Leishmania and HIV co-infection: dermatological manifestations

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Leishmania species can cause a wide spectrum of cutaneous disease in HIV-positive patients: asymptomatic, localized cutaneous, mucosal, muco–cutaneous, diffuse cutaneous or post-kala-azar leishmaniasis. In such cases, which are usually severely immunocompromised, the leishmanial parasites reach the skin of the human host by dissemination after either a new infection (resulting from the bite of infected sandfly or, probably, the sharing of contaminated syringes by intravenous-drug users) or the re-activation of a latent infection. Recent experience and past observations on the dermatology of leishmaniasis in those with Leishmania/HIV co-infection are reviewed here.

The leishmaniases are a group of diseases caused by parasites belonging to the genus Leishmania. The human leishmaniases are usually classified as visceral, localized cutaneous, diffuse cutaneous or muco–cutaneous, and their manifestations can present a wide clinical spectrum. The differences in the clinical pattern are related not only to the type and virulence of the parasite involved but also to the immune response of the infected human. Viscerotropic and dermotropic strains of Leishmania infantum appear to be the only causative agents of leishmaniasis in south–western Europe (Alvar et al., 1996).

Since HIV infection has extended to areas in which human leishmaniasis is endemic, the incidence of human leishmaniasis in the regions where the parasites and virus co-occur has been progressively increasing, especially among adults. Epidemiological data reveal that 50% of all adult cases of visceral leishmaniasis (VL) are now HIV-positive and that 1.5%–9% of patients with AIDS in south–western Europe suffer from newly acquired or re-activated VL (Desjeux, 1999). Since the first description of leishmaniasis associated with HIV infection 15 years ago (De la Loma et al., 1985), many new cases of such co-infection have been reported. They have occurred world-wide, from a total of 30 countries. Most, however, have been observed in southern Europe, where the number recorded has increased from about 700 cases in 1995 to more than 1500 cases currently. Intravenous-drug users (IVDU) are clearly identified as the major population at risk of the co-infection in Europe, many cases occurring in young adult male IVDU in which human leishmaniasis is endemic, who are severely immunosuppressed (<200 CD4 cells/μl) and often affected by other opportunistic diseases, such as candidiasis, tuberculosis, toxoplasmosis, Pneumocystis carinii pneumonia or Kaposi’s sarcoma. In Spain, over 800 cases of leishmaniasis in HIV-positive patients have been reported, of which 50% are IVDU. In this risk-group, human–human transmission may occur, with the co-infected individuals — who often have
numerous leishmanial amastigotes in their skin and blood, and who, in terms of diagnosis and treatment, are particularly difficult to manage — acting, like dogs, as reservoirs for the parasite (Martínez et al., 1993; Alvar and Jiménez, 1994). Although most HIV-infected patients are thought to be infected with *Leishmania* when they are bitten by an infected sandfly, the leishmanial infection of IVDU by their use of contaminated syringes is thought to be becoming more frequent (Martínez et al., 1993; Alvar et al., 1996).

This review, which is based on the unpublished results of recent investigations as well as the published results of earlier studies, is intended to summarize the clinical and histopathological manifestations of the dermatological lesions that sometimes occur in *Leishmania/HIV* co-infection.

**FORMS OF CUTANEOUS LEISHMANIASIS**

Acute, chronic, recidivans, disseminated and post-kala-azar forms of human cutaneous leishmaniasis (CL) have been recognized.

The acute lesions usually begin as single papules, resembling non-specific arthropod bites, at the site of the vector bite(s). In a week or two, many of the lesions resolve and only one or a few persist. The persistent lesions may become nodules, ulcerate and eventually heal, leaving a scar. Several to many lesions may appear in exposed parts of the body when there are multiple inoculation sites. Inflammatory satellite papules may develop around the primary lesion. The cutaneous lesions can be elongated, following Langer’s lines, or may assume different morphologies, including eczematoid, plaque, hyperkeratotic, warty, zosteriform, erysipeloid, and sporotrichoid. Solitary or multiple subcutaneous nodules representing nodular lymphangitis may develop, and regional lymphadenopathy may be present (especially following infection by *Leishmania* spp of the New World).

