Indian J Lepr 2009, 81 : 199-203 http://www.ijl.org.in

Case Report

Severe form of type 2 reaction in patients of Hansen's disease after withdrawal of thalidomide : case reports

R Rattan, V Shanker, GR Tegta, GK Verma

Thalidomide, a racemic glutamic acid analogue, was first developed in 1954 and subsequently marketed in Europe, Australia and Canada as a sedative and anti-emetic. It was approved by the Food and Drug Administration (FDA) in the USA in 1998 for the treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and suppression of the cutaneous manifestations of ENL recurrences. It is a good choice for management in patients who are dependent on corticosteroids. Common side effects of thalidomide are teratogenicity, peripheral neuropathy, sedation and constipation. We report 4 cases of Hansen's disease with recurrent ENL who were adequately managed on thalidomide. On sudden withdrawal of thalidomide, they relapsed with severe type 2 reaction including necrotic ENL.

Key words : Type 2 reaction, Thalidomide, Hansen's disease

Introduction

Type 2 reaction is also known as lepromatous lepra reaction and erythema nodosum leprosum (ENL) (Pfalzgraff and Ramu 1994). It is characterised by crops of erythematous, painful, tender, papulonodular, evanescent lesions along with any or all of the systemic features like fever, malaise, neuritis, myalgia, arthalgia, arthritis, deep bone pain, iridocyclitis, epididymo-orchitis, proteinuria and tender lymphadenopathy. The term ENL is preferably used only for skin lesions whereas other features such as neuritis, iridocyclitis, orchitis, etc. are considered manifestations of type 2 reaction (Jopling and McDougall 1996).

Risk factors for developing type 2 reaction are lepromatous leprosy (LL) and borderline lepromatous leprosy (BL), bacteriological index > 4+ and age < 35 years. LL patients are 8·4 times more likely to develop ENL than those with BL disease (Walker et al 2004). ENL is classified as single acute episode in which complete response to steroid therapy is there, recurrent acute episodes in which patient is symptom free without any maintenance treatment in between the episodes and chronic ENL in which corticosteroid treatment is needed for more than 6 months (Pocaterra et al 2006).

Thalidomide was first developed in 1954 in West Germany (Wu et al 2005) and subsequently used in Europe, Australia and Canada as a sedative and anti-emetic. It was withdrawn in 1961 because of its teratogenicity. Sheskin, in 1965, first reported the rapid and dramatic subsidence of the clinical

R Rattan, MBBS, MD (Student)
V Shanker, MD, Professor and Head
GR Tegta, MD, Assistant Professor
GK Verma, MD, Registrar
Department of Dermatology, Venereology and Leprology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India
Correspondence to : V Shanker **Email :** shankervinay@hotmail.com

manifestations of type 2 reaction in patients of Hansen's disease in a small group of patients from Israel. In 1998, thalidomide was approved by the US Food and Drug Administration (FDA) for ENL. It is also used in many currently unapproved dermatological conditions that are refractory to other medications (Wu et al 2005). However, the dispensing of thalidomide is highly restricted through the system for thalidomide education and prescribing safety (STEPS) programme, implemented to reduce the potential for foetal toxicity.

Case reports

Case 1

A 54 years old male patient was diagnosed as a case of LL Hansen's disease with type I deformity of both hands and feet. His initial bacterial index (BI) was 6+ and morphological index (MI) was 10-15%. During the course of MDT-MB, patient suffered with recurrent episodes of type 2 reaction. Initially, the episodes were managed with tapering doses of corticosteroids as per World Health Organization (WHO) regimen but was later started on 100 mg of thalidomide thrice daily in order to avoid repeated use of systemic corticosteroids. Thalidomide was gradually tapered to 100 mg per day and the patient was well maintained on thalidomide for 6 months. Subsequently, the drug was stopped abruptly because of unavailability. After 3 weeks, the patient relapsed with severe type 2 reaction with necrotic ENL lesions (Figure 1).

