Case Report

Fatal mucosal leishmaniasis in a child*
*Leishmaniose mucosa fatal em criança**

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Abstract: American cutaneous leishmaniasis, an endemic and increasing disease in Brazil, can present as skin ulcers and lesions in the mucous membranes of the nose, mouth and pharynx. Pentavalent antimony is the first choice drug for treatment, with a less favorable response of the mucosal forms. The difficulty of diagnosing and treating a case of mucosal leishmaniasis in a five-year-old child, with negative parasitological and immunological tests and polymerase chain reaction is emphasized. Only after several attempts was the smear test positive. The patient developed persistent secondary bacterial infection on the lesions, lack of response to specific drugs and antibiotics and evoluted to septicemia and death.
Keywords: Fatal outcome; Mucocutaneous leishmaniasis; Septicemia

Resumo: *A leishmaniose tegumentar americana, doença endêmica e crescente no Brasil, pode manifestar-se por úlceras na pele e lesões nas mucosas nasal, oral e faringiana. O antimônio pentavalente é a droga de primeira escolha no tratamento, com resposta menos favorável nas formas mucosas. Destaca-se a dificuldade para diagnosticar e tratar um caso de leishmaniose mucosa em criança de cinco anos que teve exames parasitológicos, imunológicos e reação em cadeia da polimerase negativos. Somente após várias repetições o esfregaço foi positivo. A paciente apresentou infecção bacteriana secundária persistente das lesões e falta de resposta a drogas específicas e antibióticos, evoluindo para septicemia e óbito.*
Palavras-chave: Evolução fatal; Leishmaniose mucocutânea; Septicemia

INTRODUCTION

Prevalence of American Cutaneous Leishmaniasis (ACL) in Brazil is the highest in the Americas. Annual average has been of 35,000 cases.[1,2] The main species causing the disease in the country are *Leishmania (Viannia) guyanensis, Leishmania (Viannia) braziliensis* and *Leishmania (Leishmania) amazonensis*.[2]

Disease can be present in located cutaneous (CL), disseminated cutaneous (DL), diffuse cutaneous (DCL) and mucosal (ML) forms, with or without skin lesions.

Mucosal Leishmaniasis (ML) occurs in a percentage ranging from three to 5% of cases of infection by *L (V) braziliensis*,[3,4] is more severe and can leave sequels. It generally begins after months or years after involution of skin lesions. Most frequently affected mucosas are those of the nose, pharynx, larynx and mouth. It can be complicated by infections such as rhinitis, sinusitis, meningitis and bronchopneumonia, the latter being the main responsible for fatal outcomes.[4]

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Diagnosis is made by means of clinical features, epidemiology and laboratorial exams. Direct examination is positive in 75% of lesions whose evolution range from two to six months, and in 20% thereafter.[1,4] Culture and inoculation in hamsters have a sensitivity of respectively 30 and 50%.[1,4] Montenegro's intradermal reaction (MIDR) is positive in 82.4 to 100% at the moment of diagnosis.[5] It may be negative in patients with up to four months of disease evolution, in DCL and in the immunosuppressed.

Indirect immunofluorescence (IIF) is positive in 71% in CL and 100% in ML.[6] Fresh polymerase chain reaction (PCR) is, alone, more sensitive than any other conventional method.[7] Histopathology shows a hystiolymphocitic and plasma cell infiltrate and, rarely, amastigotes. It may present tuberculosis-like granuloma.[8]

First choice treatment is pentavalent antimony in a dose from 10 to 20 20mg/SbV/kg/day, IV or IM, during 20 days for CL and 30 days for ML.[1,4] Its toxicity is dose-dependent and may manifest in the heart, kidneys or liver. Classic amphoterecin B is the second choice.

CASE REPORT

Five-year-old brown-skinned female patient, born in and coming from Distrito Federal (DF) (Federal District). Mother reported a trip to the state of Paraná (Southern Brazil) with the child at two years of age, and death of another daughter then aged four, with suspicion for cystic fibrosis. She reported that in February 2001 the child presented an erithematous papule on the right malar region, with purulent secretion and that, after treatment with a cephalosporin and topic neomycin, remitted. In June, new face lesions appeared associated with cervical micro lymph node enlargement, which also responded to the same treatment. In August, obstruction and infiltration of the nasal mucosa came along, a condition that was treated as allergic rhinitis, with no success. In November, she presented with ulceration and purulent secretion in the left nasal mucosa, which improved when treated with anti-histaminic drugs and a cephalosporin. In December, she presented perforation of the nasal septum, then receiving the indication of biopsy, which was not performed.