Chronic lesions, which persist for more than 1 or 2 years, are single, or occasionally multiple, raised non-ulcerated plaques, which can become indurated, verrucous, scaly or scarred. The recidivans (lupoid) form may appear as a complication of cutaneous infection with *L. tropica*. It consists of erythematous papules, often circinate, which develop near the scars of previously healed lesions and may mimic lupus vulgaris; a verrucous form has been described. The lesions appear as scaly erythematous papules that may evolve before the classic ulcer of acute CL has healed or develop afterwards. The number of parasites is sparse, the Montenegro reaction is strongly positive, and the mechanism underlying recrudescence is considered to be re-activation of dormant parasites, a change in the immune status of the host and/or exogenous re-infection.

The disseminated form (primary diffuse CL) develops in anergic individuals as widespread nodules and macules, without ulceration or visceral involvement. This variant is characterized by a partial response to treatment and frequent relapses, and the most frequent causal species are *L. amazonensis* and, rarely, *L. aethiopica*. This presentation, with multiple papules and nodules which can be ulcerated, is rather common in patients with HIV co-infection, regardless of the species of *Leishmania* involved.

Post-kala-azar dermal leishmaniasis (PKDL) is endemic in Africa and India and is primarily caused by *L. donovani*. It is seen in 5% of patients recovering from VL in Africa and in 20% of such patients in India. The eruption of African PKDL is papular and lasts for months. In India, however, PKDL usually begins as erythematous and hypopigmented macules that enlarge into patches and may later become long-standing non-ulcerative reddish nodules that contain great numbers of amastigotes. This variant of leishmaniasis bears a great resemblance to lepromatous leprosy, and is epidemiologically very important, since the patients behave as natural reservoirs of *L. donovani*. 
Muco–cutaneous leishmaniasis is usually caused by New-World species of *Leishmania* but is also an uncommon complication of *L. amazonensis* infection and, exceptionally, of infection by any other *Leishmania* species. The initial lesions of muco–cutaneous (American) leishmaniasis resemble those seen in the cutaneous form. Vegetating, verrucous and sporotrichoid lesions may also occur. In up to 20% of cases, destructive lesions of the mucous membranes develop, particularly in the nasopharynx and at body orifices. This complication, known as *espundia*, may develop up to 25 years after the apparent clinical cure of the lesion. The disseminated anergic form is a rare complication, but may occur in patients with AIDS.

**CUTANEOUS LEISHMANIASIS AND HIV**

In some HIV-infected patients, CL develops as isolated papules or plaques on exposed areas, which are indistinguishable, on either clinical or histopathological grounds, from the similar lesions that develop in non-immunosuppressed patients (Gonzalez-Ruperez *et al.*, 1997). HIV-positive patients with such lesions should be checked carefully, by the microscopical examination and culture of bone-marrow aspirates, to see if they have VL. Purely cutaneous leishmaniasis in those co-infected with HIV tends to be associated with the initial stages of HIV infection and/or minimal degrees of immunosuppression, and, like CL in the immunocompetent, generally responds well to intralesional antimonial treatment. Disseminated CL in the absence of visceral involvement has also been reported, as the first manifestation leading to the diagnosis of HIV infection (Durand *et al.*, 1998).

