Treatment of refractory ulcerative necrobiosis lipoidica diabeticorum with oral thalidomide

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ABSTRACT

Ulcerative necrobiosis lipoidica (NL) in diabetic patients is a rare, painful condition. It is a difficult-to-treat condition, impairing quality of life of patients. Although various drugs have been tried, none of them is consistently effective. Biologics in the form of TNF-alpha inhibitors show promising results in the treatment. But because of their high cost we chose thalidomide, which also has TNF-alpha inhibiting properties to successfully treat a long-standing case of ulcerative NL, which was refractory to various treatment modalities.

Key words: Diabetes, necrobiosis lipoidica, thalidomide, ulcerative necrobiosis lipoidica

INTRODUCTION

Necrobiosis lipoidica (NL) affects 0.3%-1.2% of diabetic patient.[1] It is more common in female with female-to-male ratio of 3:1. The etiopathogenesis is still unclear. Not all the cases of necrobiosis are associated with diabetes; hence the terminology necrobiosis lipoidica diabeticorum has been abandoned. Ulceration occurs in about 15% patients with NL,[2] usually following minor trauma. The ulcers run a refractory course and usually are resistant to treatment. The ulcers in NL are quite painful leading to impaired quality of life of these patients. We present a case of ulcerative NL, which failed to respond to traditional treatment modalities but responded quickly to thalidomide.

CASE REPORT

A 58-year-old woman with 15 years history of insulin-dependent diabetes presented with nonhealing ulcers on her shin since 5 years. Five years ago she noticed redness and thickening of skin over her left shin. It was associated with mild itching. Four months later, she noticed a pinhead sized lesion over the red area, which enlarged and ulcerated. Three similar ulcers [Figure 1a and b] appeared on the shin over the next one month. The ulcers were non healing and extremely painful but not associated with any constitutional symptoms. Local wound care, topical corticosteroids, topical calcineurin inhibitors were tried along with oral antibiotics, dapsone, pentoxyphylline, and analgesics, without much relief. She continued on insulin and oral antidiabetics with good glycemic control. On examination she had multiple discrete tender ulcers over a waxy, erythematous, atrophic plaque on the anterior aspect of her left leg, variying in size from 3 × 2 cm to 1 × 1 cm. The borders of ulcer were undermined, base was indurated, and floor was covered with necrotic debris. Her general and systemic examination results were within normal limits. On investigation her hemogram, renal and liver function tests, and venous Doppler test results were normal. Fasting blood sugar was 120 mg/dL. Pus culture grew *Staphylococcus aureus* sensitive to linezolid, amoxycillin and clavulanic acid, and tazobactam–piperacillin. Nerve conduction studies did not reveal any abnormality. Skin biopsy from the edge of the ulcer revealed a hyperplastic, sclerotic epidermis and a dense superficial and deep dermal infiltrate of lymphocyte and plasma cells concentrated around the blood vessels and sweat glands [Figure 2 a-c]. There were

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several granulomas arranged in a horizontal manner in mid and lower dermis. The upper dermis had numerous eosinophils scattered interstitially. No significant stasis changes were seen. The appearences were consistent with ulcerated NL. We started the patient on oral linezolid 600 mg twice daily for 7 days and chloroquine 250 mg once daily for 4 weeks along with local dressings. There was no change in ulcer size and pain was persistent. Topical human recombinant epidermal growth factor, oral clopidrogel and aspirin were added to the above regime and continued for another 2 months, with no improvement. Oral thalidomide 100 mg was started, with local wound dressings. Pain reduced dramatically within 2 weeks and the ulcers healed completely after 4 weeks [Figures 3a and b]. Thalidomide was reduced to 100 mg once daily and continued for another 6 weeks. There was no relapse over a follow up period of 6 months.

DISCUSSION

Ulcerated NL runs a refractory course. There is no consistently effective therapy, and lack of uniform guidelines make treatment more challenging. Many theories were put forward to explain the pathogenesis of NL: Diabetic microangiopathy due to deposition of glycoprotein in the blood vessel wall could lead to impaired blood supply to the skin;[2] greater cross-linking of the collagen fibres in NL could lead to thickening of the basement membrane zone;[3] immune complex deposition in the dermal blood vessel walls could lead to vasculitis;[4] Recently a role of disturbance in glucose transport by fibroblasts has been postulated. Glut-1 is the human erythrocyte glucose transporter, which mediates facilitative transport of glucose across epithelial and endothelial barrier tissues. This protein was expressed in the sclerotic collagen of NL patients, indicating insulin resistance in these tissues.[5]

Several drugs have been tried in treatment of NL.[4] These include cutaneous blood flow enhancers, such as dypyridamol, clopidrogel, aspirin, pentoxyphylline; topical and intralesional steroids, and topical calcineurin inhibitors; wound healing enhancers such as epidermal growth factors, platelet-derived growth factors, collagen gel, hyperbaric oxygen; surgery and pulse dye laser; and immune modulators such as antimalarials, cyclosporine, and biologics.

