

Erythema Nodosum Leprosum and HIV Infection: A Therapeutic Experience¹

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ABSTRACT

The relationship between leprosy and HIV infection is not yet fully understood, as not much is known about the natural history of the co-infected patients. The matter has become more confusing because of conflicting reports. Type-1 lepra reactions and neuritis appear to be severe and more frequent among them. But erythema nodosum leprosum too is not as uncommon among these patients as it was once thought.

Management of these co-infected patients is often difficult for want of clear-cut guidelines on clinical care. We report here our experience of treating recurrent, severe erythema nodosum leprosum in a patient concurrently having leprosy and HIV infection. Early institution of antiretroviral therapy appears to provide an edge in improving the therapeutic outcome for him. It also suggests a direct and more complex interplay of HIV and *Mycobacterium leprae* infection.

RÉSUMÉ

La relation entre la lèpre et l'infection par le VIH n'est pas encore complètement comprise, comme peu de choses sont connues sur l'histoire des patients co-infectés. Le sujet est devenu d'autant plus confus que des rapports contradictoires ont été publiés. Les réactions lépreuses de type 1 et les névrites seraient plus sévères et fréquentes parmi les patients co-infectés. Mais l'érythème noueux lépreux n'est pas aussi rare parmi ces patients que ce qui avait été originellement considéré.

La prise en charge clinique de ces patients co-infectés est souvent difficile, car elle manque de recommandations claires pour le traitement. Nous rapportons ici notre expérience à traiter un érythème noueux lépreux récurrent et sévère chez un patient souffrant concomitamment de lèpre et d'infection par le VIH. La mise en œuvre rapide d'une thérapie anti-rétrovirus semble avoir joué un rôle pivot dans l'amélioration du résultat thérapeutique chez ce patient. Cela suggère une interaction directe et plus complexe entre les infections par *Mycobacterium leprae* et le VIH.

RESUMEN

La relación entre la lepra y la infección por el VIH no está completamente entendida, como tampoco se conoce mucho acerca de la historia natural de los pacientes co-infectados. El tema ha llegado a ser todavía más confuso debido a la publicación de reportes conflictivos. Las reacciones tipo-1 de la lepra y la neuritis parecen ser graves y muy frecuentes entre los pacientes co-infectados pero el eritema nodoso leproso no es tan raro como antes se creía.

El manejo de estos pacientes co-infectados a menudo es difícil debido a la ausencia de lineamientos claros sobre su tratamiento y cuidado clínico. Aquí, nosotros reportamos nuestra experiencia sobre el tratamiento recurrente de eritema nodoso leproso grave en un paciente con lepra co-infectado por el VIH. La administración temprana de la terapia anti-retroviral favoreció el resultado de la terapia general en el paciente. Se analiza el caso y se reconoce el interjuego directo y muy complejo entre el VIH y la infección por *M. leprae*.

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The relationship between leprosy and HIV infection remains obscure due to conflicting reports appearing over a period of time. By analogy with the development of active tuberculosis and other mycobacterial infections among HIV positive patients, an increased prevalence of leprosy was expected, particularly towards lepromatous spectrum, and possibly also the prevalence of erythema nodosum leprosum (ENL) reaction, in areas where both leprosy and HIV are endemic. Earlier literature is also replete with reports on increased frequency of Type-1 lepra (reversal) reactions, severe neuritis, poor therapeutic outcome and relapses among HIV infected leprosy patients^(5, 9, 23), without reports on ENL reaction. More recent data, however, show that HIV infection has no significant effect on epidemiology, clinical, histological, and immunological spectrum of leprosy⁽⁴⁾. Reports on ENL among HIV positive leprosy patients, too, have started to appear^(13, 14). Studies on granuloma formation and immune patterns in co-infected patients reveal no greater risk for development of multibacillary (MB) leprosy or ENL and, rather contrary to expectations, a satisfactory response to antileprosy treatment has been recorded⁽¹³⁾.

Due to lack of information on the natural history of co-infected patients and the absence of guidelines for the management of such cases, it is often a challenge to the ingenuity of the treating clinician. We report here our experience treating recurrent, severe ENL in a leprosy patient concurrently having HIV infection without HIV-related clinical disease.

