Case report

Patient with cutaneous leishmaniasis treated with miltefosine in an endemic area in Brazil

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Paciente con leishmaniasis cutánea tratada con miltefosina en un área endémica de Brasil

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Abstract
Case presentation. The patient is a 45-year-old woman with an oval-shaped ulcer on the left thigh, with well-defined and raised borders, no discharge, no crust, and painless; she presented a lesion of 60 days of evolution, which started as a punctate papule of progressive increase in size and depth until it became an ulcer, four weeks after a three-day trip to a rural area endemic for American tegumentary leishmaniasis. **Treatment.** The diagnosis of localized cutaneous leishmaniasis was confirmed; consequently, the patient received outpatient treatment with miltefosine 50 mg orally every eight hours for 28 days, accompanied by clinical and laboratory follow-up. Clinical outcome. There were mild side effects, including nausea that subsided with treatment with ondansetron and omeprazole, and later hyporexia, which persisted until the end of treatment. There were no significant laboratory alterations. The patient was periodically evaluated according to the recommendations of the Brazilian Ministry of Health, and the lesion improved gradually, reaching a clinical cure on the 90th day.

Keywords
Cutaneous Leishmaniasis, Drug Therapy, Neglected Diseases.

Resumen
Presentación del caso. Se trata de una mujer de 45 años con úlcera en el muslo izquierdo, con forma ovalada, bordes bien definidos y elevados, sin secreción, sin costra, e indolora, que presentó una lesión de 60 días de evolución, que inició como una pápula puntiforme de aumento progresivo en tamaño y profundidad hasta generar una úlcera, después de cuatro semanas de haber realizado un viaje de tres días a un área rural endémica para leishmaniasis tegumentaria americana. **Intervención terapéutica.** Se confirmó el diagnóstico de leishmaniasis cutánea localizada, en consecuencia, recibió tratamiento ambulatorio con miltefosina de 50 mg por vía oral cada ocho horas por un total de 28 días, acompañado de seguimiento clínico y de laboratorio. **Evolución clínica.** Se presentaron efectos secundarios leves, entre ellos, las náuseas que cedieron con el tratamiento con ondansetrón y omeprazol, luego presentó hiporexia, que persistió hasta el final del tratamiento. No hubo alteraciones laboratoriales significativas. La paciente fue evaluada periódicamente según las recomendaciones del Ministerio de Salud de Brasil y se observó una mejoría clínica gradual de la lesión, hasta que en la evaluación del día noventa fue determinada la cura clínica.

Palabras clave
Leishmaniasis cutánea, quimioterapia, enfermedades desatendidas.

Introduction

Leishmaniasis is a neglected tropical disease caused by the intracellular protozoa of Leishmania. The transmission cycle is complex and involves hematophagous vectors *Phlebotomus* or *Lutzomyia spp.* and vertebrate hosts that function as reservoirs. Worldwide, between 1.5 and 2 million new cases are reported, and 70 000 deaths occur each year.[i] It is endemic in 88 countries, 72 considered developing countries. According to the World Health Organization, in 2018, 94 % of all new cases of leishmaniasis were reported in seven countries: Brazil, India, Kenya, Somalia, South Sudan, Ethiopia and Sudan.[ii]

In the Americas, the most common clinical form is known as American tegumentary leishmaniasis (ATL),[iii] which is also subdivided into localized cutaneous leishmaniasis, diffuse cutaneous leishmaniasis, and mucosal leishmaniasis.[iv] Clinical manifestations are varied and depend on the species of *Leishmania* involved and the type and magnitude of the host immune response. In broad terms, it is described as a lymphocyte-mediated immune response. On the one hand, a Th2-type response characterized by antibody production is ineffective in controlling infection and is associated with disseminated forms with high parasitemia. On the other hand, an overly robust Th1-type response with highly elevated levels of interferon-γ and TNF is characterized by low parasitemia, and abundant tissue damage evidenced in the mucosal type.[v] The best response is a moderate Th1-type response, which effectively controls the infection and allows evolution to cure possible.[vi]