Our patient was treated with various drugs but failed to respond. In several case studies, TNF-alpha inhibitors such as etanercept, adalimumab, and infliximab[6] were shown to improve ulcerated NLD. Our patient refused these drugs because of adverse effects and cost.

Kukareja and Peterson have reported the usefulness of thalidomide in refractory NL.[7] Thalidomide has TNF-alpha-inhibiting properties.[8] TNF-alpha has been found in high concentrations in the sera and skin of patients with NL[9] Thalidomide acts as an anti-inflammatory agent by suppressing TNF-alpha via degradation of its messenger RNA and by decreasing the ratio of helper T cells to suppressor T cells.[10] Our patient tolerated the drug well with slight sedation as the only complaint. The ulcer healed rapidly and thalidomide was withdrawn over 12 weeks, with no relapse till date.

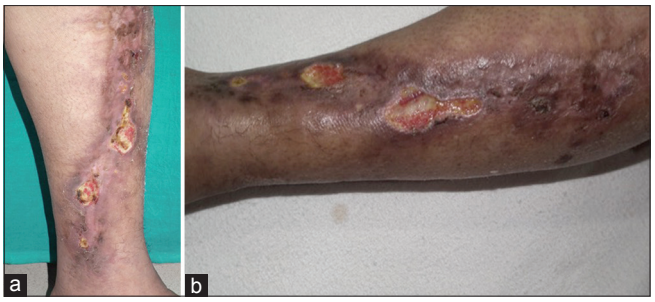

Figure 1: (a and b) Multiple non healing ulcers over the shin

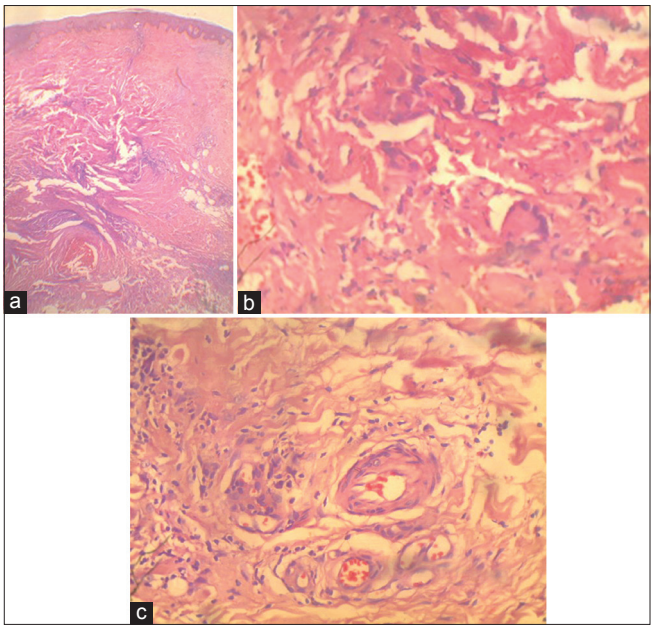

Figure 2: (a-c) Hyperplastic, sclerotic epidermis and a dense superficial and deep dermal infiltrate of lymphocyte and plasma cells concentrated around the blood vessels and sweat glands with several granulomas arranged in a horizontal manner in mid and lower dermis. (H and E, ×10, ×40, ×40)

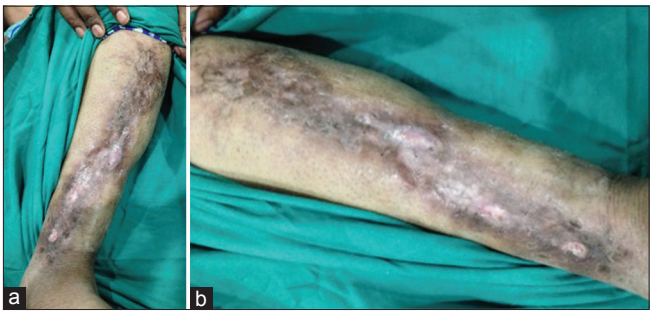

Figure 3: (a and b) Complete healing and softening of skin after treatment with thalidomide

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Conflicts of interest

There are no conflicts of interest.

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