

## Case Report

## Diagnosis and treatment of american tegumentary leishmaniasis in a patient from rural Ceará: case report

### *Diagnóstico e tratamento de leishmaniose tegumentar americana em paciente da zona rural do Ceará: relato de caso*

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**ABSTRACT:** Introduction: American Tegumentary Leishmaniasis (ATL) is an infectious disease, non-contagious, of chronic development, endemic in some regions of Brazil, which in recent years, has shown a significant increase in the number of cases, being the State of Ceará as one of the major areas affected by this infection. Objective: to discuss a clinical case of ATL, encompassing diagnosis and treatment in an adult patient living in the rural area of the State of Ceará. Method: Case report and data analysis, diagnosis, and management based on the literature regarding ATL, using the integrative review method. Results: The diagnosis was made through an incisional biopsy of the lesion and, after obtaining a positive result for ATL, the patient was referred to the state reference unit for the treatment of infectious pathologies, Hospital São José (HSJ). The patient started the treatment with drugs administered orally, however, these medications were not efficient, requiring hospitalization. At the end of the treatment period, the patient evolved with an improvement in the clinical picture, with re-epithelialization of the lesions, regression of the ulcers, and was later referred for outpatient care. Discussion: Despite the growing studies on drugs with fewer adverse effects and a greater possibility of adherence to ATL treatment, the conventional therapeutic regimen had to be used, given the non-efficacy of the alternative therapy. Conclusion: The development of drugs that can be used more effectively, with fewer adverse effects, and with the potential to provide treatment adherence is urgent, whereas existing treatments must become more effective

through the decentralization of the health service for endemic regions so that patients affected by neglected diseases, such as ATL, can be treated in their surroundings.

**Keywords:** American Tegumentary Leishmaniasis. Diagnosis. Treatment.

**RESUMO:** *Introdução:* A Leishmaniose Tegumentar Americana (LTA) é uma doença infecciosa, não contagiosa, de evolução crônica, endêmica de algumas regiões do Brasil, que, nos últimos anos, vem apresentando um expressivo aumento no número de casos, destacando-se o Estado do Ceará como uma das principais regiões acometidas por essa infecção. *Objetivo:* discutir um caso clínico de LTA, englobando diagnóstico e conduta de tratamento em paciente adulto morador da zona rural do Estado do Ceará. *Método:* Relato de caso e análise de dados, diagnóstico e conduta baseada na literatura referente à LTA, sendo empregado o método de revisão integrativa. *Resultados:* O diagnóstico foi realizado mediante biópsia incisional da lesão e, obtido o resultado positivo para LTA, o paciente foi encaminhado à unidade de referência estadual no tratamento de patologias infecciosas, o Hospital São José (HSJ). O paciente iniciou o tratamento com fármacos administrados por via oral, porém, essas medicações não se mostraram eficientes, sendo necessária a internação. Findo o período de tratamento, o paciente evoluiu com melhora do quadro clínico, apresentando reepitelização das

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lesões e regressão das úlceras, sendo posteriormente encaminhado para acompanhamento ambulatorial. *Discussão:* Apesar dos crescentes estudos sobre fármacos com menos efeitos adversos e com maior possibilidade de adesão ao tratamento de LTA, o esquema terapêutico convencional teve de ser empregado, visto a não eficácia do tratamento alternativo. *Conclusão:* O desenvolvimento de fármacos que possam ser empregados com maior eficácia, menos efeitos adversos e com maior potencial para proporcionar adesão ao tratamento se faz premente, ao passo

que os tratamentos já existentes devem se tornar mais eficazes, por meio da descentralização do serviço de saúde para regiões endêmicas, de modo a propiciar que os pacientes acometidos por doenças negligenciadas, como a LTA, possam ser tratados em seu peridomicílio.