Although, in immunocompetent populations, the global incidence of CL exceeds that of VL, most cases of HIV/Leishmania co-infection develop the visceral disease. In general, VL in HIV-positive patients does not differ significantly, in terms of the clinical picture, from that of classical VL caused by *L. donovani* (i.e. kala-azar) but it runs a more severe and protracted course, is more prone to relapse, and is often resistant to antimonial therapy (Peters *et al.*, 1990). Some co-infected patients develop cutaneous lesions, either associated with VL or as the only clinical manifestation of the disease. Cutaneous dissemination in VL has occasionally been reported in immunocompetent hosts but is much more common in the HIV-infected population. Postigo *et al.* (1997), for example, observed it in six patients of a group of 32 HIV-positive individuals with VL. When such dissemination occurs, the skin lesions do not present a uniform or specific appearance, even though they tend to localize symmetrically on acral zones. They consist of erythematous papules and hypopigmented macules on the dorsa of the hands, feet, and elbows, small subcutaneous nodules on the thighs, and erythematous-violaceous, scaly plaques on the face. In many cases, these lesions accompany the other symptoms and/or signs of VL, respond variably to antileishmanial treatment, and are sometimes the first indicator of a recurrence of the leishmaniasis. In many ways, this presentation is similar to PKDL (Rios-Buceta *et al.*, 1996).

erythrodermic pattern (Belma Mira et al., 1994), generalized CL resembling diffuse anergic leishmaniasis (Rosatelli et al., 1998), and psoriasiform (Rubio et al., 1997) or dermatomyositis-like eruptions (Dauden et al., 1996). It appears that the recidivans form of CL has never been reported in an HIV-infected patient, possibly because this clinical variant is extremely rare in CL caused by *L. infantum* — the *Leishmania* species responsible for most cases of *Leishmania*/HIV co-infection reported from Europe.

In other HIV-positive patients with skin lesions, the presence of *Leishmania* in the skin appears to be coincidental — simply the result of dissemination during VL in the presence of a deeply impaired immunity and/or HIV infection — and not responsible for the cutaneous lesions, which may be attributable to Kaposi’s sarcoma (Smith et al., 1989; Romeu et al., 1991; Taillan et al., 1992; Perrin et al., 1995; Gallego et al., 1996; Abajo et al., 1997; Yebra et al., 1998), herpes simplex (España et al., 1990) or herpes zoster infection (Barrio et al., 1996; Del Giudice, 1996), bacillary angiomatosis (Herrera et al., 1996), dermatofibroma (Castellano et al., 1999; Colebunders et al., 1999) or even tattoos (Colebunders et al., 1999). *Leishmania* amastigotes have been detected in the healthy skin of HIV-positive patients with VL (Yebra et al., 1988; Taillan et al., 1992; Belma Mira et al., 1994; Perrin et al., 1995; Dauden et al., 1996). The demonstration of *Leishmania* amastigotes in phagocytic cells from the peripheral blood of HIV-positives reflects the inability of the patients’ cellular immune mechanisms to eradicate the parasite. In those co-infected, hypervascularization and the presence of inflammatory cells in the lesions could explain the intense concentration of leishmanial amastigotes in Kaposi’s sarcomas (Del Giudice, 1996; Abajo et al., 1997).

Mucosal lesions seldom occur in the course of *L. infantum* infections in immuno-competent patients, although labial, lingual, palatine, nasal and laryngeal localizations have all been reported (Ferlito et al., 1986; Borzoni et al., 1991). In some of these cases, the mucosal lesions might represent sites of inoculation. The association of an oro-pharyngeal mucosal localization with VL is occasionally observed (Marsden, 1986; Abbas et al., 1992). Although some mucosal lesions have been observed in patients with VL and HIV infection (Montalbán et al., 1990; Michiels et al., 1994), they should not be considered as mucocutaneous leishmaniasis because they have always been associated with visceral involvement. *Leishmania braziliensis* and *L. aethiopica* are the most common causative agents of mucocutaneous leishmaniasis, but a few cases of mucocutaneous leishmaniasis have been observed in areas where neither of these *Leishmania* species can be found. As *L. major*, *L. mexicana* and *L. infantum* have also been reported as causative agents, it seems that any *Leishmania* species infecting humans can be responsible for mucocutaneous lesions. In Europe there have been very few cases of mucocutaneous leishmaniasis that were not probably imported and these have been assumed to be the result of *L. infantum* infection, although the parasite was identified in only one case (Alvar et al., 1990).