In March 2002, she presented partial destruction of the left nasal wing cartilage and septum perforation, granulous lesion in the hard palate, infiltrated lesions in the mentum and left malar region, and cervical multiple node enlargement (Figures 1 and 2).

Main diagnostic hypotheses were leishmaniasis and lymphoma. The following exams were normal or negative: blood count, biochemistry, complement, various cultures for leishmania, mycobacteria and fungi, c-ANCA, ANF, PPD, immunoglobulin dosage, anti-HIV, MIDR (three times), IIF for ACL (twice), inoculation in hamster (three months), PCR for leishmania, biopsy of mucosa included in paraffin, and thorax radiograph. Facial sinus tomography yielded pansinusitis. Histopathological examination revealed infiltrate with granuloma containing epithelial and giant cells, with core necrosis with neutrophils (Figure 3), compatible with tuberculosis. Immunohistochemistry was positive for CD34, without granulomatous vasculitis and negative for neoplasia markers and tuberculosis bacillus.

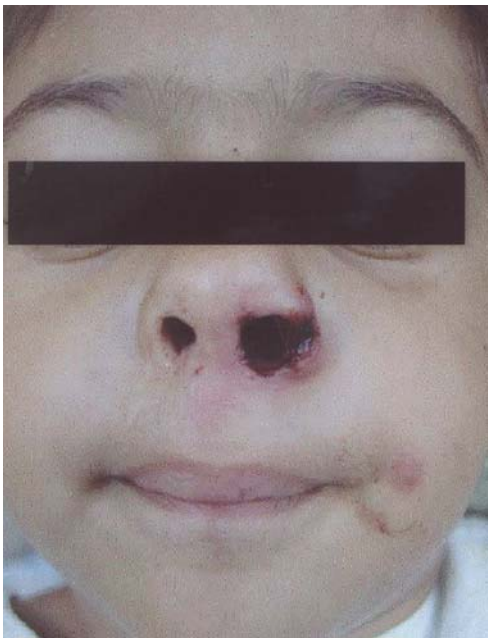

FIGURE 1: Ulceration in the left nare with an erythema halo. Two erythematic plaques with well-defined borders in the perioral region

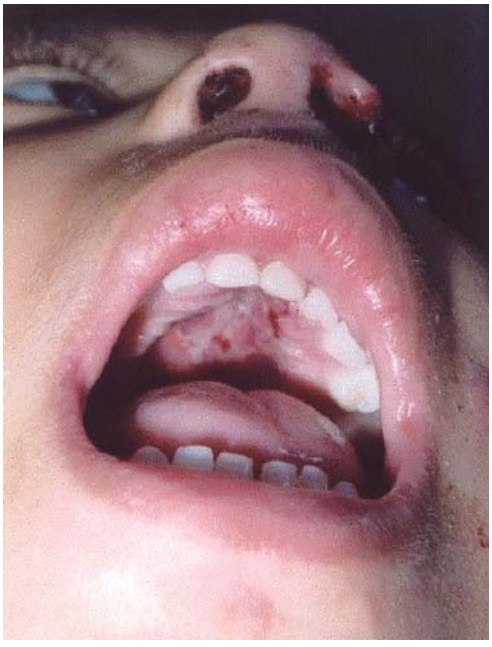

FIGURE 2: Infiltrated and ulcerated lesions in the hard palate mucosa, presenting purulent secretion and hemorrhagic spots

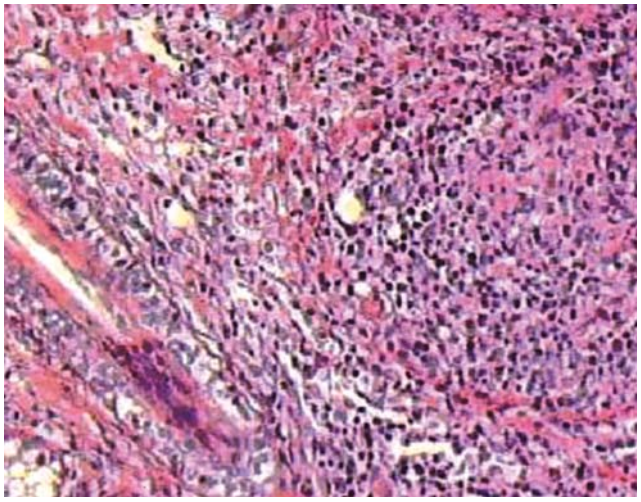

Figure 3: Granuloma with epithelial and giant cells. Core necrosis with neutrophils (HE 10x)

Because histopathological examination was compatible with tuberculosis, and all other exams negative for leishmaniasis, a triple scheme was begun (riphampicin, isoniazide and pirazinamide), after a consensus between Pediatrics and Dermatology. New lesions developed after a month of treatment, with consequent suspension of the drugs. When exams were repeated for ACL, amastigotes were found in the smear (Figure 4).