There are few therapeutic options available and those present complications such as high toxicity, high production costs, limited effectiveness, problems in administration, and the development of resistance. [ii] The first-line treatment in Brazil is meglumine antimoniate; it has been in use since 1940.[vii, viii] The administration is for 20 days, intravenously or intramuscularly, with the possibility for an extension based on clinical evolution. The medication should not be indicated for pregnant women due to teratogenicity; in addition, it is also not recommended as the first option for individuals over 50 years-old, with known hypersensitivity to the drug, and with certain chronic conditions such as cardiopathy, renal and hepatic disease. Furthermore, some adverse effects have been described, including pancreatitis, pancytopenia, peripheral neuropathy, joint stiffness, gastrointestinal symptoms, nephrotoxicity, ii and the most serious of them, the alteration of cardiac repolarization, which manifests itself as an extension of the QT segment, inversion and flattening of the T wave.[iv] Also, There are reports of as much as 40 % of therapeutic failure.[ix]

Alternative treatments for leishmaniasis include amphotericin B, pentamidine isethionate, and miltefosine.[x] These medications were originally developed for other diseases and repurposed for leishmaniasis treatment, a widespread practice for neglected diseases. [vii]

Miltefosine was initially developed for the treatment of metastatic breast cancer[ii], approved by the Food and Drug Administration in 2014,[xi] and incorporated into the Brazilian Health System in 2018.[xii] Although it is a teratogenic drug, it has some advantages compared to the others, such as its oral administration route with efficacy equivalent to that of pentavalent antimonial but with a lower incidence of adverse effects.[ix] However, it may cause gastrointestinal symptoms, hepatotoxicity, and nephrotoxicity.[ii]

Case presentation

The patient, a 45-year-old female schoolteacher, and resident in the city of Cuiabá, the capital of the state of Mato Grosso in the central-western region of Brazil, with a history of hysterectomy two years earlier due to uterine myomatosis; she was receiving daily treatment for arterial hypertension, with hydrochlorothiazide 12.5 mg and olmesartan 20 mg. The patient denied other chronic diseases.

The patient consulted for an ulcer on the left thigh after 60 days of evolution. It started as a papule with a progressive increase in size and depth, four weeks after a three-day trip to the municipality of Chapada dos Guimarães, a rural area in the State of Mato Grosso. Two individuals who accompanied her on this trip developed similar lesions.

When the condition started, the patient attended a primary care clinic and was treated with amoxicillin and clavulanic acid for five days without improvement, which caused her to consult again; on this occasion, she received treatment with cephalexin and acyclovir for seven days; she did not remember the doses of the drugs, and did not notice any improvement either. During the third consultation, the suspected diagnosis was ATL. As a result, the patient was referred to the state center for leishmaniasis cases in the city of Cuiabá, where she was received after six weeks.

Physical examination revealed an oval, painless ulcer with raised, well-defined, and hyperchromic borders. Fibrin presented at the base of the lesion without purulent secretion, crust, or any other alteration (Figure 1A).

A scraping, aspirate, and tissue sample for biopsy of the edge of the lesion and sent for anatomopathological study, direct parasitological study, culture, and polymerase chain reaction molecular study; the culture report and PCR study were positive; in the direct parasitological study there was no evidence of amastigotes, and it was considered negative. Finally, there was no report of the anatomopathological study.

Treatment

The patient was prescribed outpatient treatment with miltefosine, 50 mg every eight

hours for 28 days. She received counseling regarding the potential adverse effects of the drug and a clinical and laboratory follow-up plan. Contraceptive methods were not offered due to the history of hysterectomy.

Clinical evolution

In the first control, the patient reported moderate-intensity nausea; she received daily treatment with ondansetron 4 mg and omeprazole 20 mg. Also, since the second week, she presented hyporexia until the end of the treatment. In the third and fourth control, a gradual improvement of the ulcer was evidenced by the growth of granulation tissue in the wound bed (Figure 1B). During this period, the nutritional status evaluation registered a loss of 2.5 kg of weight, and weekly laboratory tests did not present ranges out of the normal ones (Table 1).

After 63 days of treatment, there was evidence of re-epithelialization of the ulcer (Figure 1C). Finally, on day 90, the patient had a complete re-epithelialized lesion, without crusting, desquamation, or infiltration, and smooth to palpation; therefore, the clinical cure was concluded (Figure 1D).

Clinical diagnostic

Localized cutaneous leishmaniasis was diagnosed based on clinical history, physical examination findings, and laboratory test results.