Purely mucosal or mucocutaneous leishmaniasis in association with HIV infection is an exceptional occurrence in European patients (Barbera et al., 1994; Miralles et al., 1994; Bañuls et al., 1995; Cortes et al., 1997; Vázquez-Pineiro et al., 1998; Chaudhry et al., 1999; Grasa et al., 2000), and can be the first sign of HIV infection. It appears to be more frequent in cases of leishmaniasis acquired in South America (Scaglia et al., 1989; Machado et al., 1992; Mattos et al., 1998; De Souza e Souza et al., 1998; R. Pradinaud and P. Couppie, unpubl. obs.) and North Africa (Bastuji-Garin et al., 1991), presumably because of the tropism of the infecting *Leishmania* species. There have been occasional reports of American CL in association with AIDS; even though the most frequent presentation is localized CL, there is marked variability in clinical appearance (Cnudde et al., 1994; Nogueira-Castanon...
Cutaneous leishmaniasis in association with HIV co-infection has also been reported in African patients (Berhe et al., 1995; Gillis et al., 1995; Ndiaye et al., 1996).

The histopathological findings in dermatological lesions of patients with Leishmania/HIV co-infection are variable, and can depend on the immune status of the patient. In some cases, especially in patients with solitary, localized or scarce lesions, both the clinical and histopathological features can be indistinguishable from those of CL caused by the same Leishmania species in immunocompetent patients. In acute lesions there is a massive dermal infiltrate of lymphocytes, parasitized macrophages, epithelioid cells and occasional giant cells, plasma cells and eosinophils. There can be some admixture of neutrophils in the upper dermis, especially in ulcerated lesions. Rarely, the inflammatory infiltrate extends around the small nerves in the deep dermis, in a manner similar to leprosy. The epidermis shows hyperkeratosis and acanthosis, sometimes with atrophy, ulceration or intra-epidermal abscesses. Pseudo-epitheliomatosus hyperplasia can be seen in some long-standing lesions.

The leishmanial amastigotes are round to oval, basophilic structures, 2–4 μm in diameter, and, in immunocompetent cases, are usually found within macrophages. Their morphological details can be better appreciated using Giemsa stain. They have an eccentrically located kinetoplast, and their lack of capsule is helpful in distinguishing them from Histoplasma capsulatum. In most cases of CL in HIV-infected patients, large and even huge numbers of amastigotes can be seen, both within the dermal histiocytes and free in the dermis or subcutaneous tissue, with a scarce lymphomononuclear infiltrate. Amastigotes have been seen within the epithelial cells of secretory eccrine glands and within eccrine ducts. The parasites can also be found in keratinocytes surrounding the acrosyringium, indicating that there might be transepithelial elimination through eccrine sweat glands and eccrine epithelial tropism (Perrin et al., 1995; Ara et al., 1998), or even transepidermal elimination of amastigotes (Dauden et al., 1996). There is an isolated report of a spindle-cell pseudotumour which has been interpreted as a histoid reaction to Leishmania in an HIV-infected man (Perrin et al., 1993). In an HIV-infected patient with recurrent VL, a dermatofibroma was found to contain many amastigotes, mainly within factor-XIIIa-positive spindle and foamy cells but also in extracellular areas (Castellano et al., 1999).

In recent years, the introduction of protocols for highly active antiretroviral therapy (HAART) has dramatically reduced the viral load and degree of immunosuppression in most HIV-positive patients. As the clinical manifestations of Leishmania/HIV co-infection (particularly those that result from dissemination of the amastigotes) depend on the level of immunosuppression in the host, HAART is also likely to reduce the morbidity associated with the co-infection.

REFERENCES


