Letter to the Editor

Immune Reactivity to Fractionated Leishmania aethiopica Antigens during Coinfection with Human Immunodeficiency Virus Type 1

The defective Leishmania aethiopica antigen-specific immune response is associated with a clinical picture of multiple, diffuse lesions on the face, trunk, and extremities rather than the localized dermal lesions which occur in patients with otherwise normally functioning immune systems. In the study by Laskay et al. (3), 10 patients with L. aethiopica infection and with singular dermal lesions had a remarkable lymphocytic proliferative response, including gamma interferon (IFN-γ) and tumor necrosis factor alpha (TNF-α) production. When fractions of molecular antigens of L. aethiopica had molecular masses exceeding 60 kDa, the lymphocytic proliferative response was poor and IFN-γ and TNF-α production was minimal (3). Nevertheless, in order to determine the precise role of different cytokines, e.g., IFN-γ and TNF-α, in the activation of macrophages to eliminate intracellular L. aethiopica, it is necessary to quantitate their levels in subjects coinfected with L. aethiopica and human immunodeficiency virus type 1 (HIV-1).

As the numbers of individuals with HIV-1 infection and progressive immunosuppression have increased, L. donovani has emerged as an opportunistic organism (2, 4). Coinfection of L. aethiopica infection characterized by diffuse multiple lesions, involvement of distant organs, or nonresponsiveness to the conventional therapeutic agents also appears to be linked with HIV-1 infection.

Regular screening for existing HIV infection by using polymerase chain reaction with nested primers for integrated HIV-1 sequences in the host genome (1) seems to be necessary for all patients with solitary or diffuse lesions attributable to L. aethiopica. The persistence of a proliferative response to different antigenic fractions of L. aethiopica (3) may be a prognostic marker in HIV-1 infection or AIDS. Apart from a local assay for antigenic fractions, an assay to determine functional activity of T and B cells and interleukin-2 could be possible by assaying for the soluble interleukin-2 receptor in serum and locally since high levels are associated with malignancies and immune disorders (5).

REFERENCES


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Author’s Reply

As indicated in Dr. Arya’s letter, there is sound evidence of opportunistic Leishmania infections occurring in patients infected with human immunodeficiency virus type 1 (HIV-1) (2, 3, 7, 14). Many of the reported cases of such dual infection are of residents of areas endemic for visceral or cutaneous disease who have presented clinically with unusual infections and tissue and organ distributions of Leishmania parasites, i.e., dermotropic forms of typically visceralizing L. donovani infection (2, 3, 7, 14). These reports have indicated that disseminated infections were associated with virulent pathogenesis and more often with fatal clinical outcome. Within this frame, attention has been directed to other known forms of disseminating leishmaniasis such as L. aethiopica infection.

Infection with L. aethiopica typically manifests clinically as localized cutaneous leishmaniasis (LCL), in which singular skin ulcerations form and self-heal over time. Patients with active LCL often show strong in vitro lympo-proliferative reactivity in response to L. aethiopica antigens (1). Diffuse cutaneous leishmaniasis (DCL) is a rare form (<5%) of all CL of L. aethiopica infection which is marked by the formation and persistence of multiple parasite-laden nonulcerative lesions over the face, trunk, and extremities (4, 5). The clinical form of DCL is not subsequent to LCL and occurs in both adults and children. DCL patients show specific cellular anergy to leishmanial antigens by in vitro proliferation, by lymphokine and cytokine responses, and by recall skin testing but exhibit significant specific antibody reactivity and high levels of tumor necrosis factor alpha in serum (1, 4, 5, 10, 12). Defective cellular immune responsiveness an differences in parasite virulence have been suggested as causes of Ethiopian DCL (1, 5). However, the biological basis for the development of DCL is not understood. DCL is not associated with any recognized general immunosuppression, and the immune response of DCL patients to the standard recall antigen is similar to that of the general population (5). Further, upon successful chemotherapy (lowering of parasite burden), DCL patients acquire specific cellular responsiveness to L. aethiopica antigens (1, 5).

There is a presumed association between the development of unusual forms of opportunistic leishmaniasis and altered or compromised immune reactivity due to coincident HIV-1 infection and the loss of CD4+ cells. As shown in studies of experimental infection, there is a delicate balance in the activities of T lymphocytes responsible for controlling leishmanial infections; the loss of certain numbers of CD4-equivalent cells variably affects the pathogenesis of both
visceral and cutaneous infections (reviewed in reference 11). To date, information regarding the status of specific anti-leishmania cellular immune reactivity in HIV+ subjects is needed and will help us to better understand the mechanisms of resistance for Leishmania infections in general. Without that information and without further characterization of the infecting parasites, it is difficult to relate the DCL disease caused by L. aethiopica to the opportunistic leishmaniasis seen in HIV-1+ subjects.

We agree with Dr. Arya and with the World Health Organization recommendations (13) that patients presenting with leishmaniasis should also be tested for HIV-1 infection. We know of no studies which have shown anergy in anti-HIV-1 antibody production in HIV+ subjects with leishmaniasis or which have shown a higher incidence of HIV-1 infection in DCL patients than in LCL patients. As such, it may not be necessary to perform sentinel polymerase chain reaction assays for determining HIV-1 infection status in place of standard anti-HIV-1 serological assays. In contrast, because serological assays have not proven to be useful for diagnosing active leishmaniasis, the sensitivity of DNA probe-based techniques (9) should be exploited in future assessments of patients for leishmaniasis. Dr. Arya’s suggestion of monitoring the specific immune status of HIV+ leishmaniasis patients by measuring reactivity to the antigen fractions we identified previously (8) is most interesting. While we have no experience to relate in regard to the responses of HIV+ leishmania-infected subjects, other studies using this approach to monitor the immune responses of HIV+ subjects to cytomegalovirus (CMV) have identified specific losses in immune reactivity by HIV+ CMV+ carriers to the dominant antigens recognized by healthy CMV carriers (6).

REFERENCES