Treatment was begun with 20mg SbV/kg in alternate days (23 days) by Pediatrics. The child presented new lesions, and liposomal amphoterecin B was used in a total dose of 517 mg, with a subsequent increase in seric creatinine and BUN, worsening of general state and of the lesions, which reached nose, lips, hard and soft palate, perioral and left malar regions (Figures 5 and 6).

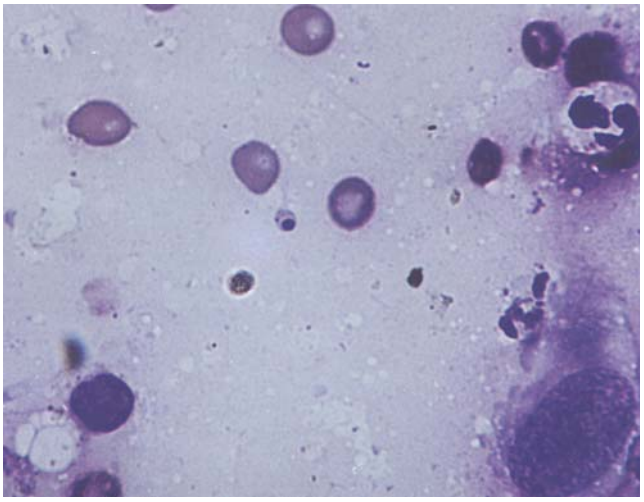

Figure 4: Amastigote form of *Leishmania* in a Giemsa-stained smear

There was persistence of secondary infection – were isolated staphylococci and pseudomonas, sensitive in vitro, but resistant *in vivo* to treatment with amoxicilin, amoxicilin-clavulanic acid association, aminoglycosides, cephalosporins, ciprofloxacin, vancomycin and imipenem. The child evolved with bronchopneumonia, sepsis and death in August 2002.

DISCUSSION

Taking ACL incubation period to be one to three months, considering that child had been infected during her trip to northern Paraná would not be reasonable, given that a symptom onset three years later is to long a period. Paraná is an endemic state,[9] but also in DF autochthonous cases have been registered sin 1980.[10] The child used to go to a ranch in DF, which was surrounded by woods, thus the possibility of infection there.

The lesion began as a papule in the face, and evolved to an ecthymatoid lesion, treated with antibiotics, without proper response. Sometimes, ACL initial lesion can go unnoticed or even resemble an insect bite, regressing spontaneously without leaving a scar, which may happen in up to 15% of cases. Other times, it can simulate impetigo, folliculitis or ecthyma, as happened in this case.

American Cutaneous Leishmaniasis can affect individuals at any age, being more frequent in the age range between 20 and 40 years. Incidence among children varies according to age range, going from 4.6 to 25% in children up to 10 years of age. I a retrospective study of a case series with 379 patients seen at the HUB Dermatology Department, the cases of children up to ten years old were analyzed, with the finding of five (22.72%) with ML, all of them presenting infiltration of the nasal septum.[11]

The great difficulty in confirming the diagnosis of this case is highlighted, given that MIDR (three exams), IIF (two exams), culture for leishmania (three times), inoculation in hamster (three months) and various smears were negative, not to mention that biopsy was performed five times, always displaying a tuberculosis-like granuloma pattern, which is rare in leishmaniasis.[8] As noted, the patient was repeatedly negative for MIDR, and literature data[4] indicate this exam to be a prognostic factor for the occurrence of relapses after treatment and as resistance to infection, corroborating the idea that immune cellular response is important for host recovery and protection against infection.