Case 2

Another 37 years old female patient, a treated case of LL Hansen's disease with type 1 deformity of both hands and feet presented with chronic type 2 reaction. Her pre- treatment BI was 6+ and MI was 10-15%. Initially, she was given tapering doses of steroids and later due to inability to stop corticosteroids, she was started on 100 mg of thalidomide thrice a day. The patient responded well to thalidomide and the drug was gradually tapered to 100 mg per day. She was maintained on thalidomide for 16 months and was free of type 2 reaction during this period. Thalidomide was stopped suddenly and after 10 days, she presented with necrotic ENL (Figure 2a and 2b).

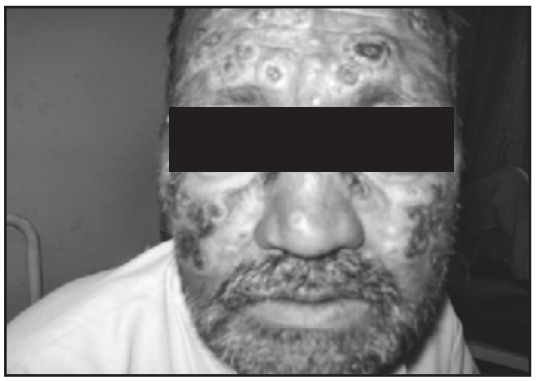


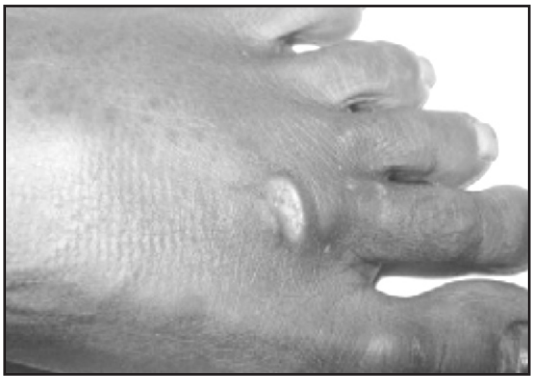
Figure 1 : Necrotic papulonodular ENL lesions over the face.

Case 3

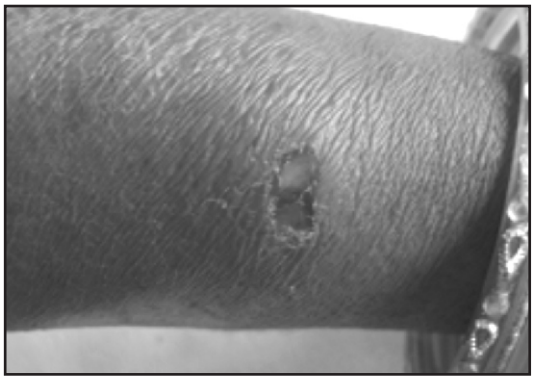
A 32 years male patient was treated with MDT-MB as a case of LL Hansen's disease with type 1 deformity of both hands and feet. At presentation, his BI was 6+ and MI was zero. After completion of MDT, the patient started getting recurrent episodes of type 2 reaction and was started on WHO regimen of systemic corticosteroids along with 300 mg of thalidomide in three divided doses and tapered gradually to 100 mg daily. He was on thalidomide for 10 months and then his thalidomide was stopped. After 4 weeks, the patient relapsed with ENL lesions and epididymo-orchitis along with other features of type 2 reaction. Ultrasonography confirmed right epididymo-orchitis (Figure 3).

Case 4

A 24 years old male patient, diagnosed as a case of LL Hansen's disease with type 1 deformity of both hands and feet with a BI of 6+ and MI 70-80%, was started on MDT-MB. During the course of MDT, he started having recurrent episodes of type 2 reaction and was started on thalidomide 300 mg per day which was gradually tapered to 100 mg per day over a period of 12 months. Then, thalidomide was stopped and after 4 weeks



2a



2b

Figure 2a and 2b : Necrotic ENL lesions over the extremities (dorsum of foot and forearm).

