Severe vasculonecrotic *erythema nodosum leprosum* following thalidomide withdrawal without tapering doses: do we have something unusual?

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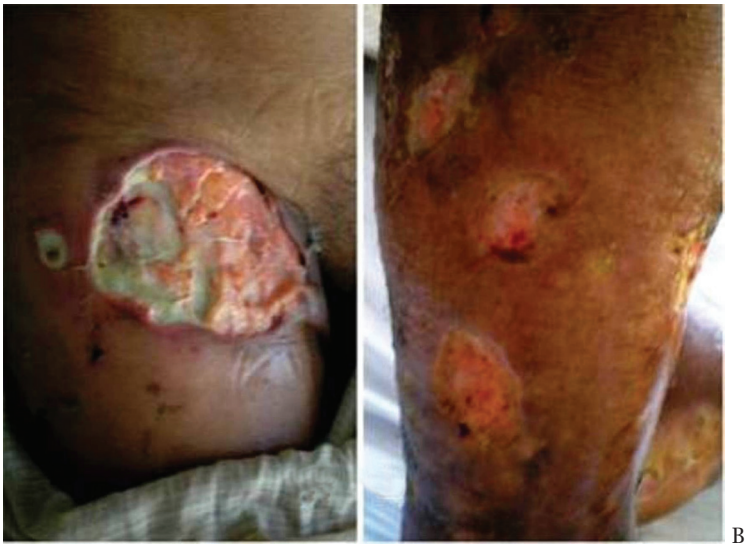
Thalidomide (300-400 mg/day in divided doses) is highly effective in chronic, recurrent or severe *erythema nodosum leprosum* (ENL). Therapeutic response is observed usually in ≥ 2 weeks after which it is tapered in 50 mg decrements every 2-4 weeks to a lowest effective dose to maintain remission.[1] We described here a case of severe ENL with vasculonecrotic ulcerations (we have used the term 'vasculonecrotic ENL' here for such a phenomenon) which we feel was precipitated by sudden withdrawal of thalidomide without tapering doses.

This 65-year-old-HIV-negative-patient of ENL was taking multidrug therapy (WHO MDT-MB) and prednisone in tapering doses for six months. He presented with fever, anemia, pedal edema, and multiple, erythematous papulo-nodulo-pustular ENL. He had stopped all the drugs on his own a month back after initial improvement. Clinically he had tender ulnar, lateral popliteal and posterior tibial nerves, glove and stocking anesthesia, madarosis, infiltrated earlobes, and 6+ BI. He had leukocytosis (24,000/mm^3), neutrophilia (86%), and macrocytic anemia (hemoglobin 4.6 g%). Serum biochemistry, G6PD estimation, blood and urine cultures, chest x-ray and urinalysis were normal. Prednisone (60 mg/day), clofazimine (100 mg three times/day), rifampicin 600 mg once a month (of MDT-MB) and other supportive treatment were re-prescribed. Dapsone was withheld in view of severe anemia. Thalidomide 300 mg was added after two weeks in view of inadequate control and prednisone was tapered to 40 mg/day. Two months later he was hospitalized with multiple painful large ulcers of varied size covered with necrotic slough over the extremities (Figure 1) and generalized multiple ENL lesions many with black eschars/crusts or pustules/blisters. He was sick, febrile (temperature 100ºF), had leg edema (extending up to lower abdomen), anemia and ulnar nerve neuritis (lateral popliteal and posterior tibial nerves were not palpable due to edema). He had stopped thalidomide for over a month due to its non-availability while continued taking the other drugs. Except for low hemoglobin (4 g%), leucocytosis (25,000/mm^3) and neutrophilia (84%), other lab investigations (includ-

Figure 1: Multiple, 1-10 cm sized, regular shaped, round/oval, deep and severe ulcers with necrotic slough, seen over **(A)** right inguinal area, and **(B)** leg. Similar ulcers were also present scattered over other body sites.



