Letter to the Editor

Peripheral Edema in Lepromatous Leprosy- Could Thalidomide be the Culprit

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Sir,

Thalidomide was first marketed by Chemie Grunenthal, a German company, under the brand name 'contergan' in 1956 as a sedative and antiemetic in pregnancy; however, it was withdrawn in 1961 owing to its disastrous teratogenic effects. Sheskin used thalidomide for the first time in refractory erythema nodosum leprosum and since then it has widely been used in treating reactional episodes and is highly effective in the management of erythema nodosum leprosum (ENL) (Shanbhag et al 2006). We report a case of lepromatous leprosy with bullous ENL on treatment with thalidomide leading to severe limb and facial edema.

A 60 year old male farmer, known case of LL Hansen's with recurrent ENL on MB-MDT for past 6 months and methyl prednisolone 20 mg/day for the past one month, presented with bilateral pedal edema and painful bullae leading to ulcer formation over the lower extremities of four days duration. There was pitting edema over the ankles and also icthyosis of bilateral lower limbs. Thalidomide was initiated in a dose of 100 mg twice daily while continuing the MB-MDT and steroids, however, fresh bullae and spontaneous ulcers continued to appear for a week following which the dose of thalidomide was then increased to 300 mg/day. This led to appearance of facial puffiness and worsening of pedal edema which now had progressed to the thighs along with hypersomnolence. All the routine hematological and biochemical parameters were normal except for serum albumin which was marginally low. Renal, cardiac and hepatic causes for edema were also excluded. With this high dose of thalidomide, the ulcerative skin lesions subsided but the facial and peripheral edema persisted. The dose of thalidomide was maintained at 300 mg/day for about 6 weeks and by the end of 7 weeks when thalidomide was stopped, facial puffiness and pedal edema gradually started to reduce.

Thalidomide chemically is alpha-N-phthalimidoglutarimide. It is orally effective and is distributed throughout most organs. The exact mechanism of action of thalidomide has not yet been clearly delineated; however, it is believed to be related to its anti-inflammatory, immunomodulatory and anti-angiogenic properties (Stirling 1988, Radomski et al 2001, Shanbhag et al 2006). Its anti-inflammatory properties include the inhibition of chemotaxis of both lymphocytes and neutrophils. In terms of immunomodulatory properties, thalidomide decreases the levels of the cytokines, TNF-α and IFN-γ. In ENL, TNF-α and IFN-γ are usually elevated and clinical improvement of patients treated with thalidomide corresponds with the reduction of these two cytokines. Also, thalidomide has been found

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to decrease the helper T- cell to suppressor T- cell ratio (Stirling 1988, Radomski et al 2001, Shanbhag et al 2006). This observation also has implications on the treatment of erythema nodosum leprosum (ENL) because helper T-cells are usually elevated in the skin lesions of these patients during acute episodes(Parikh et al 1985). Humoral immunity is also affected as evidenced by enhanced production of IL-4 and IL-5 with simultaneous inhibition of interferon-gamma. Though the most troublesome side effect of thalidomide is teratogenesis, others mentioned in the literature include parasthesia, dryness of skin and mouth, morbilliform eruptions, persistent edema of face and extremities, urticaria, nausea, constipation, increased sleep and appetite and hypothyroidism (Shanbhag et al 2006).

Parikh et al (1986) in their systematic review of 94 cases, observed that edema was the commonest side effect in patients on thalidomide and was dose related. When thalidomide was given in a dose >100 mg/day, edema was observed. Grover et al (2002) noted ankle edema in 70% of their patients on thalidomide for the treatment of multiple myeloma which is in variance with earlier studies. In 50% of these, it occurred at a dose of 200 mg/day or greater. This study also postulates Indian predisposition to edema due to stasis of blood in extremities while on thalidomide (Grover et al 2002).

The exact mechanism of thalidomide induced edema is largely unknown. Mild peripheral edema occurs in about 15% of patients while on thalidomide, whereas severe edema that limits function and does not respond to therapy is less common, occurring in upto 3% of patients (Grover et al 2002, Seldin et al 2003). In our patient, pedal edema increased within a week of starting thalidomide and at the same time patient developed facial edema also. The severity of edema in our patient was disproportionate to the ENL and the serum albumin levels which were marginally low and it was unresponsive to diuretic therapy. According to Grover et al (2002) peripheral edema usually appeared 2 weeks following initiation of thalidomide in their study and multiple episodes of pitting peripheral edema unresponsive to diuretic therapy were noted which, however, were transient and did not warrant the discontinuation or reduction in the dose of thalidomide. The authors emphasize that all the side effects such as peripheral edema and sedation reduce once tolerance to the drug develops.

Thus to conclude, even though mild edema may be present in a reactional episode, physicians and dermatologists should be aware of this particular side effect of peripheral and facial edema which may occur following the use of thalidomide in high doses. Also this effect is transient and reduces with the development of drug tolerance and usually does not require discontinuation of the drug.

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