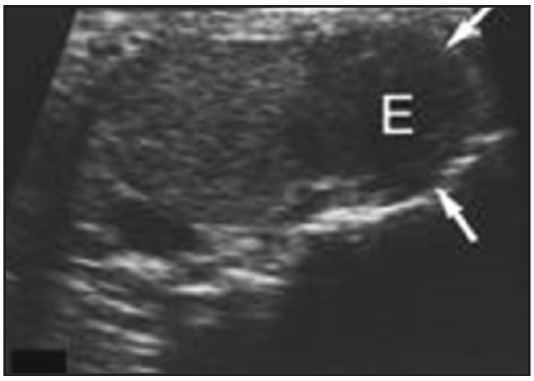


Figure 3: USG suggestive of epididymo-orchitis.

patient presented with distressing myalgias, arthralgias, ENL lesions and epididymo-orchitis. Table 1 shows the clinical details of these four patients.

Discussion

The principle event in type 2 reaction is antigen-antibody complex formation and their deposition in tissues, lymphatics and blood vessels leading to complement activation and development of local inflammation. As a result, there is tissue oedema and necrosis of blood vessels. ENL lesions show an intense perivascular infiltrate of neutrophils throughout the dermis and in the subcutis (Pfalzgraff and Ramu 1994). There is T-lymphocyte and macrophage activation and increased expression of mRNA for tumour necrosis factor- (TNF-) and interleukin-12 (IL-12) in the skin (Moraes et al 1999). High levels of circulating TNF- have been found in the serum of some individuals with ENL (Bhattacharya et al 1993).

Different drugs used for management of type 2 reaction are - corticosteroids, thalidomide, clofazimine, pentoxifylline, aspirin, indomethacin, cyclosporine, methotrexate, azathioprine, zafirlukast, infliximab, colchicine, chloroquine and zinc (Walker et al 2004). The drugs are chosen according to the severity of reaction. Commonly, an acute episode is managed with tapering doses of corticosteroids but for recurrent and chronic ENL, a steroid sparing agent is needed to avoid the side effects of steroids.

Although, thalidomide is an FDA approved drug for management of type 2 reaction, it is not that commonly used in our set up because it is not easily available over the counter and is expensive. It appears that thalidomide may have several modes of action which are as follows:

i. Sedative

ii. Immunomodulatory-Inhibition of phagocytosis by neutrophils

Inhibition of chemotaxis of monocytes and leucocytes

Decrease in the CD4 /CD8 ratio

Table 1 : Clinical profile of patients suffering from LL

S.No.	(Yrs)/ Sex	Spectrum	BI/MI	Reaction	Thalidomide	Therapy on thalidomide	Stopped in	Reaction relapse after thalidomide withdrawal	Relapse of reaction
Case 1	54/M	LL	6+/ 10-15%	Recurrent	Controlled on 300 mg and tapered	6 months	Nov 08	3 weeks	Necrotic ENL
Case 2	37/F	LL	6+/ 10-15%	Chronic	Controlled on 300 mg and tapered	16 months	Nov 08	10 days	Necrotic ENL
Case 3	32/M	LL	6+/0 10-15%	Recurrent	Controlled on 300 mg and tapered	10 months	Nov 08	4 weeks	Epididymo-orchitis
Case 4	24/M	LL	6+/ 70-80%	Recurrent	Controlled on 300 mg and tapered	12 months	Nov 08	4 weeks	Epididymo-orchitis and severe myalgias and arthralgias

Inhibition of TNF- , IL-8, IL-12

Enhancement of IL-2, IL-4, IL-5

Downregulation of expression of MHC-II antigens and cellular adhesion molecules and inhibition of cytokine-induced NF- B gene expression

iii. Others- stabilization of lysosomal membrane (Wu et al 2005).

In type 2 reaction, the mechanisms of action of thalidomide implicated are immunomodolatory, anti-inflammatory and stabilization of lysosomal membrane. Thalidomide's beneficial action in treating ENL is anti-inflammatory by decreasing levels of pro-inflammatory cytokine TNF- and reduction in plasma soluble IL-2 receptor, a marker of inflammation and reduction in the numbers of circulating CD4+ lymphocytes (Shannon et al 1992).