Discussion

Brazil reported a total of 13 044 new cases of ATL in 2022. The State of Mato Grosso was the third state with the highest number of cases, with 9.58 % of cases. At the national level, 73.85 % of the cases were male and the most affected age group was between 20-39 years old.[xiii] Rural workers have been among particularly vulnerable groups for developing leishmaniasis since agriculture, forestry, and other extractive activities increase exposure to the vector.[xiv]

Three epidemiological patterns have been identified: wild, which occurs in areas of dense vegetation; occupational or leisure, associated with tourism and extractive industries; and rural or peri-urban, related to migration to rural areas in the countryside.[iv] This case falls under the occupational or leisure epidemiological pattern. However, the patient's characteristics differ from the typical epidemiological profile of the disease, since it is about a female who belongs to the least affected age group and her occupation and place of residence and work is in the urban area. It is worth considering that the disease can affect anyone.

The *Leishmania* species responsible for the infection in this case, was not identified since this procedure is not part of the protocol for the diagnostic routine of the Julio Müller University Hospital. However, the main species in the central-western region of the country is *Leishmania* (*Viannia*)

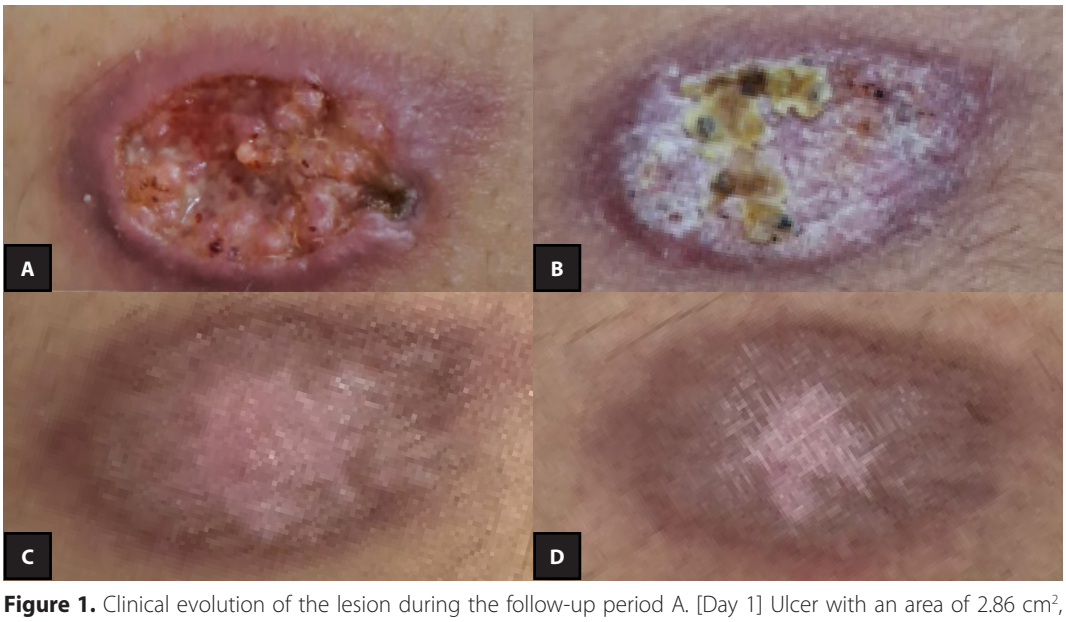

Figure 1. Clinical evolution of the lesion during the follow-up period A. [Day 1] Ulcer with an area of 2.86 cm^2, raised, well-defined and hyperchromic borders, base of the lesion with fibrin, but with a clean appearance, without purulent discharge or crust. B. [Day 28] Ulcer of 3.06 cm^2, in the process of re-epithelialization, but with abundant crusting and desquamation, slightly elevated hyperchromic edges. C. [Day 63] Re-epithelialized lesion, slight desquamation persists, slightly elevated hyperchromic borders. D. [Day 90] Re-epithelialized lesion, hypochromic center, hyperchromic and smooth borders on palpation, no crusting or desquamation. Clinical cure.

braziliensis, which is widely distributed in Brazil and Latin America in general.[iv]

