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CASE REPORT

Leishmaniasis and Rheumatoid Nodulosis in a Patient With HIV Infection

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PALABRAS CLAVE

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Abstract

We describe the case of a 44-year-old homosexual man diagnosed with HIV infection and visceral leishmaniasis. He presented nodules on the dorsum of the hands. Histological study of one of the nodules revealed necrobiotic palisading granulomas with abundant *Leishmania* amastigotes within the histiocytes and in the adjacent extracellular space. Tissue and peripheral blood cultures were positive for *Leishmania infantum*, zymodeme MON-24. A biopsy of healthy skin did not reveal the presence of *Leishmania*. A diagnosis of rheumatoid nodulosis with *Leishmania* was made and treatment was started with intravenous liposomal amphotericin, leading to slight improvement.

We believe that the presence of the parasite within the nodules was the result of its dissemination during visceral leishmaniasis in an immunocompromised patient with HIV infection, and that the *Leishmania* did not have an etiological role in the appearance of the nodules. We present the first case of the association between *Leishmania* and rheumatoid nodulosis

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Leishmaniasis y Nodulosis Reumatoide en Paciente con Infección por el Virus de la Inmunodeficiencia Humana

Resumen

Describimos el caso de un paciente varón de 44 años, homosexual, infectado por el virus de la inmunodeficiencia humana (VIH) y diagnosticado de leishmaniasis visceral. Clínicamente presentaba unos nódulos en el dorso de las manos. El estudio histológico de uno de ellos mostraba granulomas necrobióticos en empalizada y abundantes amastigotes de *Leishmania* dentro de los histiocitos y extracelularmente en la proximidad.

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Los cultivos tisulares y de sangre periférica fueron positivos para *Leishmania infantum*, con el análisis isoenzimático zymodema 24. Una biopsia de piel sana no reveló la presencia de *Leishmania*. El diagnóstico fue de nodulosis reumatoide con *Leishmania*, y se inició tratamiento con anfotericina liposomal intravenosa con leve mejoría.

Consideramos que la presencia del parásito en los nódulos fue producida por la diseminación durante la leishmaniasis visceral, en el contexto de un paciente inmunosuprimido, como en una infección por el VIH, y no tiene un papel etiológico en su origen. Es decir, no pensamos que los parásitos hayan producido los nódulos. Presentamos el primer caso de asociación entre leishmania y nodulosis reumatoide

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Introduction

In 1985 De la Loma et al¹ reported the first case of leishmaniasis associated with human immunodeficiency virus (HIV) infection. Several further cases of such an association have been reported since then, most frequently in Mediterranean countries. In Spain it is estimated that between 1% and 5% of patients with acquired immune deficiency syndrome (AIDS) are infected, with parenteral drug use a risk factor in more than 85% of cases.^{2,3} In spite of receiving appropriate treatment, a number of such patients may have a more aggressive and chronic clinical course, with atypical manifestations, a greater tendency to recurrence, and poorer response to treatment.

The term rheumatoid nodulosis was introduced by Ginsberg et al⁴ in 1975. Although the definition varies from author to author, it is considered by most to be a particular variant of rheumatoid arthritis associated with palindromic rheumatism and histologically confirmed subcutaneous rheumatoid nodules. There may or may not be minimal joint damage and other systemic manifestations. The clinical course is generally benign. Positive rheumatoid factor and radiographic evidence of subchondral bone cysts are common, but their absence does not rule out the diagnosis, especially in early phases. Although rheumatoid nodulosis may meet the diagnostic criteria of the American Rheumatism Association for rheumatoid arthritis, its clinical course is different.⁴

We present the case of an HIV-positive patient diagnosed with visceral leishmaniasis and rheumatoid nodulosis with *Leishmania* in the palisading necrobiotic granulomas of several nodules on the dorsum of the hands. We would like to draw attention to this association, not previously described in the literature, and discuss the pathogenic role of the parasite in the development of the skin lesions.

Case Report

The patient was a 44-year-old homosexual man who had been HIV positive since 1993 and had been receiving retroviral therapy since that time. He owned 10 dogs. In July 2000 he was diagnosed with syphilis and visceral leishmaniasis and suffered several episodes of oral and esophageal candidiasis. Treatment with intramuscular meglumine antimonate was initiated and continued until January 2001, achieving an apparently complete cure.



Figure 1 Nodules on the dorsum of both hands, predominantly in periarticular areas.

In July 2002 he was admitted for *Legionella* pneumonia. At that time he was receiving treatment with didanosine, stavudine, lamivudine, nevirapine, and trimethoprim-sulfamethoxazole. The patient had fever and chills, dyspnea, productive cough, and substernal pleuritic chest pain. He also presented asthenia, exhaustion, and weight loss. He reported the appearance 7 months earlier of asymptomatic nodules on the dorsum of his hands, with no joint pain or stiffness. In addition to signs of severe malnutrition, physical examination revealed well-delimited, skin-colored indurated nodules on the dorsum of both hands, chiefly in the periarticular areas (proximal and distal interphalangeal joints) (Figure 1). The rest of the examination was normal.