**Palavras-chave:** Leishmaniose tegumentar americana; Diagnóstico; Tratamento.

## INTRODUCTION

American Tegumentary Leishmaniasis (ATL) is an infectious, non-contagious and chronic disease that affects the mucosa and cutaneous epithelial tissue, being caused by protozoa of the genus *Leishmania*<sup>1-2-3</sup>.

In Brazil, the diversity of etiological agents, reservoirs and vectors are preponderant factors for the increase in the rate of cases. In this area, at least seven species of protozoans of the genus *Leishmania* in Brazil, being the species *Leishmania (Viannia) braziliensis* the most prevalent in the national territory, having been found in all states of the country<sup>4</sup>.

With regard to the vector, it is known that ATL is transmitted by the bite of infected female sandflies.

From the perspective of popular knowledge, these insects receive different names depending on the geographic location of the region, being called, for example, tatuquira, birigui, asa branca (white wing), cangalinha, among others<sup>1</sup>. In the State of Ceará, the vector that transmits ATL is popularly known as the mosquito-palha (straw mosquito)<sup>5</sup>.

Synanthropic wild animals, which are those that have adapted to live with humans, like rodents, are the species that act as the main reservoirs of the pathogenic agent of ACL. However, despite the prevalence in wild animals, cases of *Leishmania* infection have also been identified in domestic animals such as cats, horses and dogs<sup>1</sup>.

With regard to the first symptoms of ACL manifestation in humans, it is known that the initial lesion appears about two weeks to three months after the parasite is inoculated into the host, manifesting itself in the form of solid and reddish protuberances located on the skin, in the place where the host was bitten, later evolving into nodules that, not disappearing spontaneously, turn into ulcers<sup>6-7</sup>.

In typical cases of ACL, the infected individual manifests ulcerated lesions with an oval or circular appearance, with raised and well-defined borders, in addition to granularity and redness. Usually, in about 70% of cases, there is a single lesion, but other lesions distributed along the skin can appear<sup>8-9</sup>. The way in which the lesions manifest is the main way of classifying this disease as localized, disseminated, diffuse and cutaneous recurrence.

## OBJECTIVE

To discuss a clinical case of ATL, including diagnosis and treatment in an adult patient living in the rural area of the State of Ceará.

## MATERIAL AND METHODS

Discussion of a clinical case of American Tegumentary Leishmaniasis and data analysis, diagnosis and management based on the literature referring to ACL. For this purpose, the integrative literature review technique was used<sup>10</sup>, by reading the available material according to convenience and accessibility criteria, not using a time frame or language restriction. The patient, agreeing with the description and disclosure of this case report, signed an informed consent form.

The study was submitted to the Research Ethics Committee of the National Reference Center in Sanitary Dermatology Dona Libânia, receiving approval on November 18, 2022 (CAAE: 63007322.3.0000.5036; OPINION: 5.764.670).

## CLINICAL CASE DESCRIPTION

P.A.M.C., 65 years old, male, farmer, from the municipality of Pindoretama, a city belonging to the Metropolitan Region of Fortaleza, state of Ceará, sought the health service of the municipality of Aquiraz/CE, in July 2021, with skin lesions on the lower limbs and the right upper limb.

The clinical scenario, predominantly, consisted of ulcers with an oval appearance and a granular bottom, covered by a seropurulent and whitish-brown exudate, with prominent and well-defined borders on the lower limbs, as well as manifesting a crateriform-looking papule on the upper limb. As shown in Figure 1.

Unfortunately, despite being important for more accurate monitoring of the evolution of the infectious condition over time, the dimensions of the lesions were not measured.



Source: author's personal archive (2021).