In our patients, who were well controlled on thalidomide, the patients had to stop the drug abruptly, as our stock of thalidomide had finished and we could not get a new one (in our centre, we get it through Government supply). These patients ranging with in a period of 10 days to 4 weeks presented with severe type 2 reaction (Table 1). In the literature, it has been mentioned that patients of recurrent apthous stomatitis (Revuz et al 1990), muco-cutaneous lesions of Behcet's disease (Hamuryudan et al 1998) and oral lichen planus (Camisa and Popovsky 2000) who were managed well with thalidomide; recurrence was reported after withdrawal of the drug.

What could be the possible cause of severe type 2 reaction in these patients on withdrawal of thalidomide? Was it a rebound effect on withdrawal of anti-inflammatory and immuno-modulatory action of thalidomide or was it due to polymorphism in TNF- gene (Manandhar et al 1999) in these patients which is a risk for LL and ENL?

Conclusion

In our opinion, our patients developed severe form of type 2 reaction because of possible increased TNF- levels and increased levels of IL -8 and IL-12 (pro inflammatory cytokines) along with decrease in levels of IL-2, IL-4, IL-5, INF- levels (anti- inflammatory cytokines) and instability of lysosomal membrane on abrupt withdrawal of thalidomide.

Due to lack of facilities at our centre, we do not have confirmatory evidence of these events happening in these patients and the subject

remains open for further research. But, we conclude that thalidomide should not be stopped abruptly in patients of Hansen's disease with type 2 reaction and should be maintained on lower doses for a longer period. Moreover, if the patient is dependent only on the Government supply, it should rather be started only if there is sufficient amount in the stock. Also, a lower dose formulation should be available.

References

1. Bhattacharya SN, Chattopadhaya D and Saha K (1993). Tumor necrosis factor: status in reactions in leprosy before and after treatment. *Int J Dermatol*. **32**: 436- 439.
2. Camisa C and Popovsky JL (2000). Effective treatment of oral erosive lichen planus with thalidomide. *Arch Dermatol*.**136**: 1442-1443.
3. Jopling WH and McDougall AC (1996). Leprosy reactions (reactional states). In : Handbook of Leprosy, 5th edn, CBS Publishers and Distributors, India, pp82-92.
4. Hamuryudan V, Mat C, Saip S et al (1998). Thalidomide in the treatment of the muco-cutaneous lesinons of the Bechet Syndrome. A randomized, double-blind, placebo controlled trial. *Ann Intern Med*. **128**: 443-450.
5. Manandhar R, LeMaster JW and Roche PW (1999). Risk factors for erythema nodosum leprosum. *Int J Lepr Other Mycobact Dis* . **67** : 270-278.
6. Moraes MO, Sarno EN, Almeida AS et al (1999). Cytokine mRNA expression in leprosy: a possible role for interferon-gamma and interleukin-12 in reactions (RR and ENL). *Scand J Immunol***. 50**: 541-549.
7. Pfalzgraff RE and Ramu G (1994). Clinical leprosy. In Leprosy, 2nd edn, (Hastings RC, ed), Churchill Livingstone, Edinburgh, pp237-290.
8. Pocaterra L, Jain S, Reddy R et al (2006). Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. *Am J Trop Med Hyg*. **74**: 868- 879.
9. Revuz J, Guillaume JC, Janier M et al (1990). Crossover study of thalidomide vs placebo in severe recurrent aphthous stomatitis.. *Arch Dermatol*. **126**: 923-927.
10. Shannon EJ, Ejigu M, Haile-Mariam HS et al (1992). Thalidomide's effectiveness in erythema nodosum leprosum is associated with a decrease in CD4 + cells in the peripheral blood. *Lepr Rev*. **63**: 5-11.
11. Sheskin J (1965). Further observations with thalidomide in lepra reactions. *Lepr Rev*.**36**: 183-187.
12. Walker SL, Waters MFR and Lockwood DNJ (2007). The role of thalidomide in the management of erythema nodosum leprosum. *Lepr Rev*. **78**: 197-215.
13. Wu JJ, Huang DB, Pang KR et al (2005). Thalidomide: dermatological indications, mechanisms of action and side effects. *Br J Dermatol*. **153**:254-273.