Histopathological examination of 2 of the lesions showed similar findings, consisting of a nodular lesion in the dermis characterized by extensive collagen necrobiosis associated with an inflammatory infiltrate, mainly of palisading histiocytes. Abundant *Leishmania* amastigotes were detected both within the histiocytes and lying free around the necrobiotic material. *Leishmania* were also detected, although fewer in number, in the healthy adjacent dermis, and in very small numbers in the basal keratinocytes. No mucin deposits were detected (Figures 2

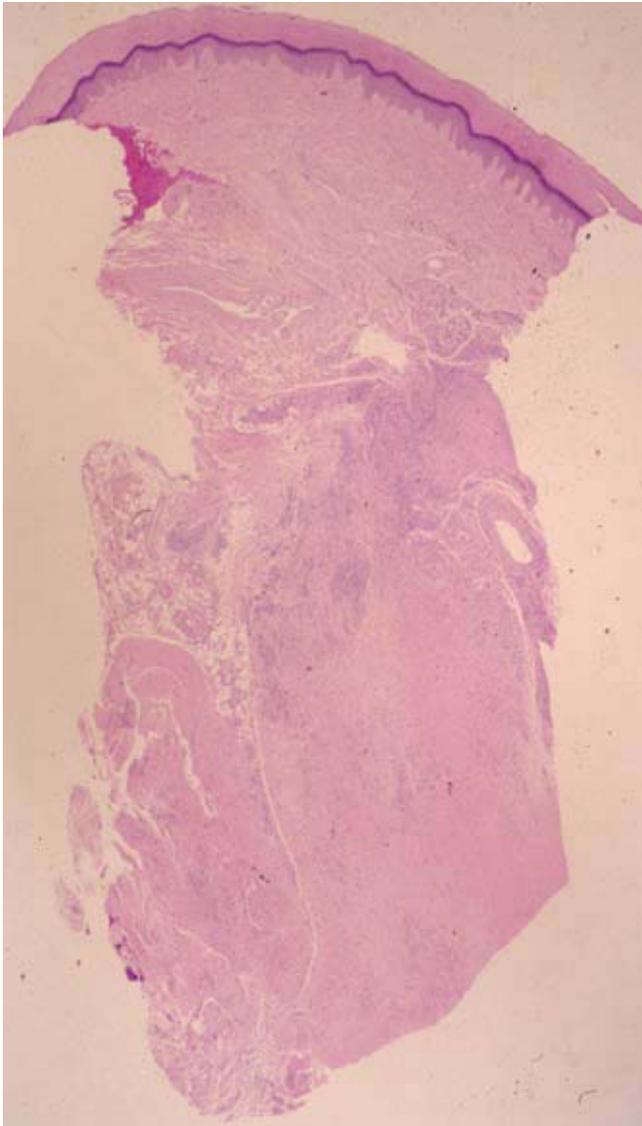


Figure 2 Necrobiotic palisading granuloma in the middle and deep dermis (hematoxylin-eosin, original magnification $\times 40$).

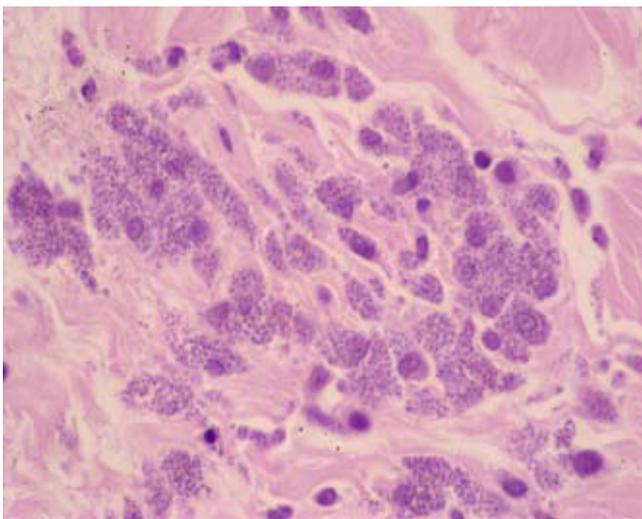


Figure 3 Close-up of *Leishmania* organisms within the cytoplasm of the histiocytes (hematoxylin-eosin, original magnification $\times 200$).

and 3). A biopsy of healthy skin did not reveal the presence of *Leishmania*. The patient refused to undergo a bone marrow biopsy. Tissue and peripheral blood cultures were positive for *Leishmania infantum*, zymodeme MON-24.

The culture of healthy skin was negative. Polymerase chain reaction results were positive for *Leishmania* in diseased skin and in blood, but negative in healthy skin.