Case Report. A 30-year-old male was hospitalized with recurrent episodes of multiple, erythematous, painful, widely spread cutaneous lesions of 4-month duration. Each episode was accompanied by fever, malaise, body aches, arthralgia, and ankle edema. Some of these lesions had also developed into necrotic crusted ulcers. Antibiotics and anti-inflammatory drugs would temporarily improve his condition. He also reported promiscuous sexual behavior. He was febrile (102°F). Dermatological examination showed diffuse infiltration, numerous, erythematous, tender papulo-nodular lesions involving the whole body except for palms, soles, and scalp. Some of them

showed central necrotic sloughing and crusting. Atrophic scars of previously healed lesions were also noted. His conjunctivae were congested. Hair, nails, and oropharynx were normal. He had no significant lymphadenopathy. Asymmetric, tender thickening of all peripheral nerve trunks along with corresponding hypoesthesia was noted over hands and feet. Slit-skin smear examination from 5 sites (World Health Organization, W.H.O.) showed 6+ BI. Ophthalmic, CNS, CVS, pulmonary and abdominal examination revealed no abnormality and there was no historical or clinical evidence of opportunistic infections. The erythrocyte sedimentation rate was 50 mm in first hour and other laboratory studies including complete blood counts, hepato-renal function tests, urinalysis, chest radiograph, VDRL and Treponema pallidum haemagglutination tests showed no abnormality. He was HIV positive by ACON rapid card chromatographic immunoassay (ACON Biotech Hangzhou Co. Ltd., China), Capillus direct latex agglutination assay (Trinity Biotech U.S.A., N.Y. 14702-1059) and Genedia HIV ELISA test (Greencross Life Sciences Corp., Korea). His CD4+ and CD8+ cell counts were 798 and 1541 cells/microl, respectively, using the Fluorescence Activated Cell Sorter counting system (Beckton Dickenson Immunocytometry Systems, California, U.S.A.), and the CD4 : CD8 ratio was 0.52 (Normal Ranges = 865 CD4+, 552 CD8+ cells/microl and CD4 : CD8 ratio 1.7)⁽¹⁶⁾. He did not consent for biopsy and could not afford the cost of viral load studies.

Clinical progress. The clinical diagnosis was lepromatous leprosy with recurrent, severe ENL and HIV infection, and the patient was initially given W.H.O. MB multi-drug therapy (M.D.T.) along with prednisolone 60 mg/d, ibuprofen 400 mg t.i.d. and colchicine 0.5 mg b.i.d. Over the next 2 weeks, healing of lesions and symptomatic improvement occurred without recurrences. Subsequently, when the dose of prednisolone was tapered off to 40 mg/d, fresh ENL lesions, ulnar nerve neuritis (without sensory motor deterioration) and systemic symptoms reappeared. He did not improve in spite of increasing the dose of prednisolone to 80 mg/d. At this juncture colchicine was stopped and thalidomide 100

mg b.i.d. was added with the plan to taper off prednisolone once the remission was achieved. The ENL and nerve tenderness decreased within a week and tapering of prednisolone was started. All the while, the patient continued to receive MB-M.D.T., thalidomide 100 mg b.i.d. and other supportive treatment.

After 3 weeks of thalidomide therapy, while still on prednisolone (30 mg/d), he developed dryness of mucosae and a generalized, pruritic, erythematous, diffuse (discrete at places) maculo-papular rash. Initial withdrawal of MB-M.D.T. did not improve the rash. The rash, however, subsided after stopping thalidomide. The dose of prednisolone was increased to 60 mg/day immediately upon recurrence of ENL. The case was reviewed and in view of apparent cushingoid features, as well as poor control of ENL, it was decided to add anti-retroviral treatment (ART) comprising stavudine 30 mg, lamivudine 150 mg and nevirapine 200 mg, all in twice daily doses (the only available and affordable regimen), to the already existing regimen of MB-MDT and oral prednisolone.

His general condition improved, recurrences of ENL stopped and dose of prednisolone could be reduced to 30 mg/d in next 10 days when the patient left the hospital on his own. On a subsequent visit after a month, he was free of ENL, continuing MB-M.D.T. and ART but had stopped prednisolone. However, he was lost to further follow-up.

DISCUSSION

As yet there is conflicting and inadequate information on the interactions of HIV and leprosy co-infection. HIV infection was thought to decrease the risk of ENL until recently when reports of ENL among co-infected patients started to appear albeit infrequently. This is contrary to increased frequency of Type-1 lepra reactions and neuritis in co-infected individuals. Nery, *et al.* (13) observed no enhanced risk of ENL among their patients. In contrast, Gebre, *et al.* (6) recorded a definite higher risk (relative risk: 5.2; 95% CI 1.7–15.9) of ENL reactions in a prospective study comprising 22 HIV positive leprosy patients. Our patient had severe, recurrent ENL reaction with necrotic lesions. Considering that lep-

rosy has a much longer incubation period the HIV infection in this patient appears a subsequent development. Possibly, like other intercurrent infections, it acted as a trigger for ENL reaction. The ENL also appears to be severe and recurrent in this group of patients similar to Type-1 lepra reactions.