The clinical manifestations of the case were typical; the first sign is usually the formation of a papule at the site of the bite, followed by the formation of a nodule, and finally, an ulcer within two to eight weeks.[xv] The ulcers are generally round or oval, with well-marked and raised borders, have an erythematous base, and are painless.[iv]

The patient's treatment was successful, as it met the clinical criteria for cure established by the Brazilian Ministry of Health. These criteria include complete re-epithelialization of all skin lesions within 90 days and the disappearance of crusting, desquamation, infiltration, and erythema within 180 days of follow-up.[iv] In this case, all criteria were met within 90 days. The patient underwent periodic evaluations with laboratory tests, which did not show significant alterations during the treatment. Nausea presented at the beginning of treatment, as well as hyporexia, are known and frequent adverse effects of the miltefosine drug[xvi] consequently, weight loss may occur.

Other drugs commonly used for treating cutaneous leishmaniasis include meglumine antimoniate, amphotericin B, and pentamidine isethionate.[x] Meglumine antimoniate has been the first-line treatment for several decades but has significant disadvantages. Treatment is usually administered intravenously at a dose between 10 and 20 mg/kg/day for 20 days, which can make adherence to treatment difficult.[vii] Systemic treatment instead of the use of intralesional administered treatment is favored.[xvii] The drug is linked to numerous adverse effects such as pancreatitis, pancytopenia, peripheral neuropathy, joint stiffness, gastrointestinal symptoms, nephrotoxicity,[ii] and also more

Table 1. Weekly nutritional evaluation and laboratory tests during the treatment period

	Day 1	Day 7	Day 14	Day 21	Day 28
Weight (Kg)	96.5	96.1	96.8	95.3	94
Body mass index	36.7	36.6	36.9	36.3	35,8
Alanine aminotransferase (U/L)	16	25	29	35	30
Aspartate aminotransferase (U/L)	14	19	18	20	20
Alkaline phosphatase (U/L)	65	71	71	69	-
Gamma-glutamyl transpeptidase (U/L)	55	49	53	64	-
Creatinine (mg/dL)	0.8	0.8	0.9	0.7	0,8
Urea (mg/dL)	33	31	38	42	-
Glucose (mg/dL)	118	116	116	112	-
Amylase (U/L)	52	49	56	61	51
Lipase (U/L)	41	43	34	36	35
Total Bilirubin (mg/dL)	0.2	0.3	0.3	0.2	-
Direct Bilirubin (mg/dL)	0.1	0.2	0.2	0.1	-
Indirect Bilirubin (mg/dL)	0.1	0.1	0.1	0.1	-
Hemoglobin (g/dL)	13.5	13.9	13.8	14.5	-
Hematocrit (%)	41.9	41.9	40	41.1	-
Leukocytes (cells/mm^3)	7080	7240	7620	6770	-
Platelets (cells/mm^3)	311 000	301 000	281 000	325 000	-
Serologic test for syphilis	Non-reactive	-	-	-	-
Hepatitis B virus surface antigen	Non-reactive	-	-	-	-
Antibody to hepatitis B virus surfaceantigen	Non-reactive	-	-	-	-
Human immunodeficiency virus	Non-reactive	-	-	-	-
Antibodies to hepatitis C virus	Non-reactive	-	-	-	-
Electrocardiogram	No anomalies	-	-	-	-

Source: clinical record.

severe manifestations such as QT segment extension, T-wave inversion, and flattening.[iv]

Amphotericin B is administered intravenously on daily bases. A total dose of 25-40 mg/kg; the total duration of treatment is variable and depends on the case and the patient's tolerance to the drug. Some adverse effects include fever, chills, tremors, dyspnea, flushing, tachycardia, hypotension, arthralgia, myalgia, and risk of nephrotoxicity.[iv]

Pentamidine isethionate is administered intravenously every other day, with three to ten total doses depending on the clinical course. Treatment is associated with hypoglycemia, hyperglycemia, hypotension, arrhythmias, QT interval prolongation, nephrotoxicity, leukopenia, hepatotoxicity, pancreatitis, and neuropathies.[xviii]

In the case described, treated with miltefosine, there was a complete cure; the advantages of this drug contributed to its adherence, such as the oral route of administration, its ambulatory use, and its higher safety profile, compared to other available drugs.

Ethical aspects

This case report complies with the Helsinki declaration and international ethical guidelines. The confidentiality of the patient's data was respected.

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