**Figure 1** – Injuries on the lower and upper limbs of the PAMC patient

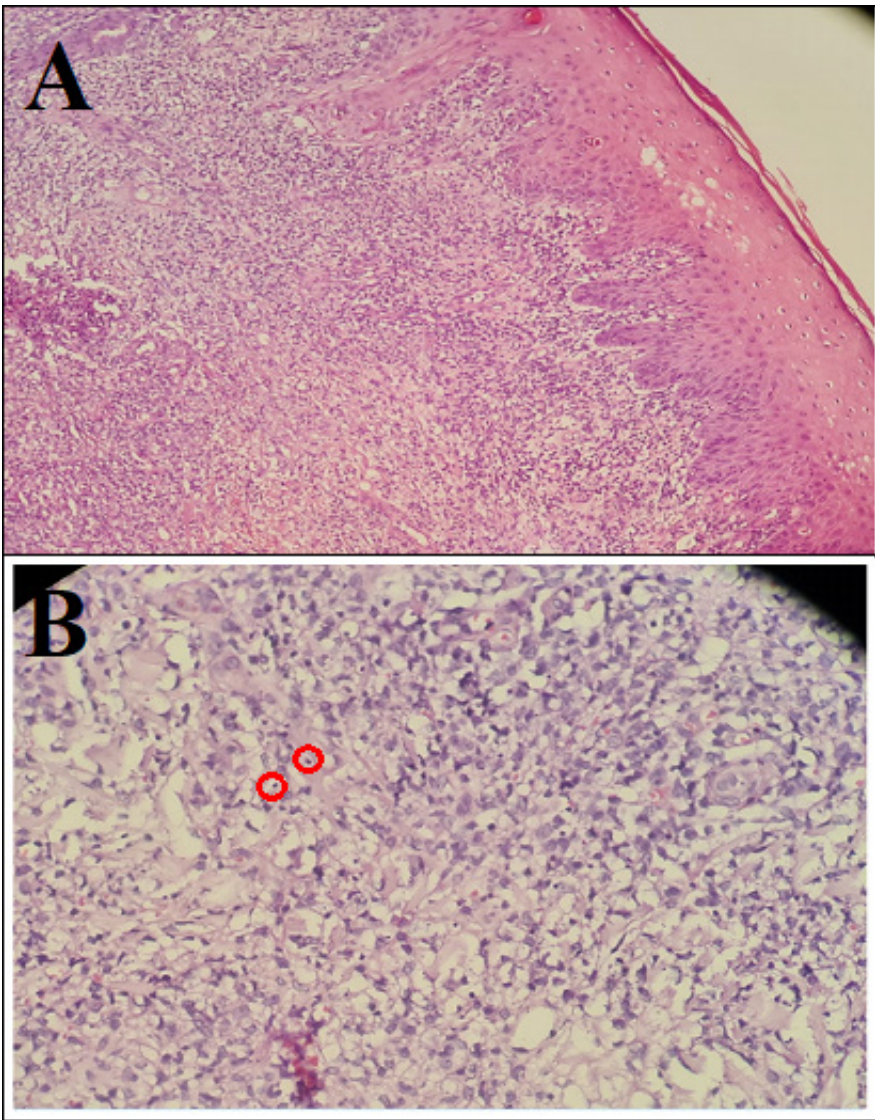
An important fact that deserves mention is the presence of multiple skin lesions. In addition to these lesions, the patient reported an episode of fever and manifestation of left inguinal lymphadenopathy, also complaining of muscle pain. Questioned about the development of previous chronic diseases, he answered negatively for hypertension and positively for diabetes, although he did not undergo treatment for diabetes.

The patient also mentioned that in the region where he lives, in a place located in the rural area of Pindoretama/CE, with the presence of dogs, cats and rodents, other

individuals have lesions similar to his. He also mentioned that the onset of symptoms dated back to June 2021.

Due to the appearance of the lesions, a direct examination for American Tegumentary Leishmaniasis was requested, through an incisional biopsy of the ulcer located on the left lower limb. Once the examination was concluded, the histopathological report showed the tissue to be extensively ulcerated, with a diffuse mixed dermal inflammatory infiltrate, highlighting the presence of small spherical structures, which were concluded to be amastigotes forms of *Leishmania*, as can be seen in Figure 2, the follow.





Source: author’s personal archive (2021).