It is hard to interpret IIF negativity, given that its positivity in mucosal ACL is considered to be 100%.[1,4] However, according to the authors' experience, there already were cases of the mucosal form

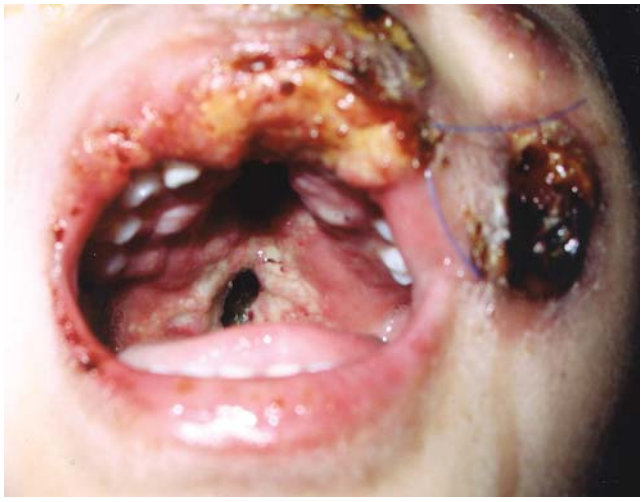

Figure 5: Ulcerations with abundant purulent secretion and necrosis in left malar region and upper lip. Eroded in infiltrated lesion in the hard palate mucosa. Presence of a fistula with purulent secretion

with both negative MIDR and IIF.

Diagnosis was confirmed by the finding of amastigotes after various smears had been carried out. The slide was evaluated by laboratory technicians, parasitologists and physicians with great experience in the identification of leishmania, which allowed for such conclusion.

Polymerase chain reaction[7] apresenta maior sensibilidade do que qualquer outro método diagnóstico usado isoladamente. Entretanto, o mesmo não pôde ser realizado *a fresco*, has a higher sensitivity than any other method used alone. Nevertheless, it could not be performed with fresh samples, for operational matters. PCR with checking for inhibition, performed in a block of paraffin from the biopsy, was negative. This method, when coupled to hybridization or agar gel, has a positivity of 75% and 69%, respectively (Pirmez, Claude; personal communication). It is believed that, in cases of parasite scarcity, any parasitologic method, even those using monoclonal antibodies and immunoperoxidase, can fail in the confirmation of diagnosis.

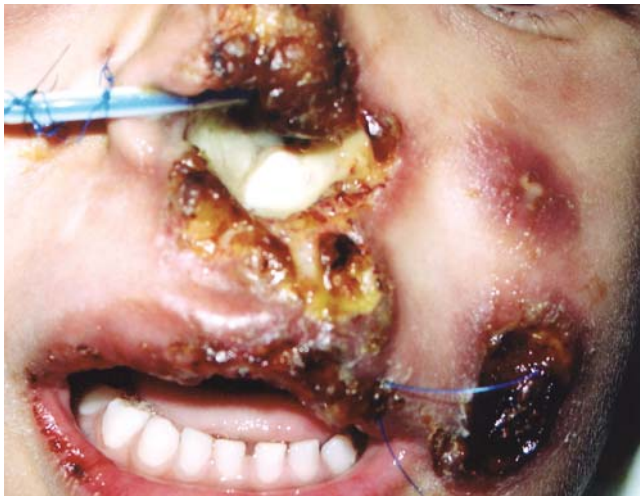

Figure 6: Total destruction of nasal cartilage with extension of the lesions to the columnela and upper lip. Infiltrated and ulcerated lesions in left malar region, in different evolutional stages0

An early diagnosis could have had a positive influence in the evolution of this case. That is the reason for the conclusion about the need for the study of more accurate and effective diagnostic methods, not to mention the implementation of reactions such as PCR in the public health services, specially for the mucosal form, harder to diagnose.

Patient did not respond to treatment with antimony, neither to liposomal amphoterecin B, having developed with new lesions, associated to progressive malnutrition and worsening of the general state. Pentavalent antimony, despite its toxicity, has been the first treatment choice for over 50 years, with failure rates of up to 40% of ML cases.[12] Cure control standard – complete healing of the lesions – is unsatisfactory and inadequate, because relapses are documented, even after standardized treatment with total healing of active lesions.[13]

Regarding amphoterecin B, the used dose of 517 was inferior to the recommended 2.5 to 3 g for adults with ML. However, even with such doses, therapeutic failures are reported.[14] Its nephrotoxicity was certainly aggravated by the use of nephrotoxic antibiotics.[15]

As to secondary infection, microorganisms that had in vitro sensitivity were demonstrated in the lesions, this notwithstanding, there was no response to antibiotics that had been inhibited in the antibiogram, which culminated in septic shock and death. Constant negativity of MIDR and PPD could justify immune cellular response deficiency, although no detailed studies were carried out. Preserved host immune system is considered to be important for a good therapeutic response of leishmaniasis, since it is caused by an intracellular parasite, thus the antimonial would act as an immunomodulator. This case demonstrates the mucosal disease as being debilitating, leading the patient to a state of malnutrition, immunodeficiency and secondary infections hat can become even more severe than the base disease. ❑

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