Among HIV seropositive patients neuritis always occurs in association with skin manifestations suggesting that nerve dysfunction is due to Type-1 lepra reaction. HIV is neurotropic and may cause necrotizing vasculitis of the nerves (15). Possibly the interaction of neurotropicity of both *Mycobacterium leprae* and HIV may result in neuropathy that is severe and unresponsive to steroid therapy (5). Vreeburg, *et al.* (24) also noted that though neuritis is equally common in both HIV positive and HIV negative patients, the therapeutic outcome with steroids was poorer in the HIV positive group. Similarly, HIV-induced vasculopathy might aggravate immune complex mediated vasculitis/paniculitis of ENL that responds poorly to steroid therapy as has been observed in our patient.

Thalidomide, 100–400 mg/d, is currently the recommended drug for recurrent, moderate to severe ENL reactions. Its use has been associated with normalizing effects on TNF, IFN, and helper-suppressor T-cell ratio (20), decreases in dermal infiltration of polymorphonuclear leukocytes and T-cells, and down regulation of the expression of ICAM-1 and MHC-1 antigens on epidermal keratinocytes (20). Its exact mechanism of action in ENL, however, remains unclear. Recently it has also been reported to produce an anti-retroviral effect without any negative effect on immunocompetence (21), possibly through inhibition of TNF production and by blocking TNF stimulated HIV replication (18). Due to these properties it appears to be the drug of choice for treating ENL among HIV infected leprosy patients. However, in view of other reports of increased HIV viral counts caused by this drug it should be used with caution for these patients until further studies are available (17). Apart from its well known teratogenic effects other common adverse reactions like peripheral neuropathy, somnolence and constipation limit its routine use. Hypersensitivity skin rash is uncommon and usually

appears 2 to 10 days after treatment and subsides after its withdrawal. Thalidomide was effective in our patient also. However, he developed a generalized cutaneous rash in spite of simultaneously receiving 30 mg/d prednisolone. Curiously these patients seem to tolerate the drug poorly and this phenomenon has also been previously correlated with lower numbers of pre-existing CD4+ cells (21).

The predominance of CD8+ cells in lepromatous lesions as compared to predominance of CD4+ cells in the typical granulomatous response seen in tuberculoid lesions (13) and the presence of ICAM 1, HLA DR, TNF, IFN at lesional sites suggests no difference in immune response in both HIV positive and negative leprosy patients (19, 20). The tissue cellular immunity (CMI) against *M. leprae* appears well preserved irrespective of low CD4 + cell counts in the peripheral blood of HIV infected patients or the stage of HIV infection (13). The exact pathologic mechanism of ENL among these co-infected patients is, however, not fully understood. There is indirect evidence consistent with increased CD4+ lymphocytes activity in ENL (11, 23). The relative lack of ENL (immune complex mediated) reaction as compared to reversal (cell mediated) reactions among HIV positive lepromatous cases and no therapeutic effect of thalidomide in reversal reactions, that acts through suppression of helper T-cells activity (12), suggests some kind of involvement of CD4+ lymphocytes in ENL. Furthermore, the loss of lesional CD4+ cell function may not be complete as is postulated in tuberculoid leprosy lesions in HIV infected patients (19). It is also known that CD4+ lymphocytes become depleted as the HIV disease progresses and cytotoxic CD8+ lymphocytes, including various subsets, increase significantly (6). Findings such as these may eventually help to explain the occurrences of ENL among these patients. Furthermore, in the early stages of HIV infection some degree of immunocompetence is retained and the occurrence of ENL in early HIV infection may not be unusual as has been the case in our patient.

In our patient, despite an early HIV infection and near normal CD4+/CD8+ counts (the low CD4+ : CD8+ ratio is apparently an artifact of high CD8+ counts), the severe

ENL reaction showed poor control even with higher doses of corticosteroids. Addition of ART not only improved the therapeutic response to lower doses of steroids but also helped in their complete withdrawal subsequently. We make no attempt to speculate about the mechanisms underlying our observation. However, clinicians must bear in mind the possibility of precipitating Type-1 lepra reactions during ART/HAART due to immune reconstitution (8).

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