**Figure 2** – A. Slide of the Histopathological Report showing diffuse mixed dermal inflammatory infiltrate (4xmagnification); B. spherical structures shown in the red circle compatible with amastigotes of Leishmania (10x magnification)

**Table 1** – Drugs used in the initial treatment of the P.A.M.C. patient

Date	Drug	Drug	Drug
Start of the treatment – 28/07/2021	Ciprofloxacin 500 milligrams 1 pill 2 times a day For 14 days	Fluconazole 150 milligrams 1 pill 4 times a day – 6/6h For 6 weeks	Allopurinol 300 milligrams 1 pill 3 times a day – 8/8h For 6 weeks
Continuity – 01/09/2021	Ciprofloxacin 500 milligrams 1 pill 2 times a day For 14 days	Fluconazole 150 milligrams 1 pill 4 times a day – 6/6h For 30 days	Allopurinol 300 milligrams 1 pill 3 times a day – 8/8h For 30 days

Source: prepared by the authors (2021).

After the initial therapeutic regimen, the patient P.A.M.C. did not improve. In fact, a worsening of the clinical condition was observed, as an increase in the size of the

ulcerated lesions on the left lower limb was observed and the continuation of seropurulent exudation in these lesions, in addition to the manifestation of symptoms of hyporexia

and adynamia.

Given the severity of the condition, the patient was hospitalized at the *Hospital São José de Doenças Infecciosas* so that a new treatment scheme could be carried out. In the therapy used to combat secondary infections, treatment with the antibiotics Ceftriaxone was started for eight days and Oxacillin for seven days.

With regard to the treatment of the main infection, ATL, an intravenous administration of Amphotericin B Desoxycholate was started at a dose of 50 milligrams/day. However, right at the beginning of the treatment, the patient evolved with an increase in nitrogenous excreta, thus indicating the possibility of impairment of renal functions in case of continuation of therapy.

Thus, aiming at better tolerance of renal function, Amphotericin B Desoxycholate was replaced by Amphotericin B Liposomal, at a dosage of 200 milligrams/day, also through intravenous administration. After approximately two weeks of adherence to the treatment, the patient had evolved with an improvement in his clinical condition, decreasing the exudation of the lesions and improving the renal function.

However, despite the apparent improvement of the lesions, the secretive pattern reappeared. Thus, therapy with the antibiotic Vancomycin was initiated for a period of eight days. For a better understanding of the therapeutic scheme during the hospitalization period of the P.A.M.C. patient, see Table 2 below.

**Table 2** – Drugs used in the hospitalization phase of the patient PAMC\*

Description / Date	Fármaco
Internal Treatment – 06/10/21 a 13/10/21	Ceftriaxone For 8 days
Internal Treatment – 07/10/21 a 13/10/21	Oxacillin For 7 days
Internal Treatment – 08/10/21 a 13/10/21	Amphotericin B Desoxycholate 50 milligrams/day Intravenous Administration
Internal Treatment – 14/10/21 a 22/10/21	Amphotericin B Liposomal 200 milligrams/day Intravenous Administration
Internal Treatment – 22/10/21 a 29/10/21	Vancomycin For 8 days

Source: prepared by the authors (2021).

\*Total dose of Amphotericin B administered: 2.100 milligrams.

Shortly after the end of the treatment scheme, the patient evolved with clinical improvement of the ulcerated lesions on the left and right lower limbs, apparent improvement of the lesion on the right upper limb, as well as a decrease in the secretion pattern.

Currently, the patient is on a routine outpatient basis. After completion of the therapeutic regimen, complete re-

epithelialization of the lesions and total regression of the ulcers can be attested, with norecurrence so far, as shown in Figure 3 below.



Source: author's personal archive (2021).