Blood tests revealed severe anemia (hemoglobin, 7g/dL), leukopenia ($3.5 \times 10^9/L$), and thrombocytopenia ($100 \times 10^9/L$). Erythrocyte sedimentation rate was 123 mm; gamma-glutamyltranspeptidase, 54 IU/L; C-reactive protein, 0.9 mg/dL; and rheumatoid factor (RF), 95.8 IU/mL. The patient also had elevated immunoglobulin levels (37.8%), and positive results at a titer of 1/80 for antinuclear antibodies. Results were negative for anti-SS-A/Ro, anti-SS-B/La, anti-Sm, anti-RNP, and anti-Jo-1 antibodies. The HIV viral load was 351 000 copies/mL, with a CD4 lymphocyte count of $40/mm^3$ and a CD4:CD8 ratio of 0.23. The remaining parameters were normal. *Leishmania* serology by indirect immunofluorescence was positive at an IgG titer of 1/640.

Abdominal echography showed homogenous hepatomegaly and marked splenomegaly (18 cm). A radiographic study of the hands and feet showed an increase in the soft tissue volume of the hands corresponding to the nodules, with no other relevant findings. The report from the rheumatology department indicated rheumatoid nodulosis. Together with antibiotic therapy for the pneumonia, intravenous treatment was started with liposomal amphotericin B (3 mg/kg/48 h). The systemic alterations resolved and the skin lesions improved partially. The patient was discharged and subsequent follow-up visits were scheduled.

In view of the persistence of the hand lesions after 7 months of treatment, another biopsy was performed. The findings were similar to those of the first, but with a smaller number of parasites. The patient is currently receiving a maintenance dose of liposomal amphotericin every 2 weeks.

Discussion

Skin involvement in visceral leishmaniasis associated with HIV is infrequent, and is occasionally the first sign, preceding involvement of the internal organs. Clinical presentation is very variable and most commonly includes macules, papules, plaques, nodules, or ulcers.³ It may also present in atypical clinical forms such as erythroderma⁵ or psoriasiform, or dermatomyositis-like lesions.⁷

However, there have been descriptions of patients with both visceral leishmaniasis and AIDS in whom *Leishmania* were detected fortuitously in the course of biopsies performed to study other skin pathologies. This suggests that the finding is incidental and not the cause of the disease. In fact, the parasite has been found in lesions of Kaposi sarcoma,⁸ of herpes simplex or herpes zoster coinfection,^{9,10} of bacillary angiomatosis,¹¹ of Reiter's syndrome,¹¹ of dermatofibroma,^{11,12} of psoriasis,¹¹ of cryptococcus coinfection,¹¹ and of oral aphthae.^{11,13}

In some cases the detection of *Leishmania* in these lesions has led to the diagnosis of unsuspected visceral

leishmaniasis.¹¹ Histopathological studies may also reveal the presence of amastigotes in the healthy skin of patients with visceral leishmaniasis and immunosuppression, especially AIDS.^{6,14}

Our patient was diagnosed with visceral leishmaniasis associated with HIV infection and severe immunodeficiency (AIDS category C3). Also noteworthy was the presence of nodules that had appeared several months earlier on the dorsum of the hands, mainly in the periarticular area. The clinical morphology of the nodules, their histology showing palisading necrobiotic granulomas, and blood tests showing an elevated rheumatoid factor in the absence of signs or symptoms of rheumatoid arthritis were all suggestive of rheumatoid nodulosis, and the diagnosis was confirmed by our hospital's rheumatology department.

While there have been reports in the literature of nodules as the clinical presentation of visceral leishmaniasis, we believe that in our case the presence of amastigotes in the nodules did not play a pathogenic role in the appearance of the lesions. This hypothesis is supported by the clinical and pathologic characteristics of the nodules, the small number of *Leishmania* found in the healthy dermis adjacent to the granulomas, and the lack of response to treatment. The presence of the parasite in skin diseases with which it is not normally associated can be explained by its massive dissemination in patients with a totally ineffective immune system, as in the case of HIV infection. The highly vascular nature of these lesions and the presence of abundant histiocytes (the reservoir of *Leishmania*) may favor invasion. It is not currently known whether the parasites can affect the severity or the chronic nature of the rheumatoid nodules.

We found no association between *Leishmania* and rheumatoid nodulosis reported in the literature. A case has been published of an HIV-negative patient who had both rheumatoid nodules and cutaneous *Leishmania* infection. The patient had been diagnosed with rheumatoid arthritis 10 years earlier and was receiving treatment with methotrexate and prednisone. In one of the nodules the parasites were found in both intracellular and extracellular locations. The authors suggested that the macrophages in the nodules act as a safe reservoir for the parasites.¹⁵

We would like to draw attention to the presence in our patient of *Leishmania* amastigotes within the keratinocytes of the epidermis. These parasites have occasionally been reported to have been found in the epithelial cells of the eccrine glands and inside the eccrine ducts,¹⁴ but they only exceptionally invade the keratinocytes.^{6,16} Such findings suggest the possibility of the elimination of the parasite through the epidermal keratinocytes.¹⁶

We present the first case of the association between *Leishmania* and rheumatoid nodulosis. We believe that rheumatoid nodulosis should be added to the list of diseases in which a finding of *Leishmania* is merely an indication of

the passive presence of the parasite in an inflamed area, where the accumulation of the parasites may be stimulated by certain local factors.

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