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ing wound-swab culture, serum biochemistry, and urinalysis) and systemic examination were normal. Histology revealed superficial and deep necrotizing vasculitis, features of lobular panniculitis/ENL and dermal necrosis, and numerous fragmented acid-fast bacilli on special staining. Treatment restarted with prednisone (60 mg/day), clofazimine (100 mg three times/day), rifampicin (600 mg once a month), thalidomide (100 mg three times/day) and other supportive measures (including blood transfusion for severe anemia). Wound care comprised surgical debridement of necrotic slough and daily antiseptic dressings. The lesions/ulcers showed involution in four weeks. He was discharged on prednisone 40 mg/day, thalidomide, clofazimine and rifampicin (in earlier doses). A month later repeat lab investigations were essentially normal and most of the ulcers had healed or showed healthy granulation tissue/healing. Thalidomide was tapered off over the next two weeks. Other drugs and prednisone, tapered to 30 mg on alternated days, were continued without recurrences during eight-month of follow-up.

DISCUSSION

The occurrence of ENL when prednisone is being tapered off is a well-known phenomenon and was observed in our patient as not so severe initial episode. Most of the clinicopathological features of vasculonecrotic ENL[2,3] in our patient developed subsequently and apparently after stopping thalidomide without tapering doses while being on prednisone/clofazimine and resolved completely in four weeks after reinstitution of thalidomide. Several studies have recorded high relapse rates and flare-ups in patients of thalidomide treated for aphthous ulcers (AU), Behçet's syndrome (BS), discoid lupus erythematosus (DLE), and even ENL[3,4] upon its discontinuation. In a large multicenter, double-blind crossover study > 50% AU patients using thalidomide had complete resolution but relapsed on switching over to placebo.[5] Hamza[6] observed complete resolution in a patient of BS and palmoplantar pustulosis treated with thalidomide 200 mg/day for two months followed by 100 mg/day for 12 months but discontinuation was associated with disease flare-ups which were controlled with restarting the drug. Similarly, 71% DLE patients relapsed after marked regression when thalidomide was stopped.[7] Welsh *et al.*[4] also treated a patient of ENL who had relapsed when thalidomide dose was decreased to 50 mg/day. Although the exact mechanism of these relapses remains un-elucidated, they suggest that thalidomide has only a suppressive effect. The beneficial effect of thalidomide in ENL has been attributed to its ability to inhibit inflammatory cytokines TNF-α, IFN-γ, vascular endothelial-derived growth factor (VEGF), and basic fibroblast growth factor (bFGF) in RNA processing.[8] Additionally, it effectively controls various clinical manifestations of ENL perhaps due to normalizing effects on CD4/CD8 ratio, decrease dermal infiltration of polymorphonuclear leukocytes and T-cells, and down regulation of ICAM-1 and MHC class-I antigens expression on keratinocytes.[8] Premature withdrawal of thalidomide without tapering doses perhaps causes a sudden spurt of these inflammatory cytokines, reversal in CD4/CD8 ratio, and neutrophils-lymphocytes chemotaxis as a rebound phenomenon. In other words, there is catastrophic reversal of thalidomide induced suppression of inflammatory process manifesting clinically in severe vasculonecrotic ENL. However, the validation of such hypotheses will depend on further and more comprehensive studies.

The adequate characterization of such a phenomenon and to anticipate possibility of its occurrence in ENL cases is important particularly in view of thalidomide therapy now being used frequently. Due to the side effects of thalidomide, its irregular availability in many countries, and now the possibility of vasculonecrotic ENL, its indiscriminate use needs to be curtailed. Clofazimine and pentoxiphylline can be one of the options in such situations.[4] Encouraging results have also been reported with addition of pulse dexamethasone and azathioprine in patients not responding to steroids alone.[9] Designation of such a phenomenon as Lucio's phenomenon should also be avoided where corticosteroids or thalidomide are of controversial or no therapeutic value while these will dramatically resolve vasculonecrotic ENL. The nomenclature 'vasculonecrotic ENL' for this form of severe ENL seems more appropriate. Nevertheless, our points of view are open to debate.

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