**Figure 3** – Healing of Injuries of the patient P.A.M.C.

## DISCUSSION

Among the states in the Brazilian Northeast, Ceará is one of the main states where ATL occurs most frequently. From this perspective, in a survey carried out between 2007 and 2020, 9,224 cases were diagnosed, making an average of 659 annual diagnoses of ATL in the State. Of this amount, 65.83% of the cases occurred in rural areas, which allows inferring the predominance of infection in locations and communities that have not yet been urbanized<sup>11</sup>.

At this juncture, it is common to observe in these interior regions a large number of reservoirs of the parasite<sup>5</sup>. Indeed, this statement could be verified in a visit *in loco*, where the presence of felids, equidae, rodents and canids were identified, highlighting the latter. It should be added, however, that the animals were not tested, which has significant repercussions in terms of public health, since, as reported, it can be inferred that there is a local dynamic of transmission, with these animals having an important role since they are potential reservoirs of the parasite.

As previously explained, the clinical manifestations of ATL are directly related to the environment in which the infection occurs, the species of parasitic leishmania



and the immune system of the host organism. Under this bias, the appearance of the wounds, where multiple lesions distributed over three body segments were observed, muscle pain, malaise and episodes of fever reported are characteristic of disseminated cutaneous leishmaniasis.

Thus, once a positive diagnosis was made for disseminated ATL, the patient was referred to the state reference unit for the treatment of infectious diseases, Hospital São José.

In this perspective, the therapeutic protocol of the *Ministério da Saúde* (Ministry of Health) for patients diagnosed with disseminated ATL comprises the use of Meglumine Antimoniate, at a dose of 20 milligrams Sb<sup>+5</sup>/kg/day for 30 days. In the case of patients with heart, kidney or liver failure, as well as in more severe cases or in which the number of skin lesions exceeds 20, the therapeutic scheme suggests the use of Liposomal Amphotericin B at a dose of 2 milligrams to 3 mg/kg/day<sup>1</sup>.

However, despite the proven efficacy of the aforementioned drugs for the treatment of ATL, it should be noted that the side effects and the need for parenteral application of these drugs, making it unnecessary for patients to travel to the care unit, are factors that contribute significantly to therapeutic abandonment<sup>12</sup>. In this sense, the use of other drugs is constantly being studied regarding their effectiveness for the treatment of ATL<sup>12</sup>.

In this perspective, the initial treatment indicated for the patient P.A.M.C. consisted of a combination of Ciprofloxacin, Fluconazole and Allopurinol. With regard to the use of the first drug, it is observed that the seropurulent exudation presented by the patient in some lesions indicates a possible second infection, most likely of a bacterial nature. In this sense, the administration of Ciprofloxacin was not intended to treat the ATL itself, but, in the foreground, aimed at treating a probable secondary infection.

Regarding the administration of Fluconazole and Allopurinol, it is believed that the choice of these medications was aimed at maximizing the patient's adherence to treatment, since P.A.M.C. lives in the rural area of Pindoretama/CE, and it is very difficult for him to travel daily to the reference unit, the HSJ, for the parenteral administration of other drugs.

Regarding the efficacy of these drugs, the dosage of 8mg/kg/day of fluconazole for the treatment of ATL provided a therapeutic response similar to that one obtained with the administration of Meglumine Antimoniate<sup>13</sup>.

Other studies also obtained successful results with the administration of Fluconazole alone or as an adjuvant in the therapeutic scheme of patients with ATL<sup>14</sup>. This drug, unlike Meglumine Antimoniate and Amphotericin B, has fewer side effects and, due to its easy dosage, increases patient adherence to treatment<sup>15</sup>.

Furthermore, a study carried out in the municipality

of Barbalha, a city in the extreme south of the state of Ceará, pointed to the effectiveness of Fluconazole in the treatment of ATL for patients without comorbidities and with lesions smaller than 30 mm, with the treatment being carried out orally, in doses of 300 mg and 450 mg per day, similar to the therapeutic scheme mentioned above<sup>16</sup>.

