmaniasis. This fact supports the findings of Godal *et al*.[27], who reported that the deficient immune response of patients with lepromatous leprosy was specific for *M. leprae*.

In our study, one aspect that should be emphasized concerns the poles of the disease that specifically develop in each illness. Since both diseases develop a chronic granulomatous response, a similar type of response would be expected, which was not the case, supporting the findings of Godal *et al*.[27]. On the basis of the assessment of the immune response of the patients, together with the clinical analysis of the CL lesions, these patients were characterized as having the positive pole of CL since they developed a DTH (+) and predominance of the ulcerated form indicative of macrophage activity[32, 35, 36]. However, the immune response of these patients to *M. leprae* was different, with all patients showing an unstable response commonly observed for the borderline leprosy. These findings confirm that the granulomatous response is specific for each infectious agent in particular demonstrating that the morphological pattern of various granulomatous diseases is highly divergent[28,29, 33, 34]. However, the mechanisms of lymphocyte proliferation, which depend on the synthesis of interleukins and on macrophage activation induced by interferon-gamma, are similar in the two diseases[23, 30, 35, 36].

Another fact was the occurrence of CL on residual or active leprosy lesions. Pavithran[31], described one case of chromomycosis which developed above a leprosy patch in a patient from India. According to this author, the analgesic areas of the leprosy, associated with the occurrence of trauma, might lead to hyperkeratotic processes and the penetration of microorganisms. Although these data are sufficient for a superficial analysis, it is difficult to precisely establish how these less sensitive areas favor the development of CL since the form of transmission differs between the two diseases (CL and chromomycosis)[31]. Although not yet confirmed, one can suppose that cutaneous tissue lesions caused by a disease with a granulomatous response induced by a certain infectious agents does not imply protection against other agents, which can also trigger a granulomatous reaction, as reported by Pavithran[31].

The consequences of the co-infection of CL+leprosy in the same patient - two factors clearly demonstrate the problem: 1) patient L.S., treated for leprosy for 1 year and 7 months, had to discontinue treatment due to the side effects of the concomitant use of Sb^{5+} (arthralgia and fever). Although no direct mutual interference with the efficacy of treatment of the two diseases was observed, this fact suggests that the simultaneous occurrence of these diseases in the same patient represents a serious problem, since the evolution and treatment of one disease may aggravate the condition of the patient as a whole, especially in the presence of complicating infections facilitated by immunodepression. 2) Patient J.S.S. presented fever, shivering, abdominal pain and diarrhea on the 11th day of treatment with Sb^{+5} and the 1st year of polychemotherapy, requiring hospitalization and discontinuation of the two treatment regimens. Antibiotic therapy led to regression of the symptoms, thus confirming the presence of an associated complicating infectious process.

We conclude that, in general, the concomitance of CL and leprosy leads to reciprocal interference with the evolution and treatment of the patients, and also favors the occurrence of additional infectious processes.

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