The administration of Allopurinol, in turn, proved to be effective when associated with the use of other drugs, such as Meglumine Antimoniate and Amphotericin B<sup>17</sup>. In this scenario, unlike Fluconazole, Allopurinol has no proven efficacy when administered alone, however, when used as an adjuvant to pentavalent antimonials in the treatment of ATL, promising results were observed<sup>17-18</sup>.

However, despite the prominent studies related to the treatment of ATL with Fluconazole and Allopurinol when used in association with drugs recommended for the treatment of ATL, after the initial treatment period, the patient did not show clinical improvement. In view of this, it was necessary to hospitalize the patient so that the administration of conventional drugs used in the treatment of ATL could be administered.

Thus, the medical professional at HSJ, with the aim of combating secondary infections evidenced by seropurulent exudation, prescribed the use of Ceftriaxone, which is a broad-spectrum antibiotic, associated with the administration of Oxacillin, a drug used when there is suspicion of staphylococcal infection<sup>19</sup>.

Initially, these drugs were effective, as they reduced exudation, which allowed us to infer the remission of the infection. However, about a week after the end of treatment with these drugs, the patient began to report pain at the sites of the skin lesions, as well as the secretion pattern increased again, showing the recurrence of the secondary infection.

Thus, given the resistance of the agent causing this infection to the drugs used, an antibiotic considered more potent, Vancomycin, was administered. Effectively, after treatment with Vancomycin for eight days, the patient's condition improved, with the disappearance of exudation and no more reference to localized pain in the ulcerated lesions.

It is believed that the constant recurrence of the secondary infection can be attributed to the fact that the patient has Diabetes, which negatively influences the healing process of the lesions<sup>20</sup>.

As for the treatment of American Tegumentary Leishmaniasis, it is noted that the therapy performed with Amphotericin B Desoxycholate, despite fighting the main infection, was overloading the patient's renal function. In view of this, the drug was replaced by Liposomal Amphotericin B, which is the most indicated in the case of Disseminated Leishmaniasis in patients who have comorbidities<sup>1</sup>.

Notably, together with Meglumine Antimoniate, Amphotericin B is the main drug used in the treatment of

ATL. This was clearly evidenced by the fact that the PAMC patient showed significant improvement after adhering to treatment with this drug.

However, such drugs have some obstacles that make massive therapeutic adherence difficult, for example: the need for parenteral administration and the various side effects caused. In the reported case, for example, the patient lives in the rural area of a city that is more than 50 km from the treatment unit, so that, without the hospitalization, the patient would not be able to adhere to the therapy.

Thus, while facilitating the patient's adherence to therapy is important for the effectiveness of the treatment, the pharmacological scheme used for the patient P.A.M.C. may have been a factor that further aggravated the aforementioned condition, since, as time passed without until the patient was cured, the transmission chain of the parasite remained active, increasing the risk of infection for the other residents of that region while the patient continued to be affected.

## CONCLUSION

In the case reported here, the alternative treatment involving Fluconazole and Allopurinol was not effective, requiring the patient's hospitalization to carry out the conventional therapeutic scheme based on the administration of Amphotericin B. After completion of the therapeutic scheme, the patient presented total re-epithelialization of the lesions, with no recurrence of the ulcers.

In this perspective, while the development of drugs that can be used with greater efficiency, less adverse effects and with greater potential to provide adherence to treatment is urgent, it also becomes substantial that the existing medications are more accessible to the population, requiring joint actions between municipal, state and federal health spheres, with the aim of decentralizing care, which is currently restricted to "satellite cities", to endemic regions, in order to provide treatment of neglected diseases, as is the case of the ATL, at the peridomicile of the affected citizens.

**Conflict of interest:** the authors declare, for all purposes, that there are no obstacles or conflicts of interest of any kind.

**Authors participation:** *Dodo FDB* – Interpretation of data, planning and writing of the work. *Farias LP* – Conception, critical intellectual review of the work. *Farias Junior LP* – Data interpretation and normative review. *Costa JP* – Interpretation of data and translation of the